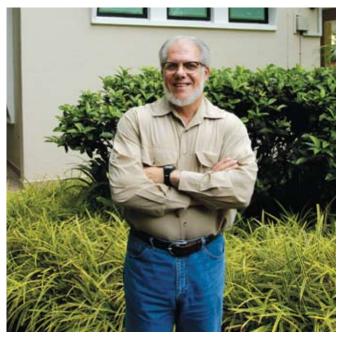## Mathematical Conversations

Eduardo Massad: Infectious Diseases, Vaccines, Models

Eduardo Massad

Interview of Eduardo Massad by Y.K. Leong

Eduardo Massad is internationally acclaimed for his work in the field of infectious disease epidemiology, both in the mathematical modeling of infectious diseases and in the introduction of successful disease control programs in Brazil.

Originally trained in medicine, Massad went on to obtain a degree in physics and a PhD in experimental pathology. Together with his collaborators, he did important work in the mathematical modeling of infectious diseases such as dengue, yellow fever, hepatitis A, vaccine preventable diseases, parasitology, HIV and antimicrobial resistance.

His extensive research work is contained in almost 200 joint papers and 4 books. During his distinguished research career, he has supervised 21 doctoral students. His scientific contributions extend beyond the theoretical aspects of modeling in infectious diseases and epidemiology to the successful implementation of disease control programs in Brazil. Fluent in six European languages, he also has research interests in evolutionary biology and telemedicine.

Massad is Professor of Medical Informatics at the University of São Paulo in Brazil and has been an Honorary Professor of Infectious and Tropical Diseases at the London School of Hygiene and Tropical Medicine since 2003. He is a Chartered Mathematician and Fellow of the Institute of Mathematics and Applications and a Chartered Scientist, Science Council, United Kingdom.

In 2003, the Courage Fund was set up in Singapore to meet the deadly challenge posed by the Severe Acute Respiratory Syndrome (SARS), and a grant of S$3 million was presented to NUS to set up the Visiting Professorship/Fellowship in Infectious Disease and Epidemiolgy. In 2005, Massad was invited to Singapore as the inaugural Visiting Professor to initiate the building up of expertise in epidemiology management and control. In 2007, he was Chair of the Institute's *Workshop on Mathematical Models for the Study of the Infection Dynamics of Emergent and Re-emergent Diseases in Human* held from 22 – 26 October 2007. During his visit to IMS, he was interviewed by Y.K. Leong on behalf of *Imprints* on 29 October 2007. The following is an edited transcript of the interview in which he gave us a rare insight into the collective efforts of medical and academic specialists in the ongoing prevention and control of infectious diseases around the world. We also get a glimpse of how mathematics, statistics and computer science have put in their share of efforts in the continuous struggle to maintain the healthcare of humanity.

Imprints: You originally started with a diploma in medicine and then went on to concurrently obtain a bachelor's degree in physics and a medical degree. Why did you choose a degree in physics, why not chemistry, say, or even mathematics?

Eduardo Massad: Well, it's actually not that easy to describe. I did not choose chemistry because chemistry was not exactly what I wanted to do. I was in doubt between physics and mathematics. I chose physics because that course at my university at São Paolo was more applied than the mathematical one. I intended to be an applied scientist. I then chose the physics course degree because there was a balance of applications in that course.

I: Was your education taken mainly in South America?

M: Yes. I was trained in São Paolo and then I did my graduate study in England.

I: When you say graduate study, are you referring to …?

M: I mean, as a postdoctoral graduate in England.

I: Which part of England?

M: I stayed for one year in Sussex University, and then for two years at Imperial College.

I: Was the training in physics directly useful in your subsequent research work in the medical sciences?

M: Actually it was not really useful; it was determinant because everything I do is professional nowadays. Thanks to my training in physics, it was very central indeed.

I: So it's the training rather than the actual knowledge?

M: Yes, the form of training.

I: One of your research areas listed is "medical informatics". How different is it from bioinformatics?

M: Well, it's quite different because actually bioinformatics is part of medical informatics in a sense. Bioinformatics deals strictly with information from genomic science and the huge amount of data that is coming from the human genome project while medical informatics deals with information in medicine as a whole, with medical records, artificial intelligence as applied to medicine and so on.

I: It's a much wider science.

M: Much wider than bioinformatics.

I: Is this a very new kind of discipline?

M: Bioinformatics is new but medical bioinformatics has a history of 35 years.

I: Did it come about as a result of the computer revolution?

M: It's a compromise between computer science and medical doctors in the sense that there is a growing interest in applications of computer science to solve medical information problems.

I: In the early years, they were talking about expert systems.

M: Yes, expert systems is one of the specialties of medical informatics. There are a number of very interesting systems that are able to do medical diagnosis nowadays.

I: How recent is the field of mathematical modeling in the medical sciences?

M: In the sexual disease field, it's quite old in the sense that it was the first field to which mathematical thinking was applied in order to understand events in sexual diseases... Sir Ronald Ross in 1911, 1918 – he was the man who discovered that malaria was disseminated by mosquitoes. Then in the 20s, a couple of researchers started to apply more formally mathematics into the study of sexual diseases, and in the 70s, the field exploded. So it's about 40 years and it has consolidated since then.

I: Is it true that not many doctors are well equipped to do modeling?

M: No, not that many doctors. You see, it's very rare to have a doctor apply mathematics directly.

I: You are involved in training doctors to do the modeling?

M: Yes, yes. I have many doctor students.

I: Are there any general laws or principles that can be formulated in medical modeling like those in physics or chemistry?

M: Oh yes, certainly there are. There are some central principles that you can call general laws, like the law of mass action that is interaction between susceptible and infected people, the basic reproductive number.

I: Do epidemiological models depend on the size of the domain affected? In other words, are there such things as local models versus global models?

M: Very much so, yes. You have global models that are applied to explain diseases anywhere in the world. You have global models for certain kind of infection like vector-borne disease, and you have local models that are applied to specific communities, whereas the global models can be applied to any community whatsoever. You can distinguish between local and global models. There are certain models that are applicable only to certain communities.

I: How successful is computer simulation in predicting or preventing disease outbreaks?

M: I think it is very successful indeed. The problem is to convince the decision makers to believe in such a model. So the main problem in the actual application of such predictions is convincing the decision makers that the model is correct and reliable. The main problem is communication rather than the technology.

I: How do you convince the policy makers?

M: Normally, the logic behind some models can be explained to them, but if you make them too complicated, they tend not to believe you.

I: I think most of them would believe you if you can show them the results.

M: Yes.

I: I believe you have actually applied some of these models to solve problems in São Paolo.

M: Yes, we applied the models to real problems there.

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I: You have no problems in convincing the authorities there?

M: Well, some 15 years ago, we had one Secretary of State in São Paolo who really understood what our model was about and he was the one who supported the application of models as a whole in the state of São Paolo. We were lucky to find this man behind the job.

I: Have you applied your methods to formulate ecological models?

M: Yes, indeed. We applied some of our methods to simulate ecological models for vector-borne infections. The ecology of mosquitoes in the disease can be formulated according to the mathematical approach.

I: In your models, you have some kind of parameters where you have to measure something. How do you decide what these parameters are?

M: The parameters are determined by the model you structure. In a sense, the theoretical model anticipates the field work.

I: Before you formulate the model, do you collect the data first?

M: Yes. You know the problem and you know the natural history of the disease. Then you formulate a model that mimics this natural history. Then you go after the parameters in the field in order to check the model's position.

I: Does that mean you have to refine the model again and again?

M: You refine the model according to the data.

I: How do you know when you have reached the ideal model?

M: Normally if you know the natural history of the disease well, you don't have too many competitive models to choose from. You normally have only one model that mimics the natural history. The structure of the disease must be behind the structure of the model.

I: Are your models stochastic or deterministic models?

M: They can be either stochastic or deterministic. It depends essentially on the size of the population involved. For smaller populations, you have to apply stochastic models. For larger populations, you cannot apply a simply deterministic approach.

I: How do you pick up the necessary mathematical tools?

M: I was trained as a physicist. The essentials I know, but I work together with more accomplished mathematicians who help me on the project.

I: Are your models intuitively motivated?

M: Oh yes, intuition is very important indeed and is an essential part of the job.

I: Does that come from experience?

M: It can come from experience.

I: You have been highly successful in using modeling to control disease outbreaks in São Paolo. What was the greatest breakthrough behind those successes?

M: I think the greatest breakthrough is that we manage to succeed with the model which determines the introduction of the rubella vaccine in the state of São Paolo in 1992. At that time the health authorities have some doubts whether they should introduce the vaccine or not because, you know, rubella is a problem that affects pregnant women. And the vaccine causes a shift in the average age of infection. Before the introduction of the vaccine, the average age of infection for rubella is about 6 years of age. But when we start to vaccinate, this age shifts about. The fear at that time was that they did not manage to vaccinate the maximum portion of children in order to avoid the reproductive window which is between 15 and 40 years of age. We manage to calculate that and design a model which guided the introduction of vaccine in the form of a mass vaccination campaign. After the mass vaccination campaign, we introduced the vaccine in the local calendar of vaccination.

I: Was the result immediate?

M: Well, the immediate result was that the number of congenital rubella syndrome, which is something that affects the babies, dropped close to zero one or two years after the introduction of vaccination.

I: That is rather dramatic.

M: Yes, very dramatic indeed.

I: You collaborate with a lot of people. It's typical in biology, isn't it?

M: Yes, in biology it's common. Biology is team work. In the medical profession, even if you are working with some basic side of a medical problem, you have to work with a team of people in the background. We have doctors

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trained in infectious diseases, epidemiologists; we have mathematicians, statisticians, psychologists, meteorologists – a lot of different people working together.

I: Are diseases dependent on the actions of human beings?

M: Oh yes. Almost any infectious disease is behavioral dependent. It depends on how people behave in order to get the disease. It's important to know that.

I: How do you control the behavior of people?

M: You can't control the behavior of people. You just can only educate people.

I: What about intangible things like mindset and cultural attitudes?

M: That's the basic barrier in the HIV epidemic. It's a clear example of that – you know, to make educational contact in order to inform people what are the risks and the behavior that they should follow or what they should avoid and so on.

I: You have many research students. What is the secret of your ability to attract so many students into your research area?

M: Well, first it's because they were available. You know, full-time research in the medical school is a rarity. The sheer availability attracted some students. Second aspect is the novelty of this kind of method that I tried to apply some 25 years ago. So this attracted some students mainly because of their curiosity and the novelty of the approach. But, more recently, I'm not attracting so many students any more, mainly because I have to compete with microbiology and other novelties at this time.

I: These are the newer areas.

M: Yes, newcomers, and you have to compete with young and bright people with other interests.

I: What are your views about the prospects of controlling diseases in the future?

M: I think that vaccination is the key for any infectious disease. As soon as you find an effective and cheap vaccine, you can control any kind of infectious disease. The problem is that for some diseases, it is more difficult to develop vaccines, like dengue fever.

I: Vaccination is more like prevention. But once a disease has started . . .

M: Once a disease has started, you have to treat it. That is the greatest challenge of modern medicine – to find new antimicrobicide, antibiotics, anti-viral drugs.

I: What about global warming issues? Do you consider them?

M: Yes. At the moment, we are looking at one model that is trying to understand how the seriousness of diseases can be affected by global warming; in particular, those diseases that are transmitted by mosquitoes.

I: What is the impact of the human genome project on diseases?

M: The human genome project has a huge impact on the understanding of diseases – the fact that it can pin down the genes that are responsible for specific susceptibility to certain infection. Other parameters that are important are those genes that may facilitate the entrance of micro-organisms into our bodies and how they penetrate into our cells, how our organisms interact with this sort of micro-organisms, what is the best treatment with drugs in that specific genomic setting. Well, I would expect a huge impact.

I: What would be the ethical issues involved?

M: That is a very sensitive point because the ethical conscience would find new barriers for some kind of investigations. For instance, investigations with animal models are very much restricted nowadays for ethical reasons. And also observations on experimental human beings are very much constrained by ethical issues.

I: You mentioned animal models. Is animal testing done anymore?

M: It's still done, but each time on smaller and smaller animals. You can't do it experimentally on large animals like dogs, monkeys, cats. It's now unacceptable to carry out experiments on this kind of animals. It's restricted to large mice and guinea pigs at most.

I: What about using the computer to replace animal testing?

M: That's the great hope. We have to rely on experiments in a computing environment in order to substitute animal models.

I: Do you use the computer in your work?

M: We use the computers a lot because we have to simulate our models. Everything that we see as far as the dynamics

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of the project is concerned is carried out in a computing environment, so we can see how populations interact with each other.

I: In some sense, it's impossible to wipe out diseases; they usually morph into something else.

M: I think wiping out diseases is really very difficult. We should not aim for that. We have to better understand what is going on in these interactions between all these living beings, in particular, in the field of infectious diseases. I would not believe that we will eradicate all of them because there are so many new infections every week. The pathogens are evolving each time to be more infective, and we are evolving tools in order to be resistant. So this is a sort of arms race, and we have to keep maintaining the upper hand. That would be the aim.

I: You mentioned that vaccination is a sort of prevention, but what happens if the vaccine eventually becomes not so effective?

M: In some diseases, you have the vaccines, in particular those vaccines that apply living virus or bacteria, and sometimes it has a sort of reversion to the lethal state. We have vaccine side effects as well. It's not uncommon and it's a matter of much concern.

I: I remember that years ago people thought that tuberculosis has been wiped out, but recently they have second thoughts about it.

M: Yes, tuberculosis is still an infectious disease which kills the highest number of people in the world. It is the number one killer. We have about 3 million people dying every year from tuberculosis.

I: Is it mostly in the under-developed countries?

M: We have many problems in Africa and also in Russia, in confined populations like prison inmates and under-nourished children. It is still a global problem. Tuberculosis is still a challenge for us.

I: What is your advice to a student who wants to do research in your kind of area?

M: The advice is that you have to be prepared first of all, go after some formal courses on mathematics, statistics and computer science. Without these, it's very difficult even to interact with statisticians. The other way around, people from the mathematics background who wish to apply them should get some formal courses in biology. In order to apply

at least the language to interact with other specialists, inter-disciplinary background is important. The second important point is to mix with people from other backgrounds. You have to work with other specialists. This is a team work. It is very difficult to survive alone.

I: Do you talk to the mathematicians back home?

M: Yes, we talk a lot. I have several mathematicians in my group. They are all learning biological science as well. We have to speak the same language.

I: It's quite difficult for a mathematician to learn biology, isn't it?

M: I would think it's more difficult for a biologist to learn the mathematics than the other way around. It's easier for a mathematician to learn biology than for a biologist to learn mathematics.

I: But still, it's not easy to convince a mathematician to consider your problems.

M: No, it's not that easy but, you know, if the initiative of the mathematician is in applications rather than in such diseases, it's not that difficult to convince him or her to study some biology.

I: You have been very successful in that.

M: I think I have had some success, no complaints about it.

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