# PHOOTONICS

A Cost-Effective Photonics-based Device for Early Prediction, Monitoring and Management of Diabetic Foot Ulcers

| **Deliverable** | **D3.1 – Survey of existing medical equipment of diabetic foot** |
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# Executive Summary

This deliverable aims to provide a concise survey of **existing medical equipment** for diabetic foot monitoring, diagnosis and management. The survey includes both **photonics-enabled devices** and **non-photonics** ones, covering all the three types of sensing that the project supports, i.e., HSI NIR, Mid-IR and Thermal-IR. The survey also includes traditional medical imaging and practices for DFU, such as ultrasound and skin lesion biopsy.

The PHOOTONICS consortium's goal is for this document to be **constantly revised** throughout the course of the project in order to provide an up-to-date view of relevant equipment competitive landscape.

# 1 Introduction

The final output of this document will be an analysis of the benefits and drawbacks of each medical device category in the field of diabetic foot monitoring, diagnosis and management and the potential benefits of photonics-enabled devices along with the necessary constraints this technology causes. This survey is critical for the next steps: information presented herein will be further analyzed within the context of the meta-analysis and the definition of the technical specifications of the new devices. This will help increase their exploitability and business opportunities in the sense of making a PHOOTONICS device competitive against existing equipment in terms of cost, ease-of-use, performance etc.

## 1.1 Structure

This document is structured as follows:

Section 1: Introduction

Section 2: Traditional Diagnostic Equipment

Section 3: Photonics Based Diagnostic Equipment

Section 4: Signal Processing Tools in Medical Image Analysis

Section 5: Current practices of DFU Monitoring at Home

Section 6: Conclusions

## 1.2 Applicable Documents

AD1 PHOOTONICS Grant Agreement

## 1.3 Acronyms

*Table 1: Acronyms*

| Term | Definition | Term | Definition |
|---|---|---|---|
| AI | Artificial Intelligence | mid-IR | mid-InfraRed |
| DFU | Diabetic Foot Ulcer | ML | Machine Learning |
| HSI | HyperSpectral Imaging | NIR | Near InfraRed |
| IRT | InfraRed Thermography | QCL | Quantum Cascade Laser |
| LDIR | Laser Direct Infrared | QE | Quantum Efficiency |
| LED | Light-Emitting Diode | RGB | Red Green Blue |
| LWIR | Long Wavelength InfraRed | SP | Signal Processing |

# 2 Traditional Diagnostic Equipment

**Clinical Examination**
Diabetic foot diagnosis should include a thorough documentation of medical history, an exact clinical examination and a number of diagnostic tests.

A proper investigation should be carried out. A complete history will aid in assessing the severity and risk of foot ulceration. Foot examinations are effective in reducing the risk of amputation. The foot should be carefully inspected for abnormalities such as fissures, deformities, dry skin and callosities. Ulcerations, prominent veins etc. should be examined carefully. Changes in the foot temperature must be noted. An increase in temperature might suggest inflammation while a decrease may indicate ischemia. Capillary refilling time should be assessed. All peripheral pulses must be examined. Pain, redness and swelling of the insensate foot/ankle should alert the examiner for Charcot neuroarthropathy, which can be easily confused with septic or gouty arthritis. Plantar pressure distribution measurement (pedography) has to be recorded, in order to identify areas at risk of developing an ulcer.

In patients with Peripheral artery disease (PAD) the use of WIfI (wound/ischemia/infection) system to stratify amputation risk and revascularization benefit is highly recommended. Peripheral artery disease, generally caused by atherosclerosis, is present in up to 50% of the patients with a diabetic foot ulcer.

The **ankle brachial index** is an adjunct measure to diagnose peripheral arterial disease. It is the ratio of the highest systolic blood pressure at the ankle (dorsalis pedis artery or posterior tibial artery) to the systolic blood pressure at the arm and is measured using a **Doppler device**. Doppler arterial signals using handheld Doppler devices remains the most commonly used bedside test.

## 2.1 Vascular Ultrasound

Atherosclerosis is one of the most serious complications of type 2 diabetes. Early onset of atherosclerosis in type 2 diabetes with typical diffuse development in small peripheral vessels leads to increased stiffness of these vessels. **Ultrasonographic methods are valuable, non-invasive tools that may be repeated multiple times to assess the stage of the disease and patient's need for treatment, as well as to monitor the results of treatment procedures** (1).

**Color Doppler** imaging of the blood flow is helpful in the assessment of vessel lumen diameter. The enhancement of the color-coded flow signal is selected so as not to exceed the vessel wall. The **power Doppler** technique is another method that might help in the assessment of the lumen flow; Such possibility is also offered by coded B-flow imaging. B-flow imaging (BFI) is characterized by higher spatial and temporal resolution than Doppler imaging, that allows for a better visualization of the vessel wall. **Duplex sonography** (strictly meaning the combination of pulsed Doppler sonography with real time B mode ultrasound imaging, but in current practice usually also including color Doppler scanning) allows the detection of Doppler flow patterns in a precisely defined area within the vessel lumen, facilitating the localization of arterial stenoses. Stenosis is graded by the ratio between the peak systolic velocity of the target/stenosed vessel and adjacent or contralateral non-stenosed vessels: the peak systolic velocity ratio.

Vascular ultrasound tests require a machine equipped with 5- to 12-MHz linear-array transducers (for extremities) and 2.25- to 3.5-MHz curved linear- or phased-array transducers (for the abdomen). A vascular software package is required in addition to the appropriate transducers. Duplex scanning refers to an ultrasound scanning procedure recording both gray scale and Doppler information. This includes 2-dimensional structure and motion, Doppler spectrum analysis, and color flow velocity mapping.

### 2.1.1 Color Doppler

The pulse repetition frequency scale determines the degree of color saturation and is adjusted so that normal laminar flow appears as a region of homogeneous color. Stenosis results in the production of a high velocity jet and an abrupt change in the color flow pattern. This is identified as either aliasing or desaturation (whitening) of the color display at the site of luminal narrowing. Color aliasing, persistence, and bruit all indicate flow disturbance.

### 2.1.2 Spectral Doppler waveform analysis

A normal pulsed wave Doppler waveform is a sharply defined tracing with a narrow Doppler spectrum indicating that blood cells are moving at similar speed throughout the cardiac cycle. Flow becomes turbulent at bifurcations and luminal narrowing causing spectral broadening of Doppler waveform, with filling in of the low velocity region in the spectral waveform as the blood cells move at a wide range of velocities. The normal peripheral artery waveform is triphasic. This diastolic component is absent in stiff atherosclerotic vessels.

### 2.1.3 Power Doppler

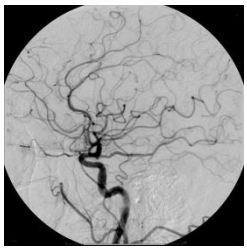
Power (or energy) Doppler is a technique that displays the total strength (amplitude) of the returning Doppler signal without distinguishing direction. Power Doppler can, therefore, identify very slow flow that may not be detected by color flow Doppler. Power Doppler is used to differentiate high-grade stenosis from occlusion, to detect collateral vessels, and to identify small vessel disease.

## 2.2 Angiography

Traditional contrast angiography, computed and magnetic angiography remain the most widely performed imaging techniques. All of the tests aim to determine regional foot perfusion and, possibly, guide directed revascularization therapy in patients with critical limb ischemia and foot ulceration.

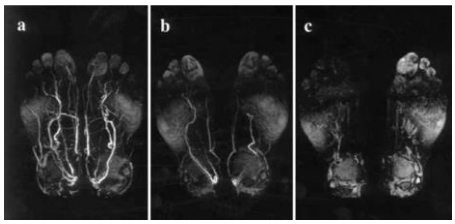
### 2.2.1 Contrast angiography

**Digital subtraction angiography** (**DSA**) is a fluoroscopy technique, performed in interventional radiology departments. The technique provides blood vessels visualization in a bony or dense soft tissue environment. Images are created by injecting contrast medium intra-arterially, while subtracting, in the same time, a "pre-contrast image" or *mask* from subsequent images. Subtraction angiography was first described in 1935 as a manual technique. Digital technology was introduced in the 1970s and made DSA the gold standard of vascular imaging.



### 2.2.2 Magnetic resonance angiography

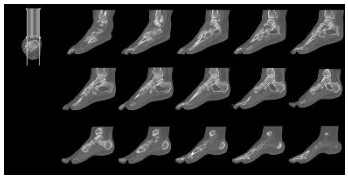
Magnetic resonance angiography (MRA) is a modern technique with promising results in diabetic PAD. High spatial resolution is necessary because of the distal location of the arterial stenosis. In addition, high temporal resolution is required to eliminate the interference of the venous signal.




Compared to contrast angiography, MRA is a less invasive imaging technique. Both time-of-flight (TOF) and phase-contrast (PC) MRA are non-contrast techniques with intravascular blood detection based on flow properties, as opposed to standard position of the surrounding tissues.

### 2.2.3 Computed tomography angiography

Recently, MDCT (multidetector computed tomography) angiography was introduced for the evaluation of peripheral vascular disease. Progress in multidetector technology improves the speed of acquisition and provides high spatial resolution.



**Comparisons**

There are differences in availability, cost, operator dependence and diagnostic accuracy among the aforementioned methods, as presented in the following table.

*Table 2: Availability, cost, operator expertise, diagnostic accuracy for DSA, CTA, MRA in LEAD diagnosis*

| **Imaging method** | **DUS** | **CTA** | **MRA** | **DSA** |
|---|---|---|---|---|
| **Availability** | +++ | ++ | ++ | +++ |
| **Costs** | + | ++ | +++ | +++ |
| **Operator expertise** | +++ | + | ++ | ++ |
| **Diagnostic accuracy** | | | | |
| Aorto-iliac | ++ | +++ | +++ | +++ |
| Femoropopliteal | +++ | +++ | +++ | +++ |
| Tibial | + | + | ++ | +++ |

Advantages and disadvantages of the imaging techniques for diabetic peripheral angiopathy, along with accuracy and indication parameters are presented in the following table.

*Table 3: Comparison of different imaging tests for patients with LEAD*

| | **DSA** | **DUS** | **CTA** | **MRA** |
|---|---|---|---|---|
| Advantages | • Delineation of the vessel lumen<br>• Roadmap (scanning of the entire vascular tree)<br>• Gold standard | • Noninvasive/ bedside technique<br>• Non-radiating/lack of complications<br>• Wide availability<br>• Low cost<br>• Anatomic and hemodynamic data | • Noninvasive<br>• Rapid<br>• Roadmap<br>• Lumen, wall (calcifications) and extraluminal information<br>• Visualization of stents, bypasses, aneurysms<br>• 3-D reformatting | • Noninvasive<br>• Non-radiating<br>• Anatomic and functional information<br>• Independent of calcifications |
| Disadvantages | • Invasive<br>• Radiation<br>• Contrast nephrotoxitity<br>• Contrast anaphylactic reactions | • Operator-dependent<br>• Poor visualization of heavy calcified vessels/poor discrimination of high grade stenosis-total occlusion<br>• Poor visualization of iliac vessels if obesity/bowel gas<br>• No clear roadmap | • Contrast nephrotoxicity/ anaphylactic reactions<br>• High radiation dose<br>• Lack of hemodynamic data<br>• Cost<br>• Limited availability<br>• Stenosis overestimation (distal arteries) | • Cost<br>• Limited availability<br>• Time consuming/ motion artifact vulnerability<br>• Overestimation of stenosis<br>• Gadolinium induced nephrogenic systemic fibrosis<br>• Claustrophobia<br>• Incompatibility with pacemakers<br>• Poor visualization of stents<br>• Limitations of selection of anastomosis site for a bypass |

| | | | | |
|---|---|---|---|---|
| Sensitivity | | 85-90% | Aortoiliac 96%<br>Fem/pop 97% | 95% |
| Specificity | | >95% | Aortoiliac 98%<br>Fem/pop 94% | 95% |
| Best practice | • Discordant non-invasive imaging results<br>• Below knee lesions in critical ischemia<br>• In combination with endovascular intervention | • LEAD detection<br>• Follow up of treatment<br>• Venous graft suitability assessment | • Aortoiliac lesions<br>• Aneurysms<br>• Extravascular pathology<br>• Stent/bypass assessment<br>• Planned intervention for revascularization | • Planned intervention for revascularization<br>• Patients with moderated renal failure<br>• Inconclusive DUS results |

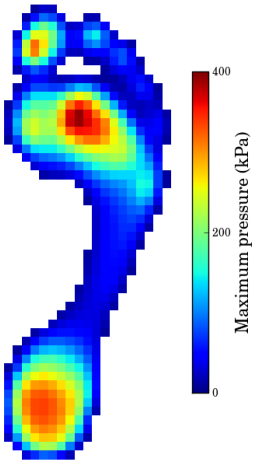
Unlike MRA, CTA and CA, duplex ultrasound (DUS) does not directly provide the familiar 'roadmap' overview of the circulation which facilitates treatment planning. However, the ultrasound operator can draw an informative diagram, particularly helpful in distinguishing the candidates for angioplasty from the patients requiring surgical reconstruction.

A further technical drawback of DUS, which may limit its utility, is the technical difficulty in assessing aortoiliac disease owing to the potential interference by bowel gas and the depth of the vessels. However, the benefits of DUS are that it avoids the possible complications associated with more invasive procedures, it does not involve ionizing radiation or the hazards and contraindications associated with strong magnetic fields, it does also not involve contrast which may cause nephropathy or allergic reactions, and it is relatively cheap and mobile (2).

Therefore, duplex ultrasound is currently indicated as the first line imaging method to confirm lower extremity artery disease lesions

## 2.3 Plantar pressure measurement

Measurement of the plantar pressure, i.e. the distribution of force over the sole of the diabetic foot, is useful as it provides detailed information specific to each region of contact. (3)(4)(5)




A wide variety of measurement systems are available on the market. In general, these can be distinguished according to different sensor principles:

- resistive,
- capacitive,
- piezoelectric

and different devices:

- platform,
- insole,
- single transducer system

Platform systems have the limitation to be used in a laboratory setting (embedded in a walkway) and only for barefoot measurements. Insole or single transducer systems can be used to detect the plantar pressures within the shoe and therefore are appropriate to assess the effects of different shoe configurations.

Platform systems include a flat, rigid array of pressure sensing elements arranged in a matrix configuration, incorporated to the floor to allow normal gait, and can be used for both static and dynamic studies.

In-shoe sensors are flexible and embedded in the shoe in a manner that reflects the interface relation between the foot and the shoe. The system is portable.

# 3 Photonics Based Diagnostic Equipment

Spectroscopy involves the study of objects based on their wavelengths when they are emitting as well as absorbing light. **Infrared** (IR) and **near-infrared** (NIR) regions of the electromagnetic spectrum have been mostly used for non-invasive methods of diabetic foot ulcer (DFU) detection. **Hyperspectral imaging** (HSI) is a technique combining spectroscopy and imaging, where each image is acquired at a narrow band of the electromagnetic spectrum.

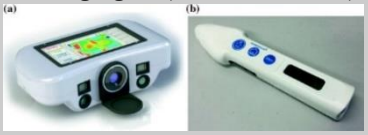
Hyperspectral imaging divides the spectrum in bands, typically covering the visible and near-infrared range. Thermal imaging is simply the process of converting infrared radiation (heat) into visible images that depict the spatial distribution of temperature differences in a scene viewed by a thermal camera. Hyperspectral and thermal imaging can be valuable technologies in the prevention and management of diabetic foot disease; thus, they have been widely used in clinical practice.

In addition, technological advancements in these imaging technologies increase their application range. Temporal changes in local epidermal thickness and oxyhemoglobin concentration are factors of great interest for diabetic foot ulcer monitoring (6). Due to the different absorption spectra of oxy and deoxyhemoglobin, hyperspectral imaging has been utilized to capture the various reflectance spectra and estimate oxygen saturation (SpO2) values from peripheral tissue (7). On the other hand, thermal imaging is also a promising technology to achieve this objective, as increased plantar foot temperature is a key sign of underlying inflammation. Infrared images are useful for measuring temperature in foot surface and for detecting temperature differences (>2.2 °C) between a foot region and the same region on the contralateral foot.

## 3.1 Medical Infra-Red Equipment for diabetic foot ulceration

Infrared cameras are increasingly applied in clinical applications as they allow fast, inexpensive and non-contact temperature measurements. Infrared thermography, which has been considered as a non-invasive diagnostic tool since 2001, is a technique used in studies of prevention and evaluation of Diabetic Foot (DF). The table below presents a summary of the infrared thermography equipment used for DFU diagnosis in published works / studies:

*Table 4: Review Table of Infrared Thermography devices used in DF Diagnosis studies (non invasive)*

| | IR Equipment | Measurement specifications |
|---|---|---|
| **1** | • RGB camera, **Canon Eos 40D** with EF-s 17–85 mm lens,<br>• IR Thermal camera, **FLIR SC305** with 16 bit resolution  | Average Temperature in regions of interest (ROIs) (7) |
| **2** | • Commercial digital RGB camera, **Canon EOS 40D**<br>• IR camera, **FLIR SC305** | Temperature differences between contralateral points (8) |
| **3** | • a) Thermal imaging device (Diabetic Foot Ulcer Prevention System (DFUPS), constructed by Photometrix Imaging Ltd) and also with b) a hand-held infrared spot thermometer (**Thermofocus® 01500A3**, Tecnimed, Italy)  | The system detects and classifies temperature differences<br>in foot sole zones as ulcerous if>2.2 °C and necrotic if<−2.2 °C. (9) |
| **4** | • **IR FLUKE TI32** IRT camera  | Mean percentage error for area detected by a difference in temperature (10) |
| **5** | • **IR FLIR ONE** thermal camera,<br>• Additional Equipment: Samsung Note five smartphone, temperature and humidity sensor, tripod, Polyurethane foam, and Accu-Chek Active meter  | Mean absolute temperature difference between the corresponding points of both feet (11) |
| **6** | • **FLIR® E60** thermal camera (FPA sensor array size of 320x240, NETD of < 50mK @ 30ºC)  | k-NN of 5 neighbors with 81.25% accuracy, 80% specificity and 100% sensitivity (12) |
| **7** | • Thermographic System **VarioCAM© hr head 680**/30mm positioned at 1m distance from the feet  | 93.16% accuracy, 90.91%<br>sensitivity and 98.04% specificity (13) |

| | | |
|---|---|---|
| **8** | • Medical 3D imaging system (**Vectra XT**, Canfield Imaging Systems) creates 3D models using a passive photogrammetry technique  | Creation of 3D thermal foot images to assess the diabetic foot skin temperature in 3D in a hospital IT environment (14) |
| **9** | • Mobile thermal camera (**FLIR ONE**)  | The developed application compares the difference between the temperature distribution on the two feet and checks if there is a Mean Temperature Difference (MTD) greater than 2.2oC (the value which indicates a possible ulcer development). (15) |

## 3.2 Medical Hyperspectral Images in Diabetic Foot

The following table presents basic equipment using hyperspectral technology (HT), to quantify tissue oxy- and deoxyhemoglobin to extract information about diabetic foot ulcer:

*Table 5: DF Diagnosis Equipment using Hyperspectral Images*

| | HSI Equipment | Measurement specifications |
|---|---|---|
| **1** | The illumination optics consisted of seven broadband visible light-emitting diodes [(LEDs), XRE WHT-L1 by CREE Incorporated, Durham, North Caroline] emitting primarily between 500 and 700 nm. The collection optics were composed of (i) a spectral separator (LCTF-10-20 by CRI Incorporated, Woburn, Massachusetts), (ii) a charged-coupled device [(CCD), Guppy F-1468 by Applied Vision Technology, Stadtroda, Germany], and (iii) a 25-mm focal-length imaging lens. The spectral separator was tunable over the range of 400–720 nm with a full-width-at-half-maximum (FWHM) value of 10 nm. | Image processing algorithm that automatically classifies ulcers as healing or non-healing. Two classes are created: ulcers that healed within 24 weeks and (ii) ulcers that did not heal within 24 weeks. (6) |
| **2** | HyperMed CombiVu-R System (HyperMed, Waltham, MA). HT uses a spectral separator to vary the wavelength of light admitted to a digital detector to provide a spectrum for each pixel—a hyperspectral scan. Tissue spectra are compared with standard spectra for oxy- and deoxyhemoglobin and tissue oxyhemoglobin (HT-oxy) and tissue deoxyhemoglobin (HT-deoxy) determined for each pixel. HT-oxy and -deoxy units represent values for oxyhemoglobin and deoxyhemoglobin found in the tissue volume measured by HTcOM (hyperspectral technology cutaneous oxygenation monitoring). For this study, a 30-s tissue scan was obtained at a 12-inch focal distance and ratioed to a calibration scan obtained using a calibrator (Check Pad; HyperMed) The spatial resolution of the HT images was 60 μm. | HT measurements of oxyhemoglobin (HT-oxy) and deoxyhemoglobin (HT-deoxy) were performed at or near the ulcer area and on the upper and lower extremity distant from the ulcer. (16) |

| | | |
|---|---|---|
| **3** | The HSI setup consists of the following components: Illumination of the foot was via 16 × 1 W white light-emitting diodes (LEDs) (LXHL-MWEC, LumiledsTM Lighting, San Jose, CA, USA) with 8 units placed on either side of the camera. The HSI camera is a "push-broom" type. The camera comprises a Peltier cooled charge-coupled device (CCD) coupled to an imaging spectrograph (ImSpector V10E, Specim Ltd.). 3D data cube contained 2D spatial images (120 x 170 pixels) over a wavelength range from 430 nm to 750 nm (272 values). | SpO2 Data Processing and Principal component analysis was applied. PCA has been applied to a hypercube, with<br>eigenvector and eigenvalue: unfold (a) 3-D datacube into (b) 2-D matrix; (c) obtain eigenvectors and eigenvalues from covariance matrix; (d) multiply the 2-D matrix by the eigenvectors<br>to obtain a score matrix; (e) refold the score matrix to form images at each principal component. (17) |
| **4** | MHSI data were obtained with a HyperMed Visible MHSI System (HyperMed Inc, Watertown, MA, USA). MHSI uses a spectral separator to vary the wavelength of light admitted to a digital camera to provide a spectrum for every pixel—a spectral image. | Medical hyperspectral imaging (MHSI) to investigate the haemoglobin saturation (S(HSI)O2; % of oxyhaemoglobin in total haemoglobin [the sum of oxyhaemoglobin and deoxyhaemoglobin]) in the forearm and foot; also used 31P-MRI scans to study the cellular metabolism of the foot muscles by measuring the concentrations of inorganic phosphate and phosphocreatine and calculating the ratio of inorganic phosphate to phosphocreatine (Pi/PCr). (18) |
| **6** | An HSI system obtains multiple images at discrete wavelengths, providing a diffuse reflectance spectrum for each pixel in the image. The system uses wavelengths between 500 and 660 nm to include oxy and deoxy absorption peaks. | The data were analyzed to detect differences between patients with DFUs that healed and those with DFUs that did not heal. (19) |

## 3.3 Mid-IR Spectrum Technologies

*Table 6: DF Diagnosis with RGB Or Mid-IR Images.*

| | **Basic Equipment** | **Measurement specifications** |
|---|---|---|
| **1** | **Quantum Cascade Laser** (EC-QCL) (Daylight Solutions DLS-TLS-001-PL), tunable in 0.9 $cm^{-1}$ wavenumber steps from 1010 – 1095 $cm^{-1}$ via the external grating. QCL chip covers a range of glucose absorption in the **Mid-IR**. The maximal average laser power lies between 20 mW and 130 mW. A mechanical chopper (New Focus Model 3501) modulates the continuous-wave (cw) laser light, which is focused by several anti-reflection coated ZnSe lenses into the PA cell. | Glucose detection in epidermal skin samples. Examine blood glucose extraction methods in addition to indicators of blood glucose level, toward development of an innovative, non-invasive extraction technology. (20) |
| **2** | Three **RGB** cameras mainly used for capturing the foot images, **Kodak DX4530, Nikon D3300** and **Nikon COOLPIX P100**. | Faster-RCNN and R-FCN deep learning methods used for image localization. Detection of DFU on foot images (variations in terms of color, size, shape, texture and site amongst different classes of DFU.) (21) |

# 4 Signal Processing Tools in Medical Image Analysis

Machine learning and signal processing methods can contribute to early diagnosis, predictive modelling, analytics and characterization of diabetic foot. Hyperspectral, near-infrared and thermal image sensing are processed to detect low tissue properties (e.g., elastin, collagen, Hb, SpO2, StO2) and temperature fluctuation in vascular tissues. There are various machine learning algorithms for early diagnosis of diabetic foot ulcers, these common tasks that can be performed for the detection of abnormalities on medical images:

- ***classification*** (refers to a type of labeling where an image/video is assigned into a certain number of categories).
- ***detection*** (draw bounding boxes around multiple objects, which may be from different classes).
- ***segmentation*** (draws outlines around the edges of target objects, and labels them [semantic segmentation]).

algorithms, for better understanding of the captured, by the photonic and imaging enabled devices, signals.

The machine learning algorithms used for early detection of diabetic foot are divided into supervised and unsupervised ones.

## 4.1 Supervised learning models

Various different models have been developed using supervised learning to detect diabetic foot ulcers. Among them are, linear kernel support vector machine (SVM-linear), radial basis function (RBF) kernel support vector machine, k-NN, ANN and MDR algorithms[1] (22). Agurto et al.[1] (23) captured infrared video sequences to characterize diabetic foot using independent component analysis (ICA) algorithm. Among the most popular techniques in image processing and analysis, convolutional neural networks (CNNs) have been used to classify normal (healthy skin) and abnormal classes (Diabetic Foot Ulcer). DFUNet was proposed, achieving an accuracy score of 0.961[2] (24). Authors considered different networks for object localization to perform on the DFU dataset -namely: Faster R-CNN and Region-based Fully Convolutional Networks (R-FCN).

Unlike general natural image recognition tasks, medical image analysis and especially analysis related to diabetic foot detection, lacks large labelled training datasets. Hence, transfer learning is introduced, in which weights learned or pre-trained during the training of a CNN on one (partially related or un-related) dataset are transferred to a second CNN, which is then trained on labelled medical data using these weights. Transfer learning involves training a machine learning algorithm on a partially-related or un-related dataset, as well as a labelled training dataset, to circumvent the obstacle of insufficient training data. The weights can be applied to some or all layers of the CNN, except the last fully connected layer. Although transfer learning techniques are commonly used in medical image analysis in conjunctions with CNNs, it is worth noting that they can be applied to other general machine learning algorithms as well (25). Cruz-Vega et al. (26) used AlexNet model for transfer learning due to lack of a sufficient number of images to train a dep learning structure from scratch.

In the medical image analysis space, RNNs have been used mainly in segmentation. In particular, using a

multidimensional LSTM, Stollenga et al. (27) segmented both three-dimensional electron microscope images of neurons as well as MRI brain scans. Shin et al. (28) describe annotating X-ray images with captions trained on radiology reports.

## 4.2 Unsupervised learning models

The problem of labelled data surpassed learning feature representations of input data in an unsupervised manner without labelled data. Autoencoders is a typical example of unsupervised algorithm that takes input data and then uses these codings to reconstruct output data (called reconstructions). The rationale behind autoencoders is that the output data must be as similar to the input data as possible, i.e., autoencoder models contain a cost function which penalizes the model when inputs and outputs are different. Autoencoders have several useful features. Firstly, they are employed as feature detectors that can learn codings in an unsupervised manner, without training labels. Secondly, they reduce the model dimensionality and complexity as codings often exist in a lower dimension. Thirdly, by having to reconstruct outputs, autoencoders generate new data that is similar to the input training data. These features are an advantage in medical image analysis, where labelled training data is scarce.

To force models to learn useful representations, constraints need to be added. One example is the Denoising Autoencoder reported by Vincent et al. (29), where Gaussian noise is added to the early hidden layers. Applying dropout i.e., randomly turning off some of the neurons in the early hidden layers, accomplishes the same goal, by forcing the model to learn useful codings to generate back the noise-free inputs in the output layer. A second example are Sparse Autoencoders (30), whereby a defined proportion of the neurons in the hidden layers are deactivated or set to zero. This is accomplished by having a cost function that penalizes the model when there are active neurons beyond a defined threshold. Variational Autoencoders (VAEs) are an emerging and popular unsupervised learning architecture described by Kingma and Welling (31). VAEs are a generative model, consisting of a Bayesian inference encoder network and a decoder network, that can be trained with stochastic gradient descent. The encoder network projects input data into latent space variables, whose true distribution is approximated using a Gaussian distribution. The decoder network then maps the latent space back into output data, trained and guided by two cost functions: a reconstruction loss function and the Kullback–Leibler divergence.

### 4.2.1 Restricted Boltzmann Machines and Deep Belief Net-Works

Boltzmann machines were invented by Ackley et al. (32) in 1985, and were modified as Restricted Boltzmann Machines (RBMs) a year later by Smolensky (33). RBMs are generative, stochastic, probabilistic, bidirectional graphical models consisting of visible and hidden layers. These layers are connected to each other but there are no connections within the layers themselves. RBMs haven't been used yet for diabetic foot detection, however, these techniques have been used for medical imaging to classify lung tissue into normal, emphysematous, fibrosed, micronodular, or ground glass tissue. For this task, they used the CT chest scans of 128 patients with interstitial lung disease from the ILD database. Convolutional RBMs were trained with either purely discriminative, purely generative, or mixed-discriminative and generative learning objectives to learn filters. These filters were then used to perform feature extraction and create feature activation maps, before classification using a random forest classifier. Classification accuracies of between 41% to 68% were obtained, depending on the proportion of generative learning and the input patch size.

### 4.2.2 Generative Adversarial Networks

Generative Adversarial Networks (GANs) (34) represent a type of unsupervised learning which holds promise for medical image analysis tasks. As its name suggests, a GAN is a generative model, comprised of two simultaneously-trained, competing models, which may be multilayer perceptrons such as CNNs. The models may be described as two players competing in a zero-sum game. One CNN is a generator that

generates artificial training images. The other CNN is called a discriminator, which classifies if images are real training images or artificial ones from the generator. The desired end-point of this adversarial arrangement is one where the discriminator is unable to tell the difference between a real and a generated image i.e., the probability of assigning an image to either data distribution is 1/2. An advantage is that both generator and discriminator can be trained with backpropagation and dropout, without unwieldly inference and Markov chains. GANs are relatively new but some applications in brain MRI segmentation and synthetic medical data generation and can partially be used to generate reliable sub-datasets, extending the current ones that are limited and hence, training the supervised algorithms with high accuracy.

# 5 Current practices of DFU Monitoring at Home

## 5.1 Current practice in - at Home - monitoring of Diabetic Foot Ulcers

As already discussed, diagnosis of foot ulcers currently relies on expert clinical judgment and dated microbiological techniques. As an example, microangiopathy, as structural and functional abnormalities in capillaries, is one of the major foot complications of diabetes. However, capillaroscopy usually requires expert judgement and is time consuming. This implies that current diagnosis is limited to visits to a doctor with the relevant knowledge of DFUs, and at a hospital, where the necessary techniques are available. This implies that access to diagnosis may be limited as not every hospital possess the necessary techniques or doctors. Diabetic neuropathy is one of the most frequent complications of diabetes mellitus. It has been diagnosed for 50% of all patients with diabetes mellitus, while a painful peripheral diabetic neuropathy develops for 16%. Frequently, this condition is not diagnosed for such patients, and even more frequently, it is not treated.

Prevention of diabetic neuropathy, early diagnosis and treatment are very important since the spread of diabetic neuropathy leads also to the high incidence of recurrent infections of lower limbs, ulcerations and amputations. The most important aim of early diagnosis of diabetic neuropathic complications are glycaemic control and foot care. Usually patients visit the doctor 3 times per year to monitor for complications such as DFU. But if they develop an ulcer, they have to visit the doctor around once a month.

The doctor's medical indication to the patients is to achieve a stable and optimal glycaemic control to reduce the symptoms of neuropathy. In addition, the patients must examine their feet each day and estimate whether there is no skin dryness, fractures, cracks, corns, early signs of infection in between the toes and around nails. If the doctor examines the feet of a patient on a regular basis, he/she may diagnose diabetic neuropathy earlier. Today, devices that use thermal imaging for example have been proposed to estimate the status of a diabetic foot. These devices can be applied for the patients and can reduce the visitation to the hospital. In the table below, we summarize the main equipment for - at home - diabetic foot monitoring.

*Table 7: Competitive Alternatives of PHOOTONICS Home Device*

| Product | Description | Comparison with PHOOTONICS |
|---|---|---|
| **Orpyx SI Sensory insoles**   | It is a plantar sensory replacement system, developed by Orpyx® that use pressure sensor- embedded shoe insoles to determine force exerted over the bottom of the feet, and wirelessly transmit collected information to a back pad, mobile device or wristwatch worn by the patient. Their clinical validation studies are ongoing. | • Collects real-time pressure data, from the foot through a sensor-embedded insert worn in the shoe, and provides feedback to the user, but it is not a diagnosis device: if something "weird" is detected, the system notifies the user.<br>• Real-time alerts allow the user to immediately relieve sustained, high-pressure areas<br>• The system requires changing the "detector" every time the user changes shoes (otherwise lesions would remain undetected), it has a high price (former solution Surrosense RX costs $2,399) and requires yearly replacement of shoe inserts (additional cost).<br>• The company is focused in a national scope (US) and does not have sales facilities in the EU (not even online orders). |

| | | |
|---|---|---|
| **Podimetrics SmartMat™**  | It is a thermo-imaging solution for the prediction and prevention of diabetic foot ulcers, developed by the company Podimetrics. It is a remote temperature monitoring technology, consisting of a wireless SmartMat™ for the home and a monitoring service that notifies patients and clinicians when temperature asymmetry presents between the two feet, a potential sign of inflammation and a developing foot ulcer. | • Their monitoring technology is based just on collecting foot temperature scans, which is a very incomplete method compared with PHOOTONICS.<br>• They focus on the US market<br>• Price: N.A |
| **Bluedrop medical** | A start-up from Ireland is developing and commercializing an internet of things enabled, home based device, which performs a daily scan of the patient's feet and sends the data to the cloud for analysis through advanced algorithms capable of detecting abnormalities and predict the formation of diabetic foot ulcers. | • Neither the technology nor the price is disclosed, and as such it is unclear whether this is indeed at a commercial stage.<br>• They focus on the US market |
| **Siren Socks**  | Siren's Socks and Foot Monitoring System continuously track foot temperature, sending information to a doctor to help track issues related to inflammation. | • Monitoring technology is based just on collecting foot temperature. Custom socks are equipped with sensors that continuously monitor foot temperature at only six key points.<br>• Only available in the US |
| **Flextrapower Smart Insole**  | A smart insole system which uses graphene's sensing technology to detect foot ulcers before they form. | • Not enough documentation. Approach is generic, no clinical studies to verify results.<br>• It is unclear whether this is indeed at a commercial stage<br>• Focus on US market |

# 6 Conclusions

This analysis provides a categorization of the existing devices with respect to several criteria. The survey includes both photonics-enabled devices and non-photonics ones, covering all the three types of sensing that the project supports, i.e., HSI NIR, Mid-IR and Thermal-IR. The survey also includes traditional medical imaging and practices for DFU, such as ultrasound and skin lesion biopsy.

The final output is a complete survey of the benefits and the drawbacks of each medical device category (and of specific equipment) in the field and the potential benefits of photonics-enabled devices along with the necessary constraints this technology causes. This survey is critical for the exploitation and business planning efforts in the sense of making PHOOTONICS device competitive than existing equipment. Therefore, this document will be constantly revised throughout the course of the project in order to provide an up-to-date view of relevant equipment competitive landscape. This applies of course to both versions of the PHOOTONICS Device: the HOME as well as the PRO version.

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