



## Felicidades al nuevo graduado de doctorado del ICFO

El Dr. Pablo Ricardo Fernandez Esteberena se ha graduado con una tesis titulada 'Preclinical and clinical studies in oncology and endocrinology with diffuse light'

September 27, 2023

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Felicitamos el Dr. Pablo Ricardo Fernandez Esteberena que hoy ha defendido su tesis en la sala Elements Room del ICFO.

El Dr. Fernandez Esteberena obtuvo su licenciatura en Ciencias Fisicas por la Universidad Nacional del Centro de la Provincia de Buenos Aires. Se unio como estudiante de doctorado en el grupo de investigacion de Medical Optics en ICFO dirigido por el profesor ICREA Dr. Turgut Durduran. La tesis del Dr. Fernandez Esteberena titulada 'Preclinical and clinical studies in oncology and endocrinology with diffuse light' ha sido supervisada por el profesor ICREA Dr. Turgut Durduran.

### RESUMEN:

In this thesis, our main objective is to utilize different kinds of quantum dynamics as resources. To do so, we investigate thermodynamics, non-equilibrium steady states, and dynamical spectroscopy in order to categorize the dynamics of quantum systems as having either no external drive (self-drive), a weak external drive, or a strong external drive respectively. In the first part, we explore the dynamics of quantum heat engines. In that, we consider dynamics that are driven by time-independent Hamiltonian, i.e., without external driving. We show that when a working system non-locally interacts with two baths at different temperatures, the engine can operate in a one-step cycle, yielding Carnot efficiency at maximum power. This advantage is exclusively because non-local operations are more powerful than local ones. To study such engines in a more systematic manner, we develop resource theory of heat engines. This provides a framework to study quantum engine operating with a working system composed of a finite number of quantum particles and restricted to few observations, i.e., in the one-shot finite-size regime. We also propose an experimentally feasible model of an engine using an atom-cavity system that yields Carnot efficiency at maximum power. In the second part, we consider open quantum dynamics where a system weakly interacts with environments. In particular, we study the Lindblad master equation-based dynamics of quantum systems weakly coupled to two thermal baths at different temperatures. In general, these dynamics lead to non-equilibrium steady states. By selectively coupling a quantum system to two different thermal baths, a synthetic thermal bath can be engineered, and the temperature of such a synthetic bath can be made negative. With this, we explore steady-state quantum thermodynamics with negative temperature. We show that the zeroth and the Clausius state of the second law remain unaltered in the case of baths with negative temperatures. However, the Kelvin-Planck statement of the second law updates in this case to incorporate the following. (i) There is spontaneous heat flow from a bath with a negative temperature to a bath with a positive temperature. In this sense, the baths with a negative temperature are 'hotter' than the ones with a positive temperature. (ii) There is spontaneous heat flow from a bath with a less negative temperature to a bath with a more negative temperature. We also introduce a continuous heat engine operating between a positive and negative temperature bath. Our analysis shows that the heat-to-work conversion efficiency for such an engine is always unity. We study the thermodynamic implications of our results. The third part of the thesis explores systems driven by strong external fields. In such circumstances, we encounter transient quantum dynamics, which cannot be described by thermodynamics. This kind of dynamics is utilized for dynamical spectroscopy. Particularly, we have studied high harmonic generation where a strong laser field interacts with matter. By utilizing the high harmonic generation mechanism, we characterize the topological features of solids. Near-infrared diffuse optical spectroscopy (DOS) techniques are capable of non-invasive measurement of microvascular hemodynamic parameters of deep tissues (>1 cm penetration). One important focus of the field has been applications in oncology, where the characterization of the tumor vasculature

re could play both a diagnostic and therapeutic role. This is mainly because malignant tissue growth requires the co-option and generation of blood vessels to be supported. Microvessel density, microvascular blood flow and hypoxia have been linked to the progression of the disease, the likelihood of metastasis and patient survival, and can thus guide diagnosis, treatment plans and prognosis.

In this thesis, I have applied DOS methodologies in two projects exploiting hemodynamic information for cancer management. The first one consists in the demonstration of a toolbox for the optimization of plasmonic photothermal therapy (PPTT) in mice, while the second focuses on the contribution to the clinical diagnosis of thyroid cancer in nodule patients. PPTT uses plasmonic nanoparticles (NPs) that are injected into the body and act as localized sources of heat upon external illumination to induce tumor cell death. Various aspects of the therapy are modulated by the optical and hemodynamic parameters of tumor tissue and can thus be studied with DOS monitoring. Moreover, it enables simultaneous quantification of NP concentration. Such information can improve the understanding and the outcome of the treatment and accelerate its slow progress to the clinics.

To prove this, we conducted experiments using DOS monitoring along PPTT to model the therapy steps and explain the variability among individuals. This was done on patient-derived orthotopic renal cell carcinoma models, injected with gold nanorods and treated with fixed conditions. The hybrid device combined continuous-wave broadband diffuse reflectance (DRS) and diffuse correlation (DCS) spectroscopies. The data was related to the NP accumulation, the temperatures reached during treatment, tumor growth and animal survival. Moreover, we analyzed the underlying mechanisms with simulations and demonstrated the extrapolation of therapy conditions for individual mice. With this, we managed to determine the relevant interactions and prognostic factors to guide the personalization of the therapy in a way that could be readily applied to other PPTT protocols. The second study was part of the LUCA project, which aimed at implementing an ultrasound-guided hybrid DOS device that could be integrated into the clinical workflow of thyroid cancer screening and provide relevant hemodynamic information to improve diagnostic capabilities. The incidence of thyroid cancer has been on the rise for decades and the low specificity of standard screening methods implies tens of thousands of unnecessary thyroid extraction surgeries are carried out each year just in Europe. Therefore, any improvement in the discrimination between benign and malignant nodules can have a relevant impact on the large scale.

A clinical campaign was carried out with the LUCA device, a state-of-the-art device combining time-resolved spectroscopy (TRS) and DCS around a regular ultrasound transducer. The properties of thyroid, nodules and neck muscles were measured in nodule patients and healthy volunteers. Data from sixty-six subjects allowed to characterize these tissues, study the effect of demographic and anatomical variables and assess their diagnostic capabilities. In this way, we gathered a large reference data set relevant to various medical

applications beyond oncology and identified the most promising indicators of malignancy. With these studies I have shown how the information obtained with DOS has important roles in these particular applications and what are some of the mechanisms behind them. These results can guide the future steps of research endeavors and have implications for the advancement of solutions to these clinical problems.

**Comite de Tesis:**

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