Institution: University of Chester

Unit of Assessment: 10: Mathematical Sciences

Title of case study: Mathematical modelling leads to advances in immunology

1. Summary of the impact (indicative maximum 100 words)

Research involving mathematical modelling is helping to unravel the complexities of key areas of biomedicine. Our study of the mammalian immune system focuses on two areas: (1) genetic evolution of HIV within the host during infection, and (2) dendritic-cell-based immunotherapy. The research has influenced understanding by biomedical practitioners of control parameters, the immune response and viral resistance to drugs. The involvement of mathematicians has led to a paradigm shift which has provided clear directions for investigation, and insights into immunisation programmes (an area of research which is still an emerging field).

2. Underpinning research (indicative maximum 500 words)

The Leverhulme Trust invested, over a period of two years in 2002-4, in an initiative having the specific objective of establishing research activity, in the areas indicated, in the Chester group through the employment of Bocharov as a Leverhulme international professor. The team had two targeted areas of research:

Area 1 - HIV-1. While HIV-1 infection poses a great challenge to the development of strategies for an effective cure, there has been major progress in controlling HIV infection with highly active antiretroviral therapy (HAART). The Type 1 virus is characterized by an extreme variability resulting from two major processes acting in parallel:

- changes in the viral genome (point mutations), and
- the multi-infection of target cells in conjunction with the recombination of viral genomes.

These processes enable the virus to escape the immune response and acquire resistance to drugs by tuning its genomic sequence. The complexity of the virus dynamics in vivo compounds the difficulty of understanding intra-patient HIV evolution.

Many groups have analysed viral kinetics following highly active antiretroviral therapy and have made inferences about HIV dynamics. The major focus in previous studies of drug-resistance was on the effect of point mutations. By contrast, we are one of only a few to have attempted to simulate HIV sequence evolution and to examine recombination effects. In seeking to appreciate the impact on viral evolution of a high frequency of multi-infected cells, with attendant recombination, one of the contributions of the Team has been to develop an in silico stochastic model (Bocharov et al., J. of General Virology, 2005) to explore the effects of major microscopic parameters (e.g., the point-mutation and recombination rates, and the proviral copy number per cell), on the dynamics of macroscopic characteristics. This model showed that the time to build up n-point mutants is enhanced by multi-infection. Previous studies were of infection with a single provirus per cell rather than of multi-infection.

In ‘neutral’ (random) evolution, where no selection occurs, mutants can be temporarily fixed over numerous rounds of replication before becoming extinct. This suggests that the majority of mutations observed in cross-sectional analyses do not arise from strong selection in reaction to drug therapy. Whenever a strong selection pressure is applied via the administration of drugs to a few sites, as under antiviral treatment, there is a rapid emergence of variants encoding the selected traits, showing partial or full resistance. Thus, under the conditions of an initial homogeneous infection, the selection of n-point mutants, which are fundamental to the development of multi-drug resistance, is generally accelerated by multi-infection and recombination, even though there is great variation in the kinetics of fixation.

Area 2 - cancer vaccines. Growing knowledge of the molecular identity of tumor-specific antigens has opened new avenues for effective cancer vaccines.

Dendritic-cell- (DC)-based immunotherapeutic approaches appear particularly promising, as indicated by a series of preclinical experimental studies in mice which demonstrated that anti-tumor immunity can be induced using DC. Significantly, the FDA has recently approved the first DC-based cancer vaccine for prostate cancer.

The research reported by Ludewig et al. (2004) has developed a mathematical model to determine the major parameters controlling DC-Cytotoxic T-lymphocyte (CTL) interaction. It found that T-cell receptor avidity greatly affects the pattern of CTL dynamics in response to single or multiple immunisations with DC. For induction of high avidity CTL, the number of adoptively transferred DC was of minor importance once a minimal threshold of cells-per-spleen had been reached.

The Unit's study indicated that as long as significant numbers of activated CTL persist and ensure rapid elimination of antigen-expressing DC, any further application of DC has only a limited 'enhancement' effect. Nevertheless, such repeated DC application is apparently necessary to maintain high levels of activated CTL. These findings impinge in particular on the use of DC in anti-tumor therapy, where the availability of high-avidity CTL against the chosen immune-therapeutical target antigen should be carefully examined. The research suggests that the translation of successful preclinical studies is likely to be hampered by complexities associated with the clinical situation. The translation of successful preclinical studies is likely to be delayed by complexities associated with the clinical situations encountered by medical practitioners.

In addition to Bocharov, members of the Chester team contributing to the ongoing work (which has continued from 2002 to the present) on mathematical immunology include (relevant contract dates in brackets) S Andrew (01/09/98 to present); CTH Baker (01/08/06 to present); JT Edwards (1993 to 31/08/07); NJ Ford (1993 to present); P Lumb (01/09/99 to present); SJ Norton (01/09/98 to 31/08/08).

3. References to the research (indicative maximum of six references)

3 selected references are marked by *.

The following selection of outputs demonstrates the dissemination of the outcomes of the research to a receptive readership. Each jointly-authored research paper includes at least two authors who had Chester affiliations.

2007: SM Andrew, CTH Baker, GA Bocharov. Rival approaches to mathematical modelling in immunology. Journal of Computational and Applied Mathematics 205: 669-686.

*2007: Luzyanina T, Mrusek S, Edwards JT, Roose D, Ehl S, Bocharov G. Computational analysis of CFSE proliferation assay. Journal of Mathematical Biology. 54(1): 57-89.

*2005: Bocharov G, Ford NJ, Ludewig B. A mathematical approach for optimizing dendritic cell-based immunotherapy. Methods in Molecular Medicine. 109: 19-34.

2005: Bocharov G, Ford NJ, Edwards J, Breinig T, Wain-Hobson S, Meyerhans A. A genetic-algorithm approach to simulating human immunodeficiency virus evolution reveals the strong impact of multiply infected cells and recombination. Journal of General Virology. 86 (Pt 11): 3109-18.

*2005: CTH Baker, GA Bocharov, JM Ford, PM Lumb, SJ Norton, CAH Paul, T Junt, P Krebs, B Ludewig. Computational approaches to parameter estimation and model selection in immunology. Journal of Computational and Applied Mathematics 84(1): 50-76.

2004: Ludewig B, Krebs P, Junt T, Metters H, Ford NJ, Anderson RM, Bocharov G. Determining control parameters for dendritic cell-cytotoxic T lymphocyte interaction. European Journal of Immunology. 34(9): 2407-18.

Key grants: Leverhulme Trust Visiting Professorship (Bocharov), 2002-2004, £50,885.

4. Details of the impact (indicative maximum 750 words)

Overall, the research team's work has promoted awareness of the benefits of applying novel, 'high-end' techniques in computational modelling to help unravel the complexities and causalities in the cited areas of biomedicine.

The group's research described here has had a far-reaching effect, not just on the academic community, and not just in the field of mathematics, changing the way different specialisms can work together. Recognising that research papers do not necessarily attract the attention of medical practitioners, and the actions of medical practitioners are circumscribed by protocols overseen by regulators, our contacts with colleagues, described in more detail below and cited in Section 5, have been used to facilitate access to and interaction with clinicians. In affecting the perceptions and approaches of our collaborators we have had an impact on practitioners, not least by identifying potentially relevant programmes of testing.

Prof Dr Burkhard Ludewig (one of our co-authors and collaborators) is Head of the Institute of Immunology, which is part of the medical research centre and is an independent research unit of the Kantonal Hospital St. Gallen, Switzerland. Research activities are focussed on immunopathological processes in the cardiovascular system, the development of new immunotherapeutical approaches against cancer, and the biology of coronaviruses. The Institute also supports basic research projects of physicians from the clinical departments.

Prof Dr Andreas Meyerhans (another collaborator and co-author with Bocharov) is group leader of the Infection Biology Group at UPF, Barcelona with research interests in virus evolution; lymphocyte responses in persistent human infections (HIV, HCV, CMV and Mycobacterium tuberculosis). His group's work is in two main areas:
1. describing fundamental features in virus evolution i.e. the characteristics of HIV quasispecies, HIV and HBV hypermutation and HIV multi-infection of single cells in vivo.
2. quantifying human T cell responses in viral (HIV, CMV, poliovirus), bacterial (Mycobacterium tuberculosis) and yeast (Candida albicans, etc.) infections directly from the blood of patients. Part of the work is funded by 2 international grants from the Bill and Melinda Gates foundation and the EU euco.net programme.

Burkhard Ludewig (see Section 5) wrote of the ongoing joint work:

"*Changed perceptions arising from the work of Bocharov and his co-workers* [...] *relate to issues of cause-and-effect in the complex pathological states encountered in real life illness. Ultimately, though (because of the natural conservatism in applied medicine) not in the short term this should lead to increased understanding of the effects of clinical treatment procedures and the discovery of new or changing forms of medication in specific therapeutic interventions.*

The recent FDA approval of the prostate cancer drug PROVENGE [approved in 2010] *shows that such developments are possible. A recent paper "A model of dendritic cell therapy for melanoma", by DePillis, Gallegos, and Radunskaya (2013) in Frontiers in Oncology was based heavily on the model that was introduced in the paper Ludewig et al. (2004) cited above* [in Section 3]*; this will further extend the impact of our work*."

Likewise, Andreas Meyerhans (see Section 5) expresses the view that that the Chester group's work has contributed to changed perceptions.

The HIV-1 research (Bocharov et al., 2005) has had an impact on biomedical researchers working on the design of therapeutic interventions in HIV infections. Firstly, it has directed attention towards a closer examination of the role of multi-infection/recombination in the viral evolution in infected individuals. Secondly, it has identified the scenario in which the recombination may accelerate the

emergence of multi-drug resistance by 10-fold, and thirdly, it has led to the establishment (since 2008) of a research initiative for further integrative analysis by a multi-disciplinary consortium based upon two teams in Barcelona. Both involve mathematicians and one includes specialists in clinical aspects of HIV infection.

Beyond direct interaction with clinicians and immunologists, further tools for securing an impact of the research on the community include: (a) a series of well-advertised public lectures, which induced interest in this cross-disciplinary activity at the University of Chester, was delivered to an audience including medical practitioners, (b) related research publications (Section 3 details six papers on this theme).

5. Sources to corroborate the impact (indicative maximum of 10 references)

The University of Chester holds on file letters from (i) Andreas Meyerhans (Department of Experimental and Health Sciences, Universitat Pompeu Fabra), and from (ii) Burkhard Ludewig (of the Institute of Immuno-biology, Kantonsspital St. Gallen) that provide corroboration of the claims attributed to them in Section 4 of the case study.