EU-DOCS for SmUCS

CO-SUPERVISED SUBJECT PROPOSAL FOR A DOCTORAL CONTRACT

Title of the thesis project:

Artificial intelligence-driven design and development of antimicrobial materials upon transductive/inductive graph neural network approaches for biomedical applications

La Rochelle University Research Unit: Laboratoire MIA (Mathématiques, Image et Applications)	**Partner university:** Catholic University of Valencia (UCV), Spain **Cotutelle research unit:** Biomaterials and Bioengineering Laboratory
Name of the LRUniv supervisor: Thierry Bouwmans Associate Professor (MCFHC - HDR)	**Name of the co-supervisor:** Ángel Serrano-Aroca Full Professor and Principal Investigator

Non-academic partner:

ProtoQSAR (Spain) - 3rd year of PhD

Keywords *(6 max)*: antimicrobial, biomaterials, microbial resistance, artificial intelligence, deep learning, graph neural networks.

Scientific description of the research project

<u>Scientific Context:</u> The rise of antimicrobial resistance (AMR) and the need for new antimicrobial strategies represent urgent challenges in modern medicine [1,2]. Traditional antimicrobial agents such as antibiotics are increasingly ineffective due to the rapid emergence of resistant pathogens [3]. In this context, the development of novel antimicrobial materials that can overcome these resistance mechanisms is critical [4,5]. Artificial intelligence (AI), particularly deep learning (DL) approaches such as graph neural networks (GNNs), offer an innovative approach to accelerate the design and optimization of these materials [6-9]. GNNs is capable of predicting molecular interactions, allowing for the rapid identification of promising compounds and materials with enhanced antimicrobial properties. This PhD thesis project aims to leverage DL, specifically transductive/inductive graph neural network approaches, to design and optimize antimicrobial materials, making the process faster, more efficient, and more targeted, leading to the development of next-generation materials for biomedical applications to combat microbial infections.

References
[1] Duffey et al., Nature Reviews Drug Discovery 2024, 23, 461–479
[2] Serrano-Aroca et al., ACS Nano 2021, 15, 5, 8069–8086
[3] WHO. Antimicrobial resistance. https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance
[4] Serrano-Aroca et al., Advanced Functional Materials 2024, 34 (38), 2402023
[5] Huang et al., Matter 2021, 4, 1892–1918
[6] Reiser et al., Communications Materials 2022, 3, 93
[7] Wong et al., Science 2023, 381 (6654), 164-170
[8] Wang et al., Nature Reviews Bioengineering 2024, 2, 392–407
[9] Song et al., Biomedical Signal Processing and Control 2024, 91, 106011

Scientific Objectives:

The main objective of this PhD thesis proposal is to develop antimicrobial materials through the integration of DL to predict and optimize the antimicrobial efficacy of new compounds and material composites against viruses, bacteria and fungi. Key objectives include:

1. Designing novel antimicrobial materials by applying AI-based models (specifically DL) to identify the most promising molecular structures for antimicrobial activity.
2. Optimization of material properties, including biocompatibility, stability, and antimicrobial efficacy, using data-driven approaches powered by AI.
3. Testing and validation of the developed materials to assess their effectiveness against viruses, bacteria and fungi in in vitro experimentation under biosafety level 2 conditions.
4. Testing that the developed antimicrobial materials are safe for human beings testing their toxicological aspects in in vitro experimentation under biosafety level 2 conditions.
5. Identification of key factors influencing antimicrobial activity to guide the rational design of future materials.

Scientific Challenges:

This research faces several significant scientific challenges:

1. For Dl to effectively predict antimicrobial properties, high-quality, diverse datasets of molecular interactions and material properties are required. Gathering and curating these datasets can be challenging.
2. The rational design of antimicrobial materials requires understanding the complex interactions between material properties, pathogens, and the environment. These interactions are difficult to predict without sophisticated AI tools.
3. While the focus is on antimicrobial efficacy, it is also crucial that the materials are biocompatible and stable for biomedical applications. Balancing these factors while maintaining high antimicrobial activity presents a challenge.
4. To integrate AI and experimental validation to translating AI predictions into real-world applications requires extensive experimental validation to confirm the accuracy of the DL predictions.

Methods to Address Challenges:

To address these challenges, the project will utilize a multi-disciplinary approach combining AI, material science, and experimental biology and chemistry:

1. *Deep learning:* GNNs will be trained on large datasets of antimicrobial compounds and their molecular interactions to predict the efficacy of new material designs. The model will learn to identify key molecular features that contribute to antimicrobial activity.
2. *Material synthesis:* the materials will be synthesized by combining promising compounds or materials predicted by the DL models. These antimicrobial compounds will be integrated into biopolymers or nanomaterials to create composite materials.
3. *Experimental validation:* the synthesized materials will undergo a series of antimicrobial in vitro tests, including MIC (Minimum Inhibitory Concentration) assays, disc diffusion tests, and viral inhibition assays, biofilm formation, etc. to evaluate their antimicrobial properties.
4. *Optimization and iterative design:* based on experimental results, the materials will be refined and re-optimized using further AI predictions. This iterative process will allow for the continuous improvement of material properties. The collaboration with the ProtoQSAR company where the PhD candidate will perform a three months secondment will help to explore interactions between antimicrobial particles and the bioactive compounds within the materials, using molecular docking.

Expected Results:

This research is expected to yield several significant outcomes:

1. The creation of novel antimicrobial materials with enhanced antibacterial, antifungal and/or antiviral properties that can be applied in various biomedical fields, such as wound healing, medical devices, and drug delivery systems.
2. The development of a predictive AI framework using Dl that can guide the design of antimicrobial materials, reducing the need for trial-and-error experiments and speeding up the material development process.
3. A deeper understanding of the structure-activity relationships that govern the antimicrobial properties of materials, providing insights into how to optimize materials for specific pathogens.
4. A validated approach for integrating AI-driven predictions with experimental testing, enabling more efficient development of future antimicrobial materials.
5. The successful completion of this project will contribute to addressing the global health challenge of antimicrobial resistance and provide a scalable approach for designing innovative

materials with specific biomedical applications. By leveraging AI, this research will pave the way for the development of advanced materials that could significantly impact healthcare and the pharmaceutical industry.

Scientific alignment with EU-DOCs for SmUCS objectives

The proposed PhD thesis aligns closely with the EU-DOCs for SmUCS program's scientific objectives by addressing critical global health challenges through the development of innovative, sustainable antimicrobial solutions. Specifically, this project advances the scientific orientation of the program by exploring cutting-edge approaches in antimicrobial materials design, leveraging AI, particularly DL, to accelerate the identification and optimization of antimicrobial materials, including those that are bio-based, biodegradable, and biocompatible. This approach not only pushes the boundaries of current antimicrobial strategies but also aligns with the program's emphasis on breakthrough research in biotechnological innovation. By focusing on the development of sustainable materials that combine efficacy with minimal environmental impact, the project directly supports the EU's sustainability goals. The use of bio-based materials in combination with AI-driven predictions contributes to environmentally conscious innovation, aligning with the EU-DOCs' priority of advancing materials that are both effective and ecologically responsible. Furthermore, this research contributes to improving public health outcomes by designing materials capable of preventing microbial infections, which has broad implications for healthcare and the development of safer, more effective medical solutions. The project is highly interdisciplinary, combining expertise in AI, microbiology, material science, chemistry, and biomedical engineering, resonating with the EU-DOCs' goal of promoting collaborative, cross-sectoral scientific endeavours. By developing next-generation antimicrobial materials using sustainable, AI-powered methodologies, this thesis not only furthers scientific knowledge but also has the potential to drive significant societal and environmental impact, aligning seamlessly with the SmUCS objectives.

Societal and economic challenges and contributions

The development of antimicrobial resistance (AMR) and the increasing prevalence of microbial infections represent significant global health challenges with profound societal and economic implications. The rise of resistant pathogens threatens to render many existing antibiotics and antimicrobial treatments ineffective, leading to longer hospital stays, increased medical costs, and higher mortality rates. Additionally, the environmental impact of conventional antimicrobial materials, including non-biodegradable and toxic substances, exacerbates the need for more sustainable solutions. These challenges underline the urgency of developing innovative, effective, and environmentally friendly antimicrobial materials. This PhD thesis directly addresses these challenges by focusing on the design and development of sustainable, AI-powered antimicrobial materials. By integrating AI, specifically DL, into the material design process, the project aims to accelerate the discovery of bio-based, biodegradable, and highly effective antimicrobial solutions. The use of AI enables a more efficient and targeted approach to material design, reducing the time and resources typically required for traditional trial-and-error methods. This can have substantial economic benefits by lowering the cost and speeding up the development of new materials for biomedical applications, ultimately leading to more affordable healthcare solutions. Furthermore, the project contributes to the circular economy by emphasizing the use of materials, including those that are biodegradable and eco-friendly materials, which aligns with the global shift toward sustainability. By developing materials that are not only effective against infections but also environmentally safe, the research promotes the transition to a more sustainable and responsible approach in both healthcare and manufacturing industries. In terms of societal impact, the successful development of next-generation antimicrobial materials has the potential to improve public health outcomes by providing safer, more effective treatments for infections. This could reduce the burden on healthcare systems, improve patient outcomes, and increase the availability of affordable medical solutions. Additionally, the interdisciplinary nature of the project encourages collaboration across sectors, fostering innovation and knowledge transfer that can drive further advancements in biomedical engineering, material science, and AI. Ultimately, this thesis aims to contribute to economic growth by fostering the development of innovative antimicrobial materials with broad applications in healthcare, pharmaceutical industries, and beyond. By addressing both societal and economic challenges, this project offers the potential for significant, long-term benefits that align with global priorities for healthcare innovation, sustainability, and economic development.

Partnership context

The proposed PhD thesis project brings together a strong partnership between key research institutions and stakeholders to ensure a multidisciplinary and impactful research environment. The primary partners involved are the Catholic University of Valencia (UCV) and La Rochelle University, which provide complementary expertise and state-of-the-art facilities. UCV, led by a professor with extensive experience in antimicrobial biomaterials, contributes strong capabilities in chemical engineering, material development, and characterization, while La Rochelle University, led by a researcher specializing in artificial intelligence, offers consolidated expertise in deep learning approaches such as GNNs. This collaboration extends to the 4-year European MSCA Staff Exchange project "AQUAPACK" reflecting a history of successful cooperative research and knowledge transfer. Additionally, the PhD student will benefit from a 3-month secondment with ProtoQSAR, a company specializing in molecular modelling and drug design. This secondment will significantly contribute to the development and validation of antimicrobial materials. Both universities and ProtoQSAR are committed to providing high-quality training and mentoring to the PhD candidate. The laboratories are supported through internal and national grants, ensuring financial resources for research activities, technology transfer initiatives, and dissemination efforts. This partnership is further strengthened by connections to socio-economic and innovation-focused stakeholders, enhancing the relevance and application potential of the antimicrobial materials developed.