

PhD Research and Training proposal

1. EXCELLENCE (4 pages max)

1.1. Pre-proposal's context, positioning and objective(s)

The clinical management of skin cancers is currently undergoing a significant transition, driven by the increasing availability of high-resolution digital imaging and the urgent need for earlier intervention to reduce mortality rates. Aggressive skin cancers, as Basal cell carcinoma (BCC) and melanoma, are a potentially lethal cutaneous cancers whose prognosis are intrinsically linked to their stage at diagnosis time, specifically the Breslow thickness. While the advent of deep learning, particularly Convolutional Neural Networks (CNNs) [14], has revolutionized the field of Computer-Aided Diagnosis (CAD), a large gap between experimental performance and clinical utility persists. Most existing models are designed to evaluate isolated dermoscopic images, ignoring the global cognitive [3,4] process that a dermatologist employs. In clinical practice, the diagnosis of skin cancers is not merely the classification of a single lesion based on single imaging modality but an integrative analysis of the patient's entire skin surface with various imaging modalities. The first step consists on the global comparative approach [1] based on clinical images (VECTRA 3D), known as the "Ugly Duckling Sign" (UDS) [2,5,6,10], posits that most benign lesions in a single individual share a common morphological pattern, and any lesion that deviates significantly from the most frequent pattern of a patient warrants suspicion. Once these suspicious lesions are identified, a second and maybe a third imaging modalities such as dermoscopy, RCM and/or LC-OCT are used to confirm the diagnosis at a cellular level. The multimodal approach used in clinical practice is complementary and allows the early-stage detection of skin cancers.

The proposed research project, **SkinDiag**, aims to address these limitations by adopting a multi-modal approach inspired by clinical practice. The project focuses on integrating various imaging modalities and formalizing dermatological concepts within a computational framework that prioritizes intra-individual comparative analysis. The positioning of this project is at the intersection of advanced computer vision and clinical oncology, leveraging a unique multi-modal technological asset including the VECTRA 3D body mapping system [13], dermoscopy, Line Confocal field Optical Coherence Tomography, and Reflectance Confocal microscopy RCM. These technologies allow for the standardized acquisition of high-resolution images of the entire cutaneous surface, providing the necessary data to build a patient-specific morphological baseline with VECTRA 3D, then other devices can confirm the diagnosis at a cellular level. This project seeks to develop dedicated algorithms for each imaging modality and to establish an advanced multimodal fusion framework capable of effectively handling class imbalance between benign and malignant cases.

Project's objectives and research hypotheses

The primary objective of this project is to address the limits of existing CAD systems for skin cancers diagnosis assistance. It will focus on both developing a multi-modal approach using various imaging modalities, including Reflectance Confocal Microscopy (RCM) and LC-OCT with clinical and dermoscopic images, rather than single imaging modality; then modelling dermatological concepts to improve the interpretability of models and enhance the decision-making transparency. This approach seeks to replicate the diagnostic process of a human expert more faithfully than current single-image models. We hypothesize that an automated analysis of the entire lesion set, rendered possible by VECTRA 3D, will significantly enhance the sensitivity and specificity of suspicious lesions detection by identifying outliers that might otherwise be overlooked when examined in isolation. Then, by integrating complementary information from multiple imaging modalities, the multimodal approach will increase both the sensitivity and specificity of skin cancers diagnosis, basal cell carcinoma (BCC) and/or melanoma, and can aid for treatment management by subtyping lesions.

The scientific objectives cover six major axes:

1. Construction and annotation of a multi-modalities imaging dataset, including LC-OCT, RCM, dermoscopy and clinical images for basal cell carcinomas and melanoma versus benign lesions (nevi, sebaceous hyperplasia, angioma).
2. Algorithmic Development of Comparative Models: Designing neural network architecture, specifically focusing on Residual Set-Transformers (Reset) [5], capable of processing variable-sized sets of lesions and identifying the "Ugly Duckling" through attention mechanisms.

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3. Investigation and comparison of multiple fusion approaches to combine the algorithms developed across different imaging modalities on the constructed dataset.
4. Developing solutions for handling imbalanced data between benign and malignant lesions
5. Formalization and Identification of New Concepts: Working closely with clinical dermatologists to identify and mathematically formalize morphological and contextual concepts used by clinicians for skin cancers diagnosis.
6. Explainability through Concept Discovery: Utilizing unsupervised Concept-based Explainable AI (C-XAI) methods, such as Concept Recursive Activation Factorization for Explainability (CRAFT), to extract latent representations that correspond to clinical concepts modeled previously with clinicians.

Position of the project in relation to the state of the art

The current state of the art for automatic skin cancers detection is dominated by supervised deep learning models trained on isolated images from public datasets such as the ISIC (International Skin Imaging Collaboration) dataset [12]. While these models achieve expert-level accuracy in controlled settings, they suffer from two major flaws. First, they lack "global cognitive analysis," failing to account for the fact that a lesion may appear suspicious on one patient but benign on another, depending on their overall benign lesions' phenotype and the focus on a single imaging modality instead of using various imaging modalities as the clinicians utilized in the clinical practice. Second, they operate as "black boxes," providing a probability score without a clinical rationale. Attribution methods like Grad-CAM provide heatmaps indicating the location of important pixels, but they do not explain *what* visual features (e.g., blue-white veil, atypical network) are identified.

This project advances the state of the art by addressing the two weaknesses. First a multi-model approach will be developed to address the single modality issue, this part will also deal with the common problem in medical imaging datasets consisting of the class imbalance issue [15, 16]. Two main contributions will be addressed for this part, the class imbalance problem by designing and implementing novel loss function and training strategies and the multi-modality contribution by proposing novel ensemble model for different imaging techniques alongside. Second, the explainability of models will be addressed by shifting the focus from attribution to concept-based explanation. Recent work by Fel et al. [8] on CRAFT and by Zhang et al [9]. Invertible Concept-based Explanations (ICE) has laid the groundwork for identifying human-interpretable directions in the latent space of neural networks. However, these techniques have rarely been applied to the specific challenge of intra-individual comparative analysis in dermatology and with the multimodal approach. Furthermore, the integration of low-rank matrix approximations and robust principal component analysis, as explored by Rekavandi et al. [11], offers new avenues for identifying sparse, stable concepts in medical data.

Research Aspect	Standard State of the Art	SkinDiag Approach
Data Scope	Isolated single modality images (single lesion)	Total body mapping (VECTRA 3D, set of lesions) and multi-modal approach.
Diagnostic Logic	Classification based on local features	Comparative analysis (Ugly Duckling Sign)
Explainability	Pixel-based attribution (Heatmaps)	Concept-based explanation (C-XAI/CRAFT)
Model Type	Standard CNNs (ResNet, EfficientNet)	Residual Set-Transformers (Reset)
Validation	experimental performance (Accuracy/AUC)	Clinical validation with human-AI collaboration

Methodology to reach scientific objectives

The methodology is designed to be progressive and interdisciplinary, ensuring that technical developments remain grounded in clinical reality. The research will be conducted using the annotated dataset from APHM, enriched by VECTRA 3D system (clinical images), dermoscopy, RCM, and LC-OCT of malignant lesions (melanoma and Basal cell carcinomas) and benign lesions.

Stage 1: Dataset construction and annotation, the first phase involves data acquisition with the different imaging techniques and the data annotation. We will structure the data acquired from the VECTRA 3D system (clinical images), which provides standardized 2D and 3D images. A key challenge here is the automatic segmentation and tracking of lesions across the body surface to build a coherent set for each patient. These lesions will be imaged with the other imaging techniques involved in this project to build a coherent dataset to train and evaluate the developed models later-on.

Stage 2: Single modality models development, this stage will be conducted alongside stage 1. It consists of developing a classification model for each imaging modality on publicly available datasets such as the ISIC dataset. The class imbalance problem will be addressed at this stage. This stage will also address modeling the Ugly Duckling Sign based on similarity learning with a "Reset" architecture. In fact, traditional CNNs are ill-suited for set-based processing because they do not easily allow comparison of multiple inputs with varying cardinality. We will utilize Set-Transformers, which use multi-head attention to learn relationships between elements in a set. The mathematical framework will involve the minimization of alpha-divergences for robust dictionary learning, ensuring that the identified "concepts" are not merely noise but represent stable morphological patterns.

Stage 3: developing the multi-modal approach, once the dataset built and the single imaging modality models are developed and evaluated. This stage will focus on developing a framework enabling jointly learning of the different models to develop the multi-model approach. This stage will focus on exploring and proposing a hybrid fusion approach which will combine early fusion and late fusion with adequate loss function. This stage will allow the development of a model that will be more robust and generalizable.

Stage 4: Modeling demagogical concepts, a comprehensive review of dermatological concepts and their potential computational representations will be conducted before their modelling. We will apply Non-negative Matrix Factorization (NMF) to the feature maps of the networks. NMF is particularly effective for medical imaging because it enforces parts-based representations, which align well with the way dermatologists describe lesions (e.g., "this part is asymmetric," "that part has globules"). These discovered concepts will be presented to expert dermatologists for labeling and correlation with clinical reality. The importance of each concept will be quantified using Sobol indices, providing a faithful estimation of how each morphological feature contributes to the model's final diagnosis.

Stage 5: development of unsupervised explainable AI models capable of discovering new, clinically meaningful features that can be interpreted and validated by dermatologists. We will implement baseline unsupervised XAI approaches, such as CRAFT, to identify initial clusters in the latent space of pre-trained networks. We will annotate dermoscopy, LC OCT and RCM also for the multimodal approach for the benign and malignant lesions based on this methodology.

Originality and innovative aspects

The originality of this project resides in three main contributions:

1. **Technological Innovation:** The development of a multi-modal approach with various imaging modalities for skin cancer detection, the imaging modalities include clinical images, dermoscopy, RCM and LC-OCT. This multi-modal approach will allow a high level of standardization and holistic view which was previously impossible and help with therapeutic management by subtyping skin cancers.
2. **Methodological Innovation:** Integrating unsupervised concept discovery (CRAFT) with set-based transformers (Reset) addresses the two biggest hurdles in medical AI: the lack of context and the lack of interpretability.
3. **Clinical Innovation:** The project aims to produce a "pedagogical AI." By visualizing the concepts used by the AI model for diagnosis, the system can serve as a training tool for junior dermatologists, helping them refine their own diagnostic criteria through transparent feedback loops.

Gender dimension in the research content

In the skin cancers diagnosis, there is no difference between woman and men [17]. Statistics consistently show that risk factors of skin cancers such as number of nevi, presence of atypical nevi syndrome, UV exposition and past medical history can increase the incidence of skin cancers.

Traditional AI models trained on unbalanced datasets may inherit biases that lead to lower diagnostic accuracy for specific genders. Our project explicitly addresses this dimension by:

- Ensuring gender-balanced representation in the VECTRA 3D dataset acquisition.

1.2. Interdisciplinary dimension of the project

The complexity of modeling dermatological concepts necessitates a deeply interdisciplinary approach, merging the mathematical and algorithmic rigor of informatics with the clinical expertise of dermatology.

Contribution of the Disciplines:

The **Images and Models (I&M) team at the Laboratoire d'Informatique et Systèmes (LIS)** brings world-class expertise in computer vision, image processing, machine and deep learning, and explainability. Their role is to transform clinical intuitions into formal mathematical objects, such as set-based attention mechanisms and NMF-based concept vectors. Without this technical foundation, the project would remain purely qualitative. Their work on interpretability of the model, heatmaps and shap-values or unbalanced data challenge different frameworks of fusion.

Conversely, the **Dermatology Service at APHM** and provide the essential clinical ground truth. They are responsible for the characterization of the concepts for detection of skin cancer in the different modalities of images, that serve as the baseline for algorithmic development. They perform the expert annotations, define the diagnostic relevance of the discovered features, and design the clinical validation protocols. Their clinical insight ensures that the "concepts" extracted by the AI are not artifacts of the training data but reflect actual biological and morphological phenomena. Different imaging systems are available into their clinical practice to construct dataset with annotations and multimodal approach.

Interdisciplinary Methodology: The project follows a "Co-Construction" cycle. Clinical experts define a dermatological concept. The computer vision team develops a model to capture this concept. The resulting "concept activation maps" are then reviewed by clinicians to verify their pedagogical and diagnostic value. This iterative loop ensures that the final system is both technologically sophisticated and clinically acceptable, moving past the common pitfalls of research. To develop unsupervised AI models capable of discovering new, clinically meaningful features that can be interpreted and validated by dermatologists.

International expertise: The MSKCC Skin Cancer Pathology Research Center will bring to this project their high expertise. They possess a non-commercial RCM-OCT prototype, offering a unique technological platform and recognized expertise in multi-modal imaging, closely integrated with clinical dermatology practice.

2. IMPACT (2 pages max)

2.1. Expected impact of the project on the candidate's career

This PhD project is designed to transform the Early-Stage Researcher (ESR) into a high-level specialist with a unique hybrid profile at the intersection of Artificial Intelligence and Medicine.

Technical and Scientific Excellence and interdisciplinarity: The fellow will acquire rare expertise in **Explainable AI [7] (XAI)**, interpretability, specifically in concept discovery and matrix factorization (NMF), which are currently at the frontier of machine learning research. By managing complex 3D medical datasets from the VECTRA system, the candidate will master advanced computer vision skills applicable across the MedTech and data science sectors with medical communication ability.

Professional Versatility and Employability The program emphasizes transferable skills that bridge the gap between academia and industry.

- **Management and Leadership:** Through the SCHADOC training, the fellow will gain competencies in research project management, grant writing (targeting ERC/MSCA standards), and intellectual property management.
- **Network and Mobility:** International exposure via the **CIVIS alliance** and planned secondments with non-academic partners (MedTech startups/hospitals) will significantly broaden the candidate's professional network and industrial awareness.
- **Communication:** Regular presentations to clinical experts and scientists will refine the ESR's ability to communicate complex science to diverse audiences, a key asset for leadership roles.

2.2. Expected impact for the thematic axis

The project directly contributes to the **Health and Well-Being** and **AI** axes of the SCHADOC program and the SUD region's strategic priorities.

Advancement of Research and Society

- **Scientific Contribution:** By developing context-aware, "Explainable AI," this research provides a new methodological template for interpreting medical models through clinical concepts rather than opaque probabilities.
- **Public Health:** Early skin cancers detection enabled by these tools directly reduces melanoma mortality and healthcare costs, a vital impact for the high-incidence SUD region.
- **Pedagogy:** The resulting software serves as a transparent training platform for junior dermatologists, enhancing the overall quality of regional medical expertise.

2.3. Dissemination, exploitation and communication activities planned

Scientific and Industrial Dissemination Results will be submitted to AI conferences (CVPR, MICCAI) and high-impact medical journals (Journal of Investigative Dermatology, Nature Medicine). Open science practices, including sharing code on platforms like GitHub, will ensure rapid global adoption.

Exploitation and Public Engagement Public engagement will focus on demystifying AI through regional events and digital science communication, fostering trust in automated diagnostic tools. We will present these new models and tools during faculty events for skin cancers detection and sensibilization of sun exposure.

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3. IMPLEMENTATION (2 pages max)

The implementation of this project follows a 36-month timeline, structured to ensure that scientific objectives are met through a series of logical, well-resourced work packages.

Work Planning and Achievability

The project is divided into five Work Packages (WPs), integrating research, training, and secondment activities.

Work Package	Duration	Main Tasks	Deliverables
WP1: Data & Pre-processing	M1-M6	Multimodal dataset : VECTRA 3D, dermoscopy, LC-OCT, RCM database structuring; State-of-the-art review; Ethics protocol	Literature review; Annotated dataset (v1)
WP2: single modality	M1-M14	Single modality models development and management of the class imbalance problem; Development of "Reset" (Set-Transformer); Training on patient lesion sets.	Classification models and technical report
WP3: multi-model approach and concept modelling	M15-M22	Developing fusion strategies for the multimodal approach; To develop unsupervised AI models. Implementation of baseline XAI models; First NMF-based concept extraction	Technical report, the multi-imaging model, concepts clusters
WP4: Clinical Validation	M23-M30	Clinical study with dermatologists; Evaluation of interpretability; Secondments	Validation study report; Peer-reviewed papers
WP5: Finalization	M31-M36	Thesis writing; Dissemination; Pedagogical tool prototyping	Completed PhD thesis; Software prototype

Feasibility and Resources: The project is highly achievable within 36 months because it builds upon the existing successful collaboration between Pr Djamal Merad (LIS) and Dr Jilliana Monnier (APHM/CRCM) in the context of the ANR Diamelex project. The fellow will have immediate access to:

- The noninvasive imaging platform with **VECTRA 3D system, dermoscopy coupled with AI, LC-OCT and RCM** and the associated patient cohort at Timone and Conception Hospital.
- The **high-performance computing cluster** at the LIS laboratory for training complex neural models.
- A pre-existing, large-scale database of annotated dermoscopic images for pre-training and transfer learning.

Management and Risk Mitigation

The management structure involves bi-monthly meetings between the informatics and clinical teams. A dedicated Risk Management plan has been developed, drawing on frameworks used in medical imaging implementations.

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Identified Risk	Impact	Mitigation Strategy
Technical: Concept drift or lack of interpretability	High	Use of recursive activation factorization (CRAFT) and recursive decomposition
Clinical: Insufficient number of annotators	Medium	Augmenting the number of physician to complete the annotations
Regulatory: Changes in GDPR or AI Act compliance	Medium	Continuous coordination with AMU's legal and ethical board; "Ethics by Design"
Personnel: Delays in secondment or mobility	Low	Leveraging the CIVIS network to provide flexible alternative mobility options

Feasibility of Training and Secondment: The 36-month duration accounts for the required secondments. A 3-month international secondment is planned with a leading European research center in medical imaging (e.g., via the CIVIS alliance).

4. ETHICS SELF-ASSESSMENT

This research adheres to the highest ethical standards as defined by the Horizon Europe guidelines and the MSCA framework. The primary ethical considerations involve human subjects and the processing of personal health data.

Human Subjects and Data Privacy: The project utilizes the VECTRA 3D, dermoscopy, RCM and LC OCT system to acquire images from patients.

1. **Informed Consent:** All patients participate on a voluntary basis. Explicit informed consent is obtained, informing them about the research objectives, the nature of the data collected, and their right to withdraw at any time. Ethical committee from AP-HM and validation with administrative process
2. **Pseudonymization:** All medical images and clinical metadata are pseudonymized at the point of collection. Personal identifiers are removed and replaced with a unique project code. The "key" connecting codes to patient identities is held securely by the APHM clinical team and is never shared with the informatics researchers.
3. **GDPR Compliance:** The processing of data follows the General Data Protection Regulation (GDPR). An impact assessment (DPIA) has been conducted, and data storage is restricted to secure, encrypted laboratory servers with limited access.

AI Ethics and Fairness: The "black box" nature of AI presents ethical risks regarding accountability and bias.

1. **Explainability:** By prioritizing C-XAI and CRAFT, we ensure that the AI's "reasoning" is visible. This allows clinicians to verify that the model is not relying on spurious correlations (e.g., a ruler in the image) but on actual clinical concepts.
2. **Bias Mitigation:** We explicitly audit our models for performance disparities across gender, age, and skin tone. If biases are detected, we will implement fairness-aware training techniques (e.g., re-weighting or adversarial de-biasing) to ensure equitable diagnostic outcomes for all populations.
3. **Governance:** The project includes an "Ethics-by-Design" approach, where clinical dermatologists serve as human-in-the-loop evaluators, ensuring that the technology serves the patient and respects medical autonomy.

Potential Misuse and Security: While the project focuses on diagnostic aid, we acknowledge the potential for misuse of high-resolution 3D medical data. We implement robust cybersecurity measures, including multi-factor authentication and regular security audits of our data storage infrastructure, to prevent unauthorized access or data breaches.

5. REFERENCES

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