UNIVERSITATEA DE MEDICINĂ ŞI FARMACIE CAROL DAVILA”
BUCUREŞTI

ŞCOALA DOCTORALĂ
DOMENIUL MEDICINĂ

MULTISCALE MODELS APPLIED IN MEDICINE. PERSPECTIVES TOWARDS *ONEHEALTH*

ABSTRACT OF THE HABILITATION THESIS

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Habilitation thesis entitled "Multiscale models applied in medicine. Perspectives towards OneHealth" is a comprehensive synthesis of my scientific activity, academic achievements and professional development, carried out during my 18-year scientific career, from the moment I started my doctoral studies in the field of physics (2007, Paris, France) to the moment when I hold an academic position at the University of Agronomic Sciences and Veterinary Medicine of Bucharest (USAMV B) and the position of researcher at the National Institute of Economics. Research and Development for Microtechnologies (IMT Bucharest) and associate researcher at the Carol Davila University of Medicine and Pharmacy in Bucharest.

This thesis represents a review of the different methods and the results obtained in order to have a comprehensive vision of disease: starting from the atom, molecule, cells, tissues, organ, individual and populations, moving to a metascalar model of the human being - as an integral part of a population in dynamic relationship with the living environment and the nonsense, i.e. an interdependence of human health, animal health and environmental quality. I have mentioned and illustrated almost all the methods I have used in my research career in the manuscript of this thesis structured in 4 chapters as follows:

Chapter 1, which is the most extensive, summarizes the main achievements of my scientific activity, the results of which are presented incrementally according to the pertinent scale to which the discussed approaches correspond. I started, therefore, with ***the atomic scale*** presenting my computational results regarding the state modeling and the properties of graphene together with its biomedical relevance, namely the interest in irradiation of living environments, respectively the opportunities of building new biosensors based on the cumulation of the multiple conductive properties of graphene systems.

At ***the molecular and tissue level*** , we presented the innovative studies we carried out at **the Molecular Biology Laboratory** and **the Cell Culture Laboratory at USAMV B** (**Faculty of Veterinary Medicine**). These studies in which we applied systematic and rigorous statistical methods of data processing and interpretation allowed the quantification of molecular species and the identification of correlations of indicators of the activation of signaling pathways involving molecular species such as APRIL, BAFF, IL8 and MMP2. Also, by quantifying the allelic frequencies of KRAS, NRAS, BRAF and EGFR mutations, they created the premises of a clinical-pathological model dependent on the intensity of mutations, the presence or absence of mutations (KRAS Q61 – associated with aggressiveness, KRAS G12/13 – ubiquitous mutation potentially associated with tumor initiation).

In order to illustrate the usefulness **of mathematical models at the organ level**, we presented two models: a mathematical model of neurovisual function and a statistical model for uncovering **acute** (early) and **chronic** (late) adverse reactions in patients with oncological diseases, of the gynecological sphere (breast and cervix) treated. The mathematical model of **visual function** starts from empirical data that allow ab ***initio modeling*** of retinal morphology in the context of hyperbolic geometry. Subsequently, **the topological models** of the surface allowed the modeling of the apparently random distribution of the cells that will phototransmit using rigorously constructed mathematical objects (construction theory) and the design of a prototype prosthesis with much improved potential compared to the already existing prosthetic solutions. **The statistical model for the prediction of adverse reactions related to cardiac function** (cardiotoxicity) and **hematogenous function** (hematotoxicity) has predictive value, various **association parameters** (*odds ratio, OR* and risk ratio – *RR),* respectively **a** The statistical significance of innovative models is, of course, preliminary for other studies that aim at the same objective, but on larger cohorts, with the collection of better quality and more diversified data that would allow the creation of more complex and accurate models. Even at the current stage, our results can be applied in a clinical context, **the model** can contribute to an active preventive attitude in patient follow-up.

We have illustrated through **multi-compartment models** how the results of our research can be integrated into the shadow of OneHealth – of a unique health – which allows preventive attitudes, active measures to improve nutrition, by avoiding toxic compounds (such as mycotoxins - aflatoxins) and by functionalizing foods with active, antioxidant, anti-cancer compounds such as anthocyanins.

Thus, **the most illustrative multiscale model** in the context of OneHealth is the use of a machine learning (ML) algorithm validated on the processing of satellite observation images for the processing and segmentation of computed tomography, optical microscopy - histopathology images. The use of the same tool allows obtaining knowledge graphs with concepts that can be causally correlated later. In other words, this paradigm allows the correlation **of elements extracted from** (satellite) images of **the environment** (the patient's home area - pollution, traffic, intensity of circulation, population density, density of green spaces) with **elements of aggressiveness of the disease** extracted from medical images (tumor size, nodules, lymph nodes from tomography or inflammatory infiltrated histopathological phenotype, invasiveness – extracted from microscopic images in hematoxylin-eosin staining).

In this chapter we have also presented the preliminary steps within the research in a multidisciplinary group to find *hibiz biomarkers* starting from **machine learning models applied to** multimodal data (clinical, demographic, hematological, genomic markers, proteomics, etc.) to increase the results of oncological treatment, also multimodal (chemotherapy, immunotherapy, radiotherapy, surgery). In the last two sections of this chapter, I briefly present the results of my research activity – bibliometric indexes, citations, the list of papers and projects in which I have participated throughout my scientific career.

Chapter 2 summarizes my academic career, as well as the guidance activity carried out as a teacher and researcher. My academic training has three axes: biomedical training (doctor's degrees, doctorate in biology), training in exact sciences (physical engineer, master's degree in theoretical physics and doctorate in physics, bachelor's degree in mathematics – a total of 8 years of training) and theological and literary training (bachelor's degree in theology, bachelor's degree in canon law, 2nd cycle studies in terminology and specialized translations). Also, in this chapter I emphasize the didactic activity and efforts made to develop the courses of Mathematics applied to biological sciences and Physics in the specialty of Veterinary Medicine (first year). I mention that I was the holder of these courses in series taught in Romanian, French and English, and the beginning of my activity at the Faculty of Veterinary Medicine meant a reformation of the way of teaching these disciplines and a continuous migration of their laboratories. Also, in all the research groups in which I have worked at USAMV B, at UMFCD and at IMT Bucharest, I have participated in the **guidance** of students, doctoral students and residents with an interest in the field of research.

Chapter 3 chronologically presents the teaching activity at FMV (at USAMV B) and the research activity, starting with the postdoctoral internships. In this section we have presented the scientific personalities with whom we have worked, the projects in which we have worked and the topics addressed.

Chapter IV presents the plan for the evolution and development of the academic career, starting from the development of the teaching activity, the publishing plan of the didactic works, the derivative activities and the essential plans. In this plan are the strategic directions for the development of the scientific career, which revolve around the prevention, screening, early diagnosis and treatment of cancer. Last but not least, post-therapeutic monitoring. Finally, I mention the research topics related to these directions: lung cancer screening and digitalization (within the SOLACE project, taking over the results of the TRANSITION project), early diagnosis and screening using biomarker panels and new biosensors, treatment of solid tumors with carbon beams (in high and ultra-high doses, the FLASH effect), detection and dosimetry schemes dedicated to this new therapeutic strategy.

The scientific career development plan is characterized by **the continuity of the initiated efforts** , by the exploration of skills in the field of engineering and exact sciences for biomedical applications and by the start of new directions of research and innovation.

Combining research and teaching and mentoring activity, I want to contribute with all my energy to improving the academic activity and increasing the scientific level in the institutions where I work.

4.02.2025 Assoc. Prof. Liviu Bîlteanu, MD, Ph.D.