## Mathematical Conversations

# Bryan Grenfell: Viral Visitations, Epidemic Models >>>

Bryan Grenfell

Interview of Bryan Grenfell by Y.K. Leong

Bryan T. Grenfell made important contributions to population dynamics with his pioneering work on the mathematical modeling of infectious diseases like measles and whooping cough, foot and mouth disease in farm animals and influenza of avian, equine and human types. He has done extensive collaborative multidisciplinary work at the interface between theoretical models and empirical data in population biology.

He has worked at York University, Imperial College, Sheffield University and Cambridge University, where he was Professor of Population Biology, before moving to the Center for Infectious Disease Dynamics at Pennsylvania State University in 2004 to become the Alumni Professor of Biology. He has played advisory roles to the British government on the foot and mouth epidemic in 2001 and to the National Institute of Health (United States) since 2002. He is also active in organizational work of scientific meetings. He has served on editorial boards of leading journals in theoretical biology and ecology, and currently of *Public Library of Science Biology*.

His scientific contributions have earned him the T.H. Huxley Medal, Scientific Medal of the Zoological Society of London and Fellowship of the Royal Society. He was also awarded the Order of the British Empire for his services to epidemiology and the control of infectious diseases.

He was chair of the Institute's program (August – October 2005) on the mathematical modeling of infectious diseases and was interviewed by Y.K. Leong for *Imprints* on 24 August 2005. The following is an edited and enhanced version of the transcript of the interview, in which he traced his transition from traditional zoology to his pioneering modeling work in population dynamics on infectious diseases. Here he gives us an insight into the multidisciplinary richness of a fast-growing area that is not only of immediate importance and urgency but also intellectually challenging.

***Imprints:*** Was your original training in zoology a traditional one? How did you get into your present research interest?

***B. T. Grenfell:*** My training was indeed a traditional one. It was a zoology degree in Imperial College, London. I wasn't a great field zoologist or person in the lab, so when we then had a course in the final year on population dynamics in ecology, I seized on it with open arms. I then did a PhD on applied ecology, specifically the application of models and statistics to assessing whale population sizes in the Southern Ocean. For my first postdoc, I worked, again at Imperial, on parasitic worms and childhood infections. I then got a faculty job in Sheffield University and I've worked on infectious diseases since. So the disease theme is since the 1980s.

***I:*** Practically from the beginning, you were already quite theoretical.

***G:*** Yes, reasonably, though I'm a biologist, not a statistician or a mathematician.

***I:*** How old or recent is your field of research?

***G:*** It really goes back to Daniel Bernoulli in the 1700s and then a body of work in the 19th and 20th century on infections like small pox, malaria and measles. The importance of these infections in public health terms and the quality of the data and simplicity of some of the mathematical patterns led people to use statistical and mathematical modeling approaches. I guess we can think of giant figures like Ross, Bartlett, in the 20th century. And in the late 20th century, the importance of infectious diseases that we all know about has led to another explosion in applications of mathematics and statistics in this area. There's been an explosion in disease dynamics work since the late 1970s, catalyzed by the seminal research of Anderson and May. I think it is a very lively field and it melds basic questions and applied questions in fields all the way from mathematics and statistics to immunology, virology, population dynamics and evolutionary biology. So I think it is a very exciting field.

***I:*** So it's really quite an old field.

Continued on page 9

Continued from page 8

***G:*** Yes, older than many others in terms of applications of population dynamics.

***I:*** In your modeling work on infectious diseases, which came first – the empirical data or the theoretical model? In other words, do you look at the data and then formulate the model, or do you first form an intuitive model with which to compare the data and then subsequently refine it?

***G:*** I think the overall answer is that one does both: the model and the data should be very closely linked and co-evolve. A lot of these biological systems, particularly the ones which manifest themselves at the level of interactions between people, are very complex, potentially with many parameters. The more we can tie up by comparing models with data the better. We are lucky that, because of historical notifications for many important diseases, there are sometimes very good data; for measles for example. But I must admit that I often go into the preliminary statistical analysis and so on with an intuitive model, then build a more formal structure.

***I:*** Where do you get the data from?

***G:*** A lot of infections were notifiable; they had to be notified: measles and pertussis (which is whooping cough) in the UK for example. Today, such incidence data are supplemented by freely available data on the genomic variation of influenza and other viruses. The explosion in molecular genomic data is very exciting.

***I:*** Are new statistical techniques needed to deal with the large data sets that you are faced with?

***G:*** Definitely; I guess there are there are three parts to the answer. Focusing on our work, we use wavelet analysis to explore highly nonstationary epidemic dynamics in the frequency domain. We then use mechanistic nonlinear autorepressive models to estimate epidemiological parameters. Your colleague Yingcun Xia has done seminal work here. Finally, we are now trying to unify these population dynamic analyses with phylogenetic approaches to viral molecular data.

***I:*** It sounds very cross-disciplinary.

***G:*** Very, because it blends statistics and mathematics with epidemiology, virology, immunology and evolutionary biology.

***I:*** Did you have to pick up the mathematical ideas and techniques on your own?

***G:*** Yes, though I've also been very lucky with wonderful technical collaboration.

***I:*** Is your field connected with evolutionary biology?

***G:*** Yes. Originally a lot of my work was on straight population dynamics. Once you get into influenza, you've got to think about evolution. I'm increasingly getting interested in that.

***I:*** Is biology getting more mathematical and statistical?

***G:*** I hope so. After the genomics revolution, biologists are very interested in systems biology now, which is the interaction between genes and their products leading to gene regulatory networks. If you have huge networks, you have to have some theory. So I think that the laboratory people are now using dynamic approaches.

***I:*** Can computer simulation models be used for predictive purposes?

***G:*** Let's imagine the case where you make these models before an epidemic. I certainly think they are very useful for projective purposes. They are very useful for saying, based on our assumptions about how people mix and the characteristics of the disease, what would we project would happen under different control scenarios. I certainly think that it's great to have such complex computer models but you also must have simple models – more reductionist models, just so you can interpret things. Quantitative prediction before a disease has hit is very hard; however, simpler "operational" models, fitted to the early part of an epidemic can be useful.

***I:*** Do I understand that they have actually been applied in actual projections?

***G:*** Yes; for example, we and others worked on the foot and mouth disease epidemic in the UK in 2001. A family of models was used with a range of level of complexity to project what was going to happen and they tended to be useful in making qualitative inferences about what sort of control policies one might have to adopt. Having a range of models which all pointed in the same direction was useful for the policy makers here.

***I:*** Are there any specific models being formulated for the recent SARS outbreak?

***G:*** I think if you look at the literature, there's a range of models that have been made by many groups, particularly using the high quality data from the major outbreaks.

***I:*** Has any work been carried out to determine whether epidemics play a role in the evolutionary history of birds and animals?



Continued on page 10

Continued from page 9

***G:*** Oh, certainly. Again it's not central to my work, but a lot of research has been done by geneticists, for example, looking at how some relatively stable parasites like herpes viruses co-speciate with their hosts, but also the impact of malaria, for example, and its interaction with human genetics. Then, more fundamentally, there's a lot of work on the possible role of parasitism in the evolution of sex for example.

***I:*** Are most epidemics in human history the result of human actions?

***G:*** Not in any simple sense, no; though colonization, anthropogenic changes like deforestation can play a role.

***I:*** Are there any models for cross-species pathogenic evolution?

***G:*** Not so much models, but I think the biologists are getting closer and closer to understanding the species barrier – why does a virus grow in one species and not in another – sexually transmitted is all we care about. The flu virologists are getting closer to understanding what those barriers are, and that's true for a variety of other viruses as well. But there are still always going to be the big questions to answer, particularly for more complex parasites.

***I:*** Are there any past records, from paleontology say or something, to show that epidemics could have wiped out a whole species?

***G:*** I can't think out of the top of my head that there are certain cases like that. What you might expect is that if it is a self-sustaining epidemic in a population of hosts, the epidemic often drops out before the hosts do. But if you have a big population of one species and a small population of another living cheek by jowl with it, and then you have a species jump from the big species and which could continue to jump across, you can then imagine that the small population would be very endangered by the disease. African wild dogs' diseases are certainly a problem in small populations. [The same goes for] gorillas in Rwanda and measles and so on. In small populations, of course, there's always a danger that the disease will just exert back extra toll and wipe the infection out. But I don't know of any example – there might well be one in history of a big population that's been wiped out by its own diseases. Because the disease co-evolves, it often becomes less pathogenic.

***I:*** Are there any models that predict the onset of resistance to certain diseases say in an epidemic?

***G:*** You mean things like antibiotic resistance? There are certainly models that people have used to try and understand how the evolution of antibiotic resistance is facilitated by how hospitals are managed or how the development of resistance against drugs which control parasites in farm animals, for example, depend on how the drug is used. Often though, it's direct statistical experimental evidence that's needed there for such models.

***I:*** How much of the models are related to dynamical systems?

***G:*** Pretty much all of it. For example, measles is a classical example of a (seasonally) forced oscillator. However, as we add more biology, things become more complex. For instance, measles can go [through] extinction epidemic troughs, implying a discrete state space system. As another complex, spatial heterogeneity and network mixing are often important. However, the very simplest models can still give insights.

***I:*** Do you do consultation work for the government and others?

***G:*** For the foot and mouth epidemic, I was a member of one of the modeling groups that advised the government. I also do some advisory work for WHO.

***I:*** Do you have many students?

***G:*** In Cambridge, I had a big group. There were 15 or 16 of us – maybe 8 or 9 postdocs and the rest graduate students. Having moved to the US, I'm building up the group again now.

***I:*** What you do is very critical for health control in populations …

***G:*** It's certainly got a strong applied aspect, but all the people in this field also do it because the questions are very interesting. I love dynamic processes and spatial processes, and the epidemiology is very interesting in that way.

***I:*** Do you have any advice for people who want to study these things?

***G:*** I certainly think it is a growing field and will grow much more over the next decade. There are great problems, wonderful data and great opportunities for people, particularly people with the right technical training in statistics or physics or mathematics. I know a lot of brilliant young people who have jumped across from these fields.

***I:*** Will it be easy for a mathematician who knows nothing about biology to cross over?

***G:*** Certainly I have several people that I can think of who've

Continued on page 11

Continued from page 10

done it brilliantly. Several people – again, Dr Xia for example knew no biology and did some wonderful work. Another postdoc did his PhD in astrophysics on galaxy simulation and now has a faculty job doing epidemic modeling. But, as these people did, you have to be prepared to learn and to realize that biology is complicated and that a key thing is to really get in amongst the data.

***I:*** The mode of thinking in biology is very different …

***G:*** It certainly is. A lot of the ideas are qualitative and you have to respect the fact that the folks who have been in the field or lab for a long time have got a sophisticated model understanding what is going on. As more and more data are collected on dynamic processes, quantitative skills are really important to interpret them. So I think it's a great field to get into. I encourage people to do that.