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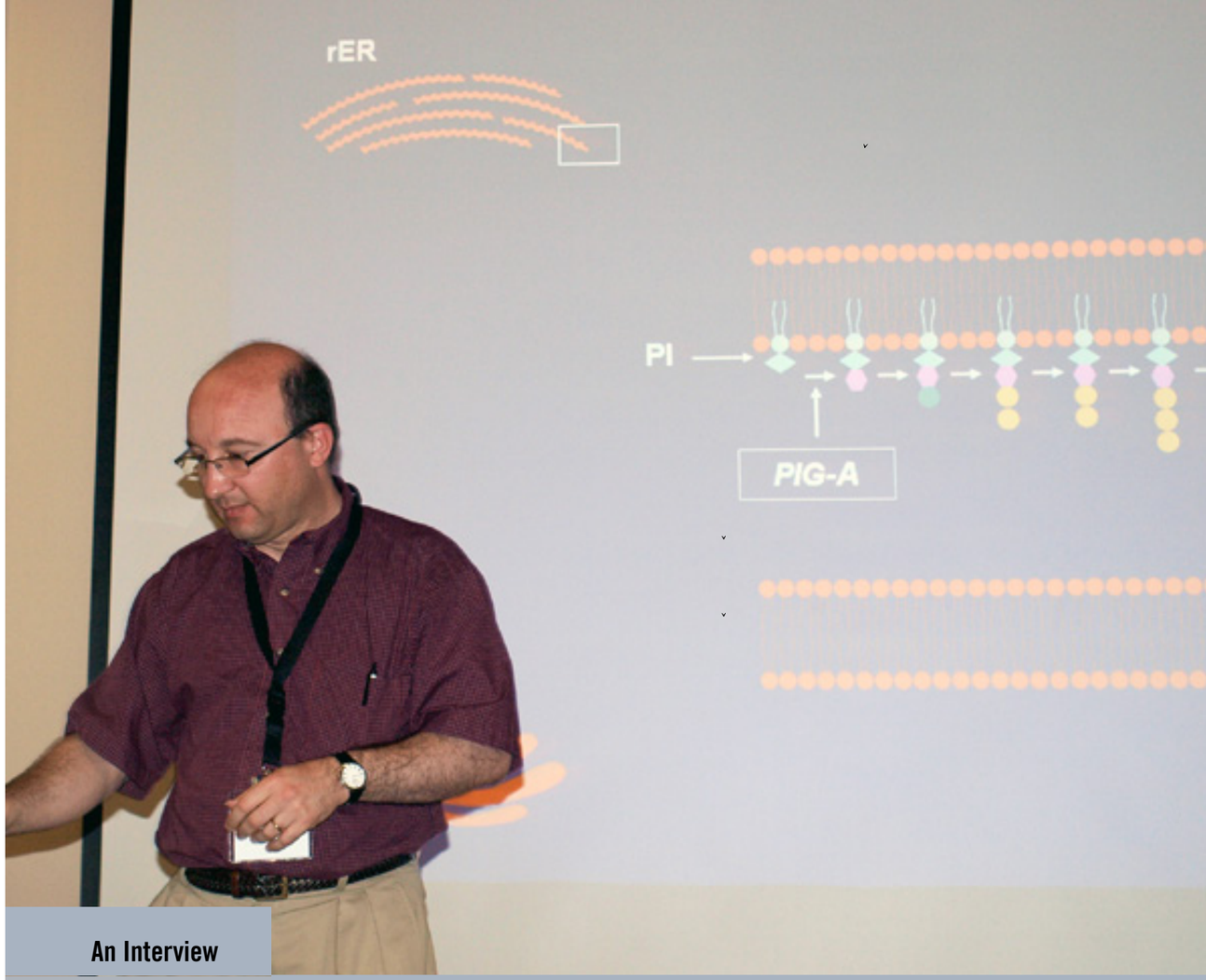

An Interview

with David Dingli

by **Francisco Santos** and **Fabio Chalub** [Universidade Nova de Lisboa]

David Dingli was in Evora for the Summer School "Dynamic Models in Life Sciences", where he presented a set of lectures called "Hematopoietic Stem Cells and Hematopoiesis". In these lectures, he introduced the audience to the state-of-the-art in the dynamics of stem cells, and their relation to blood disorders. After the conference he gave this interview to Francisco Santos and Fabio Chalub, summer school co-organizers.

Please summarize your academic/professional trajectory (just a short bio).

I am a hematologist and treat patients with various types of blood malignancies. My research initially focused on the generation of trackable, replication competent viruses to treat cancer. It became clear very early on that the interactions between oncolytic viruses, the tumor cell population and the immune system are quite complex with various outcomes. Understanding these dynamics required mathematics and as a result, while in graduate school, I enrolled in various classes to learn more mathematics. I got hooked and decided to spend more time in mathematical biology after finishing my training in hematology. I was fortunate enough to spend 2 years at the Program for Evolutionary Dynamics [PED] at Harvard University working with Professor Martin Nowak and his group. There, I established strong collaborations that continue to this day. As a result, now I devote a considerable amount of my time on mathematical modeling of various hematologic disorders. However, my laboratory still continues to work on the use of viruses to treat cancer and a considerable part of my modeling is still centered on tumor virotherapy.

How do you assess the importance of mathematics to your research?

It is not possible to understand dynamic systems without mathematics. Whenever we are dealing with a process that changes in time, we have to use mathematics for a meaningful understanding of the process. For example, with tumor virotherapy we need to know how the virus spreads in the tumor, the kinetics of the process, the rate of virus generation, cell killing etc and then try to design viruses with "optimal properties" for cancer therapy. Mathematical models are a great asset also by providing an in silico testing ground for innumerable therapeutic scenarios that can be explored rapidly and cheaply. The in vivo experiments that are time consuming and expensive can be used to test the most interesting scenarios predicted by such modeling.

How do you assess the importance of mathematics to medical practice?

The physician of the future must have a good basis in mathematics. Advances in technology mean that nowadays, acquisition of data is not the limiting factor. One can see what has happened with the 'omics' revolution. However, we're still far away from being able to understand the data being generated. Such an understanding will require new theory that can only come from mathematics, just as physics moved forward when calculus was discovered (or invented). Similarly, one can obtain multiparameter data in real time on patients in the intensive care unit. One can imagine scenarios where modeling of such data will enable understanding of the trajectory of the illness and plan therapeutic interventions of the right magnitude and at the right time to move the patient away from the ultimate stable equilibrium (death) and back to a state of health.

In your research, you work with physicists, mathematicians, etc. Was it easy to start this collaboration? Did you have to start by building a "common language"?

One of the most enriching aspects of my research has been this interaction with physicists, mathematicians and computer scientists. I was fortunate that the PED is a melting pot for scientists from different disciplines to meet and discuss science. We all come from different backgrounds and training of a physicist is quite different from that of a physician. However, it was not difficult to find common ground and start collaborating. Such interactions are mutually rewarding in the sense that if I had to explain the detailed molecular biology of a process to my colleagues, I had to understand it well myself and then strip it down to the bare bones. This is an essential exercise that helped me identify gaps in my knowledge of the subject but also enabled me to ask relevant questions for the field that ultimately translated into many joint publications. This exercise serves to establish the "common language" that you mention. However, the main issue is one of "synchronization of thinking"—a physicist looks at a problem differently from a physician. For them, cells and balls are very similar, and tumor growth is similar to nucleation of a crystal etc.

You have long-term scientific collaborations with researchers in Portugal. How did it start?

I met Professor Jorge M. Pacheco at the PED in the summer of 2005. We started almost simultaneously there and not only did we come from different backgrounds, but we also went to PED for different purposes—Jorge was working on evolutionary game theory while I wanted to study tumor virotherapy. One afternoon, we went for a walk along the Charles River and started talking about blood disorders, stem cell and bone marrow transplantation. A few incisive questions from Jorge on that fateful day established that collaboration that has been going ever since and resulted in various trips to Portugal and Jorge also visited me at Mayo Clinic. Since those initial days, the collaboration has expanded to include Dr Francisco Santos and Professor Fabio Chalub where we have applied principles from EGT to cancer.

You said once that the reward from the clinical practice is essentially immediate, while the one from research takes a long time. How do you compare the pleasure of these two facets of your work?

I enjoy meeting patients, trying to understand their illness, how it affects them and then personalize therapy for them. Often it is possible to help patients quickly with pain control, improved quality of life and then long term therapy, usually for their hematopoietic tumor. I come to know not only the patient but their family, their hobbies, interests, travel etc. In this way, each patient is unique and there is no redundancy. The frustrating part is when I reach the limit of therapy that is available…one always wants safer, more effective therapies and ultimately the cure. Research provides a different form of gratification—the intellectual musings, hypothesis generation, the critical experiments, writing code (and debugging), running simulations, etc. all take time. What I enjoy the most is the creativity, the imagination, and in some way, even the "shortcuts" that we sometimes take in our modeling efforts, all with the aim of getting some results, the first glimpse of the output.

Do you believe Summer Schools like the one in Évora are a good starting point for students wishing to work in math-biology?

Years ago, I attended a two week summer school on "mathematics and computers in medicine" organized by the late Professor Lee Segel at the Santa Fe Institute. During those two weeks I learned not only mathematics but more importantly how to apply mathematics to various medical problems—from virology to cancer, the immune response etc. The summer school in Evora was fantastic—the depth and breadth of topics explored was immense and the students had an opportunity to see how the immense power of mathematics can be used to address problems in ecology, cancer, evolution, imaging, population dynamics etc. Once students understand how to apply their skills to biological problems, they are only limited by their imagination. Such schools are essential for training of tomorrow's scientists.

Finally, do you have any practical advice for students willing to start an interdisciplinary work?

The best way to learn about interdisciplinary research is to find a biological problem of interest and read about it as much as you can. One cannot model what one does not understand—once the student is well aware of what is known about the problem, then it often becomes clear what questions can be posed in a mathematical framework for the problem at hand. Finding a mentor with a track record of research and publications in the field and who has a string of prior graduate students that have been with her/him, will increase the probability of success in the field.

Well, David, thanks a lot for this interview.
We are looking forward to seeing you again in Portugal soon!