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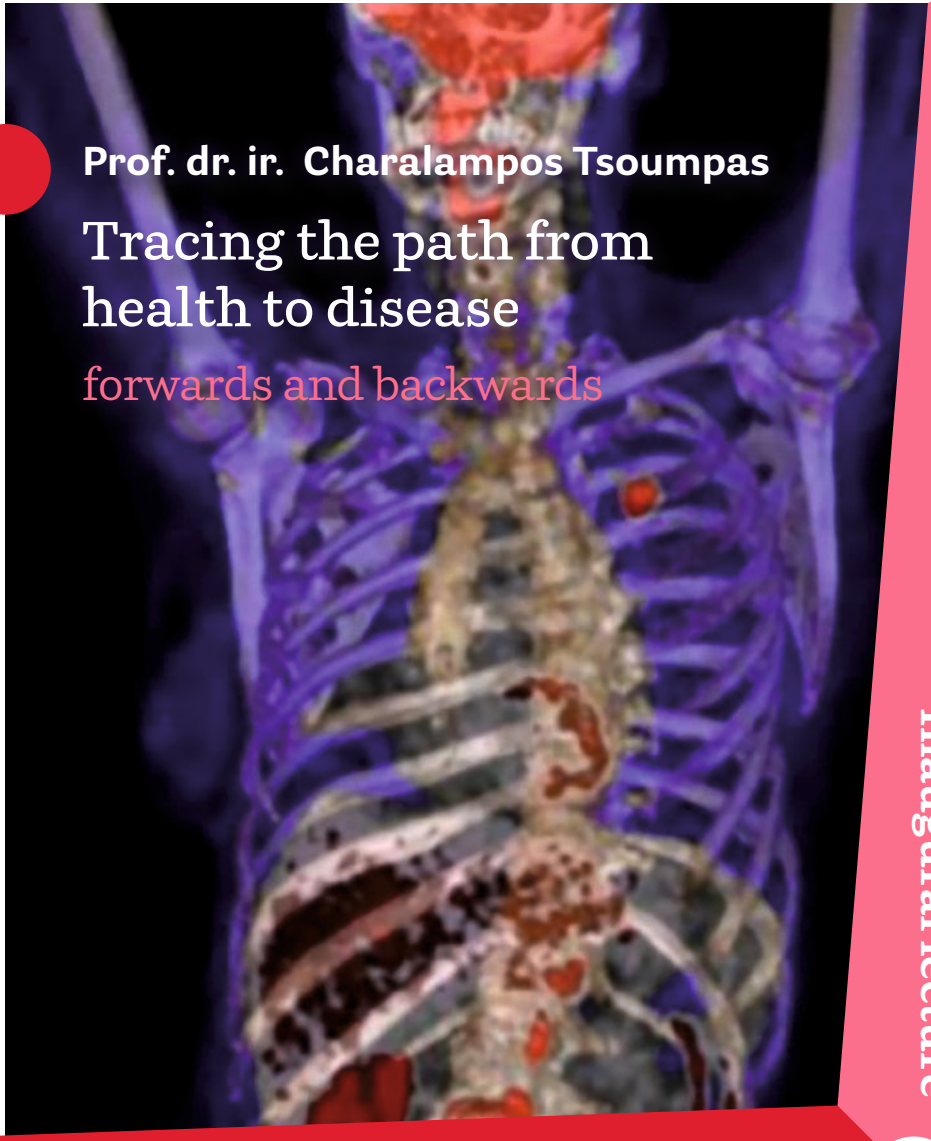

Prof. dr. ir. Charalampos Tsoumpas

Tracing the path from health to disease

forwards and backwards

Inaugural lecture

16 December 2022

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Inaugural lecture by

Prof. dr. ir. Charalampos Tsoumpas

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Dear Members of the Board of
the University, dear colleagues,
friends, and family,

Prof. dr. ir. Charalampos Tsoumpas during his inaugural lecture on 16th December 2022.

All of us here today are made by molecules. And according to our genetic information we develop, survive, and inevitably die. This makes life a dynamic process during which our molecules experience a constant battle with nature. For whatever reason and at some point, the mechanism of this dynamic process will fail leading to a malfunction which origin can be traced all the way to a molecular level. Our immune system is the first defensive mechanism to make things right. But what do we do when this is not sufficient? We have evolved in such a way to care for each other, which has led to the development of healthcare. And with weapons our intelligence and knowledge we are fighting to reverse the disease mechanisms and identify optimal ways to alleviate pain and extend our survival in this molecular drama.

So, how can we reverse a disease state back to a healthy state? There are two interconnected answers: first we need to detect, or even predict disease at the earliest possible stage and then we need to identify a cure or how to delay the disease progression with relatively small side effects. Of course, there are plentiful profound scientific achievements that have led us where we are today.

In my lecture, I will concentrate on one technique which is an invaluable tool in early molecular diagnosis and therapy

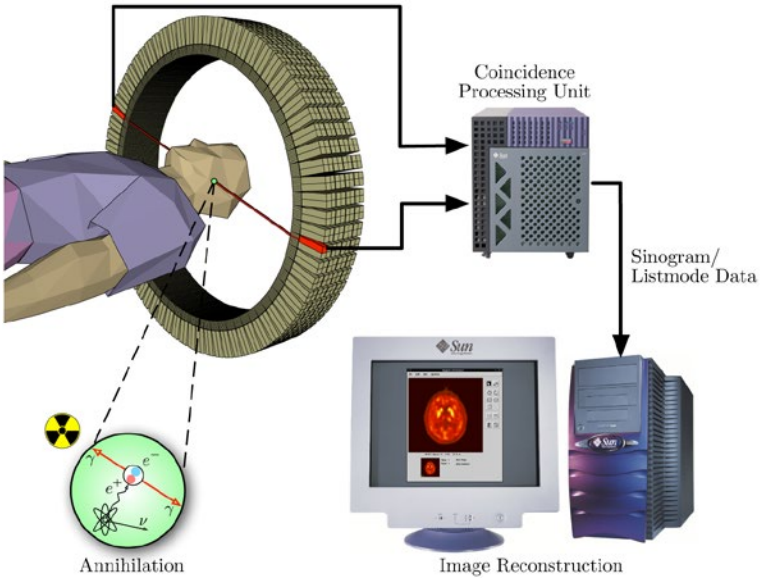
evaluation. This technique is Positron Emission Tomography, or PET scan.

But how does PET work? Since more than a century we can detect radiation consisting of high energy photons that can penetrate the human body. Furthermore, we have found ways to manipulate biologically relevant molecules which we can administer into humans and measure how their bodies respond to them. This is possible by using unstable atoms which decay with the emission of a positron. Positrons are antimatter electrons which do not exist in our universe naturally, but we can create them in the laboratory with appropriate nuclear reactions. I always find it astonishing that we can make use of exotic antimatter particles in medicine – it is exactly this that inspired me to commit myself on this scientific journey. But how do positrons make it possible to see the molecules of life? The unstable radioactive atoms are attached to specific molecules which are then called radiotracers, or simply, tracers. At some point the radioactive atoms will decay by emission of a positron which almost instantaneously will interact with an electron and disappear completely where their joint energy is converted into two photons. By measuring several of these photon pairs with a PET scanner we can identify what happens to these molecules in the human body with reasonably good accuracy, precision, and resolution.

Let me give you an example how this technique helps patients. If we give to a cancer patient a radioactive form of glucose, we are likely to see a lot of photons coming from cancer cells, thus detecting them. If the patient undergoes therapy and less photons are measured from these cells by the scanner, it will mean that it is likely that the therapy is working at a molecular level. And this is incredibly important for the patient because it allows us to adapt the treatment plan very swiftly. This powerful feedback that PET provides is now used in clinical practice daily to help save human lives or at least extend their quality life by a significant margin.

But PET can be used to detect many more illnesses, such as atherosclerosis, infection, or inflammation where millions of people are suffering daily. PET can help in detecting them early, even in patients without relevant symptoms, at which stage their treatment could be more effective and therefore help the development of drugs that can stop or even reverse the disease progression. And it can also assist in one of the emerging health challenges of the 21st century, which is related to the development of appropriate drugs for patients who suffer from multiple conditions or diseases...

But PET imaging is currently underutilised and can provide even more valuable information. After this introduction, I will share my vision for my future research plans. PET is not



The image illustrates the processing principles of a positron emission tomograph (PET) commonly used in cancer diagnostics.

merely a molecular imaging device, but I see it as a measurement device. What does it measure? Molecules and their concentration inside a living subject. And as by definition life is not a static process, PET can quantify how molecules travel inside our bodies. Therefore, it provides a direct way to measure the kinetics of biochemical reactions which have not been possible to quantify otherwise. My immediate goal is to enable dynamic imaging and kinetic analysis in clinical practice for a range of standard tracers like radioactive glucose, as well as very fast ones such as

radioactive water, or very slow ones such as monoclonal antibodies labelled with radioactive Zirconium.

Specific issues need to be resolved in the coming years to achieve more accurate and precise quantitative information in patients. For example, patient motion during the scan can mean what we measure sometimes is incorrect – especially important if we wish to perform kinetic analysis. Similarly, imaging smaller regions in the body will require the further improvement of the current scanners and their reconstruction algorithms. Furthermore, there are many positron-emitting atoms that are not in clinical use because they emit additional photons such as Iodine-124 and therefore produce relatively poor image quality. I hope with my research in quantitative image reconstruction to bring them back to the game because many of them can have a central role in the thriving area of radionuclide therapy.

But what else do we miss in quantitative medical imaging? As a Physicist, I find it incomplete to provide a measurement without a corresponding error estimate. Uncertainty quantification, a well-established field in Applied Mathematics, is so much missing from PET imaging and clinical decision making. Therefore, one of my areas of warm interest is how to provide meaningful error estimates to clinicians, and if this is not so practical, at least how to provide such information to

intelligent computational software which could make practical use of it for a better overall clinical decision making.

A relevant research area which requires attention is the development of experimental tools for validating the accuracy and precision of PET quantification. Commonly, we make use of relatively simple objects filled in with tracers which we call phantoms. The impressive developments of the last two decades in microfluidics, in 3D printing and even bioprinting technologies could be utilised in the context of PET validation, where there is a lot of space to develop much more realistic phantoms which would not only mimic human anatomy but also human physiology – and then we could call them radioactive superphantoms.

Let me now touch a sensitive issue related to PET imaging. How many of you today would you be happy to receive a PET scan? Probably, many of you would feel scared because of the use of radioactive substances. Indeed, if there was not such a barrier, PET could be used more often to scan patients, or also healthy volunteers either for screening, or for fundamental biological questions and as part of the development of new and more effective drugs with less side effects. But how many of you would not be surprised if I tell you that some of the new PET scanners permit such a low dose scan equivalent to what one receives during an intercontinental flight? In my research, I

wish to investigate how to lower the dose for a range of tracers, such that the technique is practically considered non-radioactive. I envision that we will soon be able to scan even young healthy volunteers or pregnant women much more easily. Furthermore, under my academic role, I aim to educate medical doctors, scientists, and the public not to fear the tiny amounts of radiation that we use, known also as radiophobia.

Once we reduce the radioactive dose from one tracer, it will become much easier to scan many tracers in each patient. The next exciting topic for my research will be to develop methods that will allow imaging two or more tracers simultaneously with similar accuracy and precision as if they were scanned separately. This is what I call PET 2.0. Why this can be very useful? Imagine for example that we have one tracer like radioactive glucose which identifies cancerous cells and another tracer directly related to a very expensive treatment of cancer which however works only to a percentage of patients. Simultaneous imaging will allow to evaluate pixel by pixel the potential performance of such drug and swiftly decide how to proceed with the treatment. In addition, the use of multiple tracers can be very helpful in understanding the potential crosstalk of different conditions such as cancer and cardiovascular diseases.

And here I will touch upon a strength that recent developments of total body PET imaging have brought. Medicine has traditionally specialised in different organs, e.g., the brain, or the heart and still we have a lot to learn about various disorders. But do you know that all of us here today are "atoms"? Atom in Greek means person because a person is not divisible. Does not it make more sense to study the human as one indivisible system – as one atom? I am now involved in exciting projects with my colleagues on quantification of crosstalk of different organs, for example, the gut and the brain or the heart and the brain axes. Studying the human connectome may help towards the better understanding of disorders, such as Parkinson's, depression, and many others.

The principle of PET imaging can have additional important roles in healthcare. It can be used to guide not only molecular-based therapies but also direct interventions. One such example is radiation delivered therapy that is used to directly target and destroy molecules. PET could be used for optimisation of proton therapy in real time to help eliminate cancerous cells more accurately. Or in future, PET tracers could be used to guide real-time robotic surgery, something we currently do mainly with optical imaging. However, the PET scanners for such interventions need to be redesigned, which leads to complicated image reconstruction problems. The scanners in these examples will have big gaps and the current

algorithms simply don't work. Furthermore, even if we find a solution to this problem, the images need to be reconstructed within a few seconds to allow accurate real-time feedback and makes it even a harder and exciting problem, which I wish to solve.

So far, I placed my passion, PET imaging, at the forefront of this lecture, however, it would be a remiss not to mention that there are a lot to gain by working in synergy with other imaging techniques as well as the genetic data or even habitual data, such as dietary, exercise, sleep, and lifestyle. The integration of big data in combination with the use of intelligent software will surely maximise the healthcare outcomes and could bring a quantum leap in digital medicine. This is an area I wish to explore in the future.

As much as I believe that PET provides great opportunities, we should fully acknowledge some key limitations if we wish to take it to the next stage.

The crucial limiting factors relate to the costs and logistical issues that take to setup and maintain a properly functioning nuclear medicine department with the necessary facilities. Establishing good manufacturing practices in nuclear medicine and ensuring radiation protection requires a lot of resources. The high overall costs and the very tight regulations

endanger making PET imaging and the advantages it brings in terms of early diagnosis and therapy optimisation, a technique only for countries or citizens who could afford it. One of our global challenges is the reduction of costs for entertaining the exciting benefits by all humans. Development of more efficient and cheaper PET scanners, as well as radiochemistry and radiopharmacy facilities are areas where academia and industry can play a dramatic role. We, as scientists, need to put particular emphasis on how PET can become less expensive without degrading its performance. For this reason, I am creating an international and interdisciplinary network of scientists to work on this challenge.

Perhaps however, the most expensive aspect of PET is associated with the development and clinical translation of the next generation of tracers for specific diseases. Even after several years of thorough validation of a tracer first in animals and then in humans, the rate of new molecules brought into the clinic is disappointingly low and how can we ameliorate this is still a big question and challenge. I envisage in the coming years to work more closely with chemists and other scientists to identify new ways of redefining radiochemistry of the 21st century. For example, we have lately seen the design of alien proteins by Artificial Intelligence. Can we make use of such ideas to develop the radiotracers of the future?

Today, I shared my research vision in quantitative molecular diagnostics and therapy assessment. This vision will be collectively shaped by my academic department, the faculty, and the university. Inevitably, any research priorities will follow the Netherlands and the European Union agendas in our ultra-fast changing world. But whatever the journey of extending the scientific boundaries of molecular imaging will be, it will not be a lonely one. As in the past, it will be a joint endeavour with my colleagues and collaborators, both in academia and industry without whom so many innovations would not have taken place – and to whom all I am truly grateful. And of course, I am deeply thankful to my colleagues in the Nuclear Medicine department for their trust and for giving me the opportunity to join them on this fascinating journey. My future achievements will be shared by all of them.

Ladies and Gentlemen, I am convinced that PET imaging remains the most sensitive method to measure molecules inside our bodies and trace their pathways from health to disease – forwards and backwards. Thus, it has a lot more to offer for detecting and understanding disease processes and optimising precision medicine.

Αγαπημένοι μου, σας ευχαριστώ για όλα!

Ik heb gezegd.

Charalampos Tsoumpas is a Nuclear Physicist (University of Athens) and a Biomedical Engineer (Technical University of Athens & University of Patras) who joined the Faculty of Medical Sciences at the University of Groningen as a Full Professor in Quantification in Molecular Diagnostics & Radionuclide Therapy. His chair is with the Nuclear Medicine and Molecular Imaging Department at the University Medical Centre Groningen. Prof. Tsoumpas received his PhD on "Direct statistical parametric image estimation for linear pharmacokinetic models from quantitative positron emission tomography measurements" from Imperial College London in 2008 and worked as a post-doctoral fellow at King's College London from 2008 to 2013. From 2013 to 2021 he was a Lecturer at the University of Leeds. Prof. Tsoumpas is Fellow of the Institute of Physics (IOP), Fellow of the Institute of Physics and Engineering in Medicine (IPEM), Fellow of Higher Education Academy and Senior Member of IEEE.