Mathematical Epidemiology of Infectious Diseases

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1. Introduction

Epidemiology is concerned with patterns in space and time of the occurrence of disease. From the patterns one may infer causes, predict the future and decide about the need for control measures. Many of such inferences require sophisticated statistics. When disease is caused by an infective agent, there is a second way in which mathematics may help to gain insight. Then one can build a mechanistic model for the spread of the agent and use it to disentangle how this spread is influenced by various factors, such as contact structure, population density, incubation period, etc. So one can do thought experiments where real experiments are impossible or unethical. Here the main mathematical tool is the qualitative theory of dynamical systems.

In a period of almost 30 years CWI has been actively engaged in the modelling and analysis of the spread of infectious diseases in structured populations of hosts. In the following we shall, in chronological order, very briefly present the main highlights.

2. Orientation on the classics

In 1971 CWI (then still called MC) started a (national and interdisciplinary) 'Working Group on Biomathematics' (as far as I know, the suggestion to start activities in this area came from F. van der Blij, then a member of the Board of Trustees; it was taken up by H.A. Lauwerier, P.J. van der Houwen, G.M. Willems, two Hemker brothers and J. Grasman. This working group

has been a very strong catalyser for the development of mathematical biology in The Netherlands.

The subject of epidemiology was mainly brought in by J.A.J. Metz from the Institute of Theoretical Biology of Leiden University, who himself was inspired by J. Reddingius. Central was the work of W.O. Kermack and A.G. McKendrick in 1927, an early milestone which was so much ahead of its time that forty years later 'generalizations' were published which were actually special cases.

Most likely inspired by R. Ross (who, incidentally, received the Nobel prize for medicine in 1902 for his discovery that malaria is due to the *Plasmodium* parasite, transmitted via mosquitoes, and not due to 'bad air', as the name reflects) Kermack and McKendrick established in great generality the occurrence of a threshold phenomenon: the introduction of an arbitrarily small quantity of the infective agent in a demographically closed population can only trigger an epidemic when a certain compound parameter R_0 exceeds one (in Section 4 below we shall say much more about R_0). From a biological/medical point of view this, and the further characterisation of R_0, is all that matters. From a mathematical point of view, the 'arbitrarily small' is interesting and calls for a singular perturbation analysis. The problem is non-standard because it concerns an infinite-dimensional dynamical system; in fact it requires that one first resolves how one should think about initial value problems for Volterra integral equations of convolution type; once this is settled one can formulate a result in terms of the one-dimensionality of the intersection of an unstable manifold with a cone of positive functions. A second point is that in the introduction phase the deterministic approximation is not warranted, since numbers of infected are not large. The link is via branching processes.

The applied math outlook of the late seventies on the classical mathematical theory of epidemics is nicely summarized in the MC Tract 138 by Lauwerier [3].

3. SPATIAL SPREAD

Guided by advisor L.A. Peletier (just then moving from Delft University to Leiden University) the applied math department organised in 1976 a colloquium on reaction-diffusion equations (see [1]) in which much attention was given to the then brand-new results of D.G. Aronson and H.F. Weinberger on the asymptotic speed of propagation of disturbances c_0. The idea is simple. A steady state, let's call it 0, is unstable and any (biologically) realizable perturbation, no matter how small, gives rise to a sequence of events (an orbit) which ends in a stable steady state, which we choose to call ∞. Examples include fires (combustion theory), epidemics, rumours and favourable mutant genes. How fast will the transition $0 \rightarrow \infty$ effectively take place? Remarkably, the question becomes more meaningful if

we add a spatial dimension. Then we can look for travelling plane waves, a special kind of self-similar solutions. (In a moving coordinate system the temporal transients look like 'frozen' spatial transitions!) It turns out that travelling plane waves exist for all speeds $c \geq c_0$ for some c_0 and that this minimal speed c_0 is the asymptotic speed of propagation in the sense that, for compactly supported initial disturbances, an observer moving with a speed higher than c_0 will be ahead of the transition, while an observer with a lower speed than c_0 will, eventually, experience state ∞. The following argument explains intuitively why the minimal wave speed equals the 'true' speed. By manipulating the initial condition suitably one can produce travelling waves in much the same way as one can create the illusion of steady movement in an array of electric lights by turning them on and off appropriately. Only one thing can spoil this game: if we try to make the speed too low the inherent 'infection' mechanism of our excitable medium takes over. Therefore this inherent infection speed is exactly the lowest possible wave speed!

The description above makes clear that application of these ideas to epidemic spread is all too natural. And in fact D.G. Kendall had already analyzed a special case (it has been told that Kendall obtained his results much earlier, but that he postponed publication because of the danger that they would be helpful for planning biological warfare). At almost the same time H.R. Thieme and Diekmann independently generalized the results of Aronson-Weinberger and Kendall to the Volterra-Fredholm integral equations describing general epidemic models. But at a meeting organized by the Dutch Society for Theoretical Biology, in which J.C. Zadoks of the Laboratory for Phytopathology of the Agricultural University of Wageningen presented the results of extensive simulations with a model for fungus disease spread by spore dispersal in various crops and formulated directly in computer language, while the present author presented his results in a theorem-proof style, a confusion of tongues of almost Babylonic dimension prevented effective interaction. The abstract results were not at all operational.

The next step was taken at the Institute of Theoretical Biology of Leiden University where F. van den Bosch, in a Ph.D. project guided by Metz, learnt both languages and thereby pulled the communication barrier down. In joint work with Zadoks and Metz he developed mechanistic submodels for spore dispersal, introduced flexible yet parameter sparse kernels for spore production, developed approximation formulae to determine c_0 from such ingredients with a pocket calculator in negligible time and showed that the model predictions match up to simulation studies and agree well with speeds measured in field experiments. All is well that ends well.

But in fact this was not the end. An unexpected follow-up started when the ecologist R. Hengeveld heard about these results at the inaugural ad-

dress in 1986 of the Metz-Diekmann tandem. Hengeveld was collecting and analyzing data on animal range expansions and realized that, with the appropriate interpretation of the ingredients, the results would directly carry over to this context. A fruitful collaboration originated.

4. THE BASIC REPRODUCTION RATIO R_0

For some time not much epidemiological happened at CWI. But then came AIDS and the modelling of infectious diseases became internationally a hot topic. The CWI group had no ambition to join this trend and continued to concentrate on the population dynamics of structured populations. But gradually it became clear that expertise in this area of structured populations could be used with great advantage when formulating and analyzing complicated epidemic models. And then J.A.P. Heesterbeek embarked upon a Ph.D. project and a colloquium was organized by him, Metz, Diekmann and two visitors, H. Inaba from Japan and M. Kretzschmar from Germany. Most attention was given to the basic reproduction ratio R_0 which, in biological words, is defined as the expected number of secondary cases produced by a *typical* infected individual during its entire infectious period, in a population consisting of susceptibles only. The 'typical' indicates that we take averages when individuals may differ in relevant aspects (e.g. sexual behaviour). Sometimes it is easy to average, sometimes it requires thought. In the present context the dynamics of disease transmission (i.e. the interplay of susceptibility and infectivity) determines how the averaging should be done, viz. by computing the positive eigenvector and eigenvalue of a next-generation operator (recall the Perron-Frobenius theory of positive matrices). All of this is explained in [2].

When $R_0 < 1$ the infective agent cannot invade into a virgin population of susceptible hosts, but when $R_0 > 1$ it can. This is exactly Kermack-McKendrick's threshold condition. When we know, much to our chagrin, by empirical fact that $R_0 > 1$, the threshold condition seems just a somewhat academic instrument to check our model. But once we realize that we need to bring, by control measures, R_0 to a value below one in order to eradicate an agent that is already established, it becomes clear that we can use R_0 as a practical instrument to estimate the effort needed for a successful eradication campaign.

5. MODELLING THE FORCE OF INFECTION

More or less as an outgrowth of the colloquium CWI got a contract to provide mathematical modelling expertise for the project 'Population dynamics of infections' at the Central Veterinary Institute in Lelystad (now ID-DLO) which was started then by M.C.M. de Jong. At first the effort was directed at making the abstract definition of R_0 operational (in much the same way as Van den Bosch had done with the asymptotic speed of spread c_0) by de-

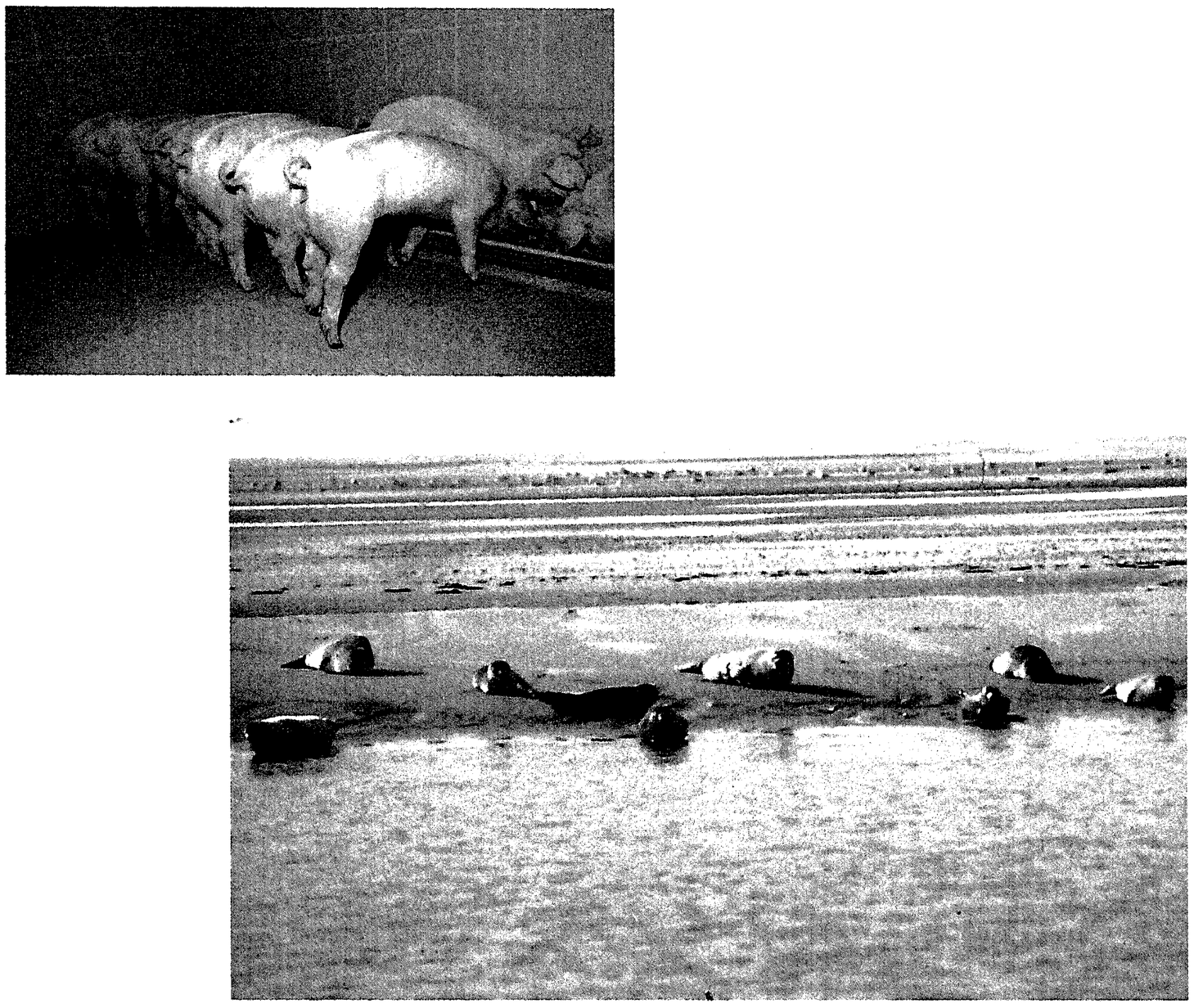

Figure 1. Mathematical models developed at CWI help to understand how farm or colony size affects the severity of an outbreak of a virus disease among pigs or seals. Photo's coutesy ID-DLO Lelystad (left) and IBN-DLO Texel (right).

veloping an algorithm to compute it in a special setting (motivated by the spread of Aujeszky's Disease Virus (ADV) among pigs on farms where the pigs are regularly shifted from one barn to another). A simple question ('When one farm is twice as large as another, what difference does it make for disease transmission?') initiated a new research direction, with field observations, lab experiments and theoretical modelling reinforcing each other.

The *force of infection* is by definition the probability per unit of time for a susceptible individual to become infected. Many viruses are transported from the mucus of one host to that of another by aerosoles when hosts 'meet'.

As a consequence one needs to model the contact process first, and then superimpose the transmission of the virus. The situation resembles that of chemical reactions, where molecules have to come close enough before they can react. Inspired by that similarity, standard deterministic epidemic models are in terms of densities and model the contact process by the law of mass action (which, in the present context, asserts that the force of infection is proportional to the density of infectives).

But in real life one often has to work with numbers, rather than densities. Indeed, both the size of a pig farm and the size of a colony of seals (see also figure 1) is usually expressed as the number of individuals that belong to it, while the density is roughly the same for each farm or each colony (in the latter case the evidence comes from aerial photos of seals sun bathing on sand banks).

It is not difficult at all to formulate and analyze a model in which density is a given constant, while population size is variable (over populations and, possibly, in the course of time). The first test on data from a classical experiment of Greenwood in 1936 (with mice suffering from *Pasteurella muris*, and living in a network of cages that was enlarged when population size increased) was inconclusive: the model with the per capita number of contacts per unit of time independent of population size, and the one for which this number was proportional to population size, could be made to fit the data with roughly the same accuracy. (Incidentally, this work was performed at the Isaac Newton Institute in Cambridge, as part of a special programme on mathematical epidemiology.

This finding prompted ID-DLO to perform experiments with ADV in groups of pigs, a large one in a large stable and a small one in a correspondingly smaller stable. Here the outcome was fortunately very clear: the hypothesis of proportionality of contact rate with population size had to be rejected.

Another convincing argument was found in the data about the spread of

Phocine Distemper Virus (PDV) during the 1988 epidemic in the coastal waters of Northern-Europe: the final size appeared to be independent of colony size (an observation which had puzzled researchers applying the 'standard' model in which contact rate is proportional to population size.

Thus a combination of modelling considerations, mathematical analysis, experiments and observations helped to disentangle some aspects of the complicated relation between mechanisms at the individual level and phenomena at the population level.

6. COMMUNICATION AND EDUCATION

It cannot be denied that a gap exists between general abstract mathematical theory and specific concrete real life situations. But one can try to make it smaller by organizing repeated exchanges of information about mo-

tivation, problems, ideas, data, methods, etc. Thus in 1995 a course on epidemic models was organized at CWI by Diekmann, Heesterbeek (now at ID-GLW), De Jong (ID-DLO), Kretzschmar (now at RIVM) and Metz. Participants came from all over the country and had backgrounds covering plant pathology, veterinary science as well as human epidemiology. Their number ranged from 40 at the beginning to 20 at the very end. The plan is to elaborate the notes to a book, hopefully with D. Mollison from Edinburgh as a sixth author and stochastic conscience. This book will then be the culmination of CWI's involvement in the development of mathematical epidemiology during a long period.

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