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# Mathematical Models for Infectious Diseases

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Within the last few years there has been increasing interest in Mathematical Epidemiology. New developments of the fundamental theory have been paralleled by the detailed description of infection processes. The most interesting feature of the more general theory is the reformulation of the classical threshold theorems in terms of the basic reproduction number whereby a link is established between the modeling in terms of partial differential equations and integral equations and stochastic views. Special features of models for infectious diseases include contact patterns, differential susceptibility, social behavior, immunization, control strategies, optimization problems. A recent but important field is the modeling of the progress of the disease within the host, e.g. spread and diversification of parasite populations, the immune response of the host etc.

The present Oberwolfach Workshop, following a conference with the same topic five years ago, was organized by K.Dietz (Tübingen), K.P.Hadeler (Tübingen), H.Thieme (Tempe, AZ).

The topics of the conference reflected the developments outlined above. They covered deterministic and stochastic approaches, notably in the form of ordinary or partial differential equations, integral equations, stochastic processes specifically adapted to epidemiology (e.g. Reed-Frost models, birth and death processes with catastrophes), cellular automata and interacting particle systems, modeling the spread of malaria, schistosomiasis, measles and rubella, and, in a sense the most urgent problem, the HIV infection.

The number of formal lectures had been restricted to some extent, and several participants have developed their ideas in a less formal evening discussion. Thus there has been sufficient time for discussions and cooperation possibly leading to joint research.

It should be underlined how important the Oberwolfach library is for fields as diverse as Mathematical Epidemiology, in particular now, when hardly any university library can offer a complete selection of journals.

The technical assistance has been perfect as usual; the participants express their thanks to the staff.

Johannes Müller

Viggo Andreasen

**SIR-type models of natural selection induced by a disease**

Using for each genotype an SIR-model of disease transmission dynamics, I describe natural selection in a continuously breeding diploid host. Variation in disease susceptibility and resistance is assumed to be small and determined by one locus with two alleles. By transforming the system into variables giving the population size, gene frequency, and Wright's fixation index for each disease class, I obtain a model that separates in two time scales. On the fast time scale, the population settles at the endemic equilibrium, the fixation index goes to zero, and the gene frequency converges to the same value in all compartments. On the slow time scale, the genetic variation in disease parameters determines the change of the gene frequency and one can give explicit expressions for the relationship between fitness and disease parameters.

Viggo Andreasen, Dept. of Mathematics, Roskilde University, Denmark

Norman Bailey

**A revised version of an operational HIV/AIDS model to assist public health decision-making, now including a very short but highly infectious initial phase**

Recent work by Jacquez et al. (J.AIDS 7: 1169-1194, 1994) makes a strong case for an initial period of the HIV infection being very short but highly infectious, compared with an earlier version (Bailey, Math. Biosci. 117: 221-237, 1993) that assumed as first approximation that infectivity was uniformly spread over the whole incubation period. To begin with, data were used, as before, from San Francisco city for AIDS incidence, 1981-87, and from the well-known SF city clinic cohort study on hepatitis B giving data on both AIDS incidence and HIV prevalence up to 1984. The new analysis makes only a small change in the parameter for the incubation period (now $13.2 \pm 0.4$ years), which, as a basic biological parameter can be regarded as approximately valid for other regions or countries. Applications have been made to several European countries including Switzerland, France, Germany etc. The latter provided the most stable data on AIDS incidence. Maximum likelihood estimation gave the transmission parameter $\hat{\beta} = 0.1818 \pm 0.0105$ per week (assuming an infectious period of 2 months); the core group size was estimated as $\underline{\hat{N}} = 34424 \pm 5275$, a not very precise result. But the size of the initial quasi-SIR epidemic was $\underline{\hat{n}} = 19004 \pm 995$, a much better determination. The goodness-of-fit $\chi^2$ was 8.06 on 11 degrees of freedom. The future course of the epidemic, in the absence of major treatments or public health interventions, would give a damped series of widely separated HIV epidemic outbreaks. The implications for simulations to project future HIV and AIDS scenarios must therefore be subject to further investigation.

Norman Bailey, Lauenen, Switzerland

Andrew Barbour

**Threshold behaviour in some epidemic models**

In models of epidemic spread in mixing populations, the initial behaviour can usually be analyzed by considering the Whittle Markov branching process approximation. A large outbreak can then only occur if a particular characteristic parameter of the system exceeds a certain threshold; a condition normally equivalent to the requirement that the basic reproduction number should exceed 1. However in the Whittle approximation to the model of a parasitic infection proposed by Barbour and Kafetzaki, which is a Markov branching process with infinitely many types, it turns out that the basic reproduction number determines whether or not a large outbreak is possible only for a certain range of parameters, and that another quantity is relevant outside this range. The phenomenon can at least partially be understood by considering the life history of heavily infected individuals.

Andrew Barbour, Universität Zürich, Switzerland

Niels Becker

**Immunization leads for preventing epidemics in a community of households made up of individuals of different types**

A method is proposed for computing an epidemic threshold parameter for the spread of a disease in a community of households, in which individuals are of $p$ types. The threshold parameter is the largest eigenvalue of a $p \times p$ matrix, whose elements depend on the rates of transmission between types and the distribution of the household size. More explicit expressions are given for diseases that are highly infectious within households. For a variety of vaccination strategies it is described how this approach can be used to determine the level of immunity required to prevent epidemics.

Niels Becker, La Trobe University, Melbourne, Australia

Vincenzo Capasso

**Saddle point behavior for an epidemic model with diffusion**

A reaction diffusion system modelling a class of Man-Environment-Man epidemics (cholera, typhoid fever, infectious hepatitis A, schistosomiasis, etc.) is studied, with $\sigma$-type forces of infection. Homogeneous Dirichlet boundary conditions are given particular attention. Conditions on the parameters are stated so that a global bifurcation pattern occurs; two nontrivial and one trivial equilibria may exist one of them being a saddle point, the other two being attractors. Computer simulations confirme the localization

effect of epidemics which start below the smallest nontrivial solution. This effect is emphasized for small values of the diffusion coefficient. Stability properties may be proven based on the Morse theory as generalized by Conley.

Vincenzo Capasso, University of Milano, Italy
and Richard E. Wilson, University of Oxford, Great Britain

Kenneth L. Cooke

**A model for HIV in Asia**

A new deterministic model is formulated in which the spread of HIV/AIDS in the community is carried out mainly due to the heterosexual interaction between young unmarried males and a core group of female prostitutes ("sex workers"). This model is proposed with the recent rapid growth of the HIV/AIDS epidemic in some countries in South and Southeast Asia in mind. The model includes four groups: the core, young unmarried males, young unmarried females and pairs. Among included features are recruitment into the core that is related to the size of the group of unmarried males, births and deaths, and pairing, yet the model is simple enough to permit complete global analysis. We obtain several threshold parameters that determine persistence of endemic proportions, persistence of total population, and persistence of an infected number within a population tending to infinity when the endemic proportions tend to zero. Several unusual bifurcations are found, including cases in which there are multiple positive equilibria and a separatrix such that introduction of infectives below the separatrix results in extinction of the infection, but introduction of infectives at a higher level results in persistence of the infection. Biological interpretations of the results are discussed.

Kenneth L. Cooke, Pomona College, Claremont, California, USA

Henry E. Daniels

**The evolution of a deterministic simple spatial epidemic**

This talk explored the possibility of using a perturbation technique for approximating the solution of non-linear epidemic equations, in a way first introduced by the speaker in 1978. The method for one dimensional travelling waves was discussed at the 1993 Cambridge conference for the simple epidemic and SIR models. The justification for its success in that case was the assumption that the epidemic changed slowly over the range of the contact distribution.
The same technique is here used to examine the evolution of a simple epidemic from an initial spatial distribution of infectives. The assumption underlying the previous

application can no longer justify the method. However, by first considering the linear case where the population of susceptibles is infinite, the perturbation technique turns out to be equivalent to finding the saddle point approximation to the inversion of the moment generating function of the number of infectives which is accurate even for small times. This encourages one to proceed to the nonlinear epidemic which behaves linearly initially.

H.E. Daniels, University of Cambridge, Great Britain

Odo Diekmann

**Reflections on contacts**

Two variants of the assumptions underlying classical deterministic theory are discussed. The first is concerned with epidemics within herds, where the density stays constant as numbers decrease due to the fatal consequences of the disease. I focus on the final size as a function of $R_0$ and survival probability. The second is concerned with an attempt to allow for the possibility of repeated contacts with the same individual in the context of a deterministic model.

Odo Diekmann, Amsterdam, The Netherlands

Zhilan Feng

**How do isolation periods affect recurrent outbreaks of childhood diseases?**

The multi-annual outbreaks of measles and other childhood diseases have previously been explained by an interaction of intrinsic epidemiologic forces generating damped oscillations and of seasonal or/and stochastic excitation. We show that isolation (i.e. sick individuals stay at home and have a reduced infective impact) can create self-sustained oscillations provided that the number of per capita contacts is largely independent of the number of individuals present. This means that the bilinear mass action term for disease incidence is modified by dividing it by the number of non-isolated individuals.

Zhilan Feng, Tempe, Arizona, USA
Horst R. Thieme, Tempe, Arizona, USA

Ursula Foryś

**Global analysis of Marchuk's simplest mathematical model of an infectious disease**

In addition to the known theorems describing the asymptotic behaviour of solutions of Marchuk's model I have proved some new global results. At first it is assumed that the organism is in a very good state:

1. If the physiological level of antibodies is sufficiently high, then the stationary state called the healthy state is globally asymptotically stable.
2. If the physiological level of antibodies is too small, then there exists an average of the solution ($\lim_{t\to\infty}\frac{1}{t}\int_0^t x(s)\,ds$, where $x$ is the solution) and it is equal to the second stationary solution called the chronic state.

Next it is assumed that the organism is in a poor state:

1. If the physiological level of antibodies is too small, then the concentration of antigens tends to infinity and the level of antibodies tends to 0.
2. If the physiological level of antibodies is sufficiently high, then for small doses of antigen initial concentration the solution tends to the healthy state, but for large initial doses the concentration of antigens also tends to infinity and the concentration of antibodies also tends to 0.

Ursula Foryś, Warsaw, Poland

Bryan Grenfell

**Measles population dynamics: nonlinear predictability, chaos and the impact of demography**

This paper begins by using analyz es of empirical data and simple mathematical models to explore the role of nonlinear forecasting in dissecting the nonlinear dynamics of measles epidemics in developed countries. Specificially previous authors here proposed that decline in predictability width prediction interval is a signature of deterministic chaos. Here, we use a simple $\varepsilon$-ball prediction method to show that predictability of measles epidemics in England and Wales, in fact, remains relatively high with prediction interval, reflecting the regular, biennial nature of the epidemics. Analyzes of these series, along with measles data from New York, also indicates that falls in predictability can be explained by secular changes in birth rate. This then leads us to analyze simple models for the effects of birth rate changes on measles dynamics. This model is shown to account for the delay, of around 5 years, observed between birth rate increases in England during the late 1940s and subsequent measles incidence.

Bryan Grenfell, Cambridge, Great Britain

Mats Gyllenberg

**Minimum viable size of a metapopulation subject to an infectious disease**

The Levins model of metapopulation dynamics states that

$$\frac{dP}{dt} = \beta P(h - P) - \mu P,$$

where $P$ is the fraction of occupied patches, $h$ the fraction of habitable patches and $E = h - P$ the fraction of empty but habitable patches. The model is simply the SIS model with the well-known threshold phenomenon: if $h < \frac{\mu}{\beta}$ all habitable patches are empty at equilibrium and if $h > \frac{\mu}{\beta}$ the equilibrium value $E^*$ of empty habitable patches equals the threshold value $\frac{\mu}{\beta}$. This result gives an important rule of thumb: The critical patch number necessary for metapopulation persistence can be simply estimated from the number of empty patches at equilibrium without knowing the details of metapopulation dynamics.

The Levins model is based on several simplifying assumptions, e.g. that all patches are identical with equal risk of local population extinction. If local extinctions are caused by an epidemic outbreak this is certainly not the case: Populations with higher density are more likely to be wiped out by the epidemic.

I presented a structured generalization of the Levins model taking variations in patch quality into account and derived criteria for when $E^*(h)$ is increasing, constant and decreasing for $h$ larger than the threshold. Applying the Levins rule of thumb when in fact $E^*(h)$ is decreasing, one would be led to a serious misjudgement. When local extinctions are caused by an epidemic $E^*(h)$ will typically be decreasing.

Mats Gyllenberg, University of Turku, Norway

Karl Peter Hadeler

**Cores and social behavior**

Two joint papers are presented, with Carlos Castillo-Chavez and with Pauline van den Driessche. In the first paper a constant population is divided into a core and a noncore. Individuals are recruited into the core depending on prevalence in the core. The infection process and educational programs work in the core. It is shown that for highly infectious diseases and rather ineffective educational programs various unexpected effects may occur: With increased educational effort prevalence in the core may go up; total number of infected may go up while prevalence in the core goes down. In the second paper these effects have been systematically explored for an SIR model with a partially educated population.

K.P. Hadeler, University of Tübingen, Germany

Günter Hasibeder

**Heterogeneities of vector-transmitted infections**

Motivated by data from a field study in Zimbabwe, a general model framework for the transmission of schistosome infection is presented which includes

- age-dependent transmission,
- immune response of the human host,
- and possible additional heterogeneities.

The basic reproduction ratio can be expressed in terms of the model parameters, but it can also be estimated from age-structured infection data. The various possibilities and difficulties of estimating the basic reproduction ratio are discussed. Also this model framework is compared with an approach by Dietz (1981).

Günther Hasibeder, Technische Universität Wien, Austria

Hans Heesterbeck

**A brief history of epidemic theory**

The genesis was discussed of two alternative explanations for the decline of epidemics, both of which arose in the middle of the 19th century : 1. Farr's hypothesis (1866) that the disease agent loses infective potency as the epidemic progresses; 2. Henle's hypothesis (1840) that decline was due to an increasing lack of susceptibles as the epidemic progressed. Hank's hypothesis can be traced through authors like Snow, Ransome, Campbell, Munro and Whitelegge to the beginning of the 20th century when Hamer and mostly Ross developed the mechanistic mass-action approach to disease spread that still survives today. Farr's hypothesis eventually "lost the battle" but not without a long "fight". It found its main proponent in John Brownlee who became almost obsessed with the idea of trying to find underlying causes of epidemic spread by studying progress curves of actual epidemics. He argued in a series of papers (1906 - 1909) that no law of infection that he could devise around Henle's hypothesis led to the almost symmetric progress curves he frequently observed. In 1915 Ross showed however that Ross' theory of happenings could easily produce symmetric curves under the same biological conditions as considered by Brownlee. Brownlee could only agree with this and concluded - since two completely different approaches led to indistinguishable symmetric curves in the same cases - that no insight into epidemic mechanism could be gained after all by only studying progress curves. With Brownlee, Farr's hypothesis finally died in the early 1920's.

Hans Heesterbeck, Wageningen, The Netherlands

Barbara Hellriegel

**Mathematical models of the within-host dynamics of two-clone malaria infections**

This work focussed on a mathematical model for the dynamics of malaria parasite populations within an individual human host (here called 'within-host' dynamics as opposed to 'between hosts'). It therefore contributes to research concerned with the population dynamics of infectious diseases and combines knowledge from theoretical ecology and parasite immunology. The model takes into account that malaria infections often are caused by more than one parasite genotype ('strain') and that a single genotype can vary its antigenic phenotype during the course of an infection. Thus it was possible to address the following questions:

- What is the influence of competition among parasite genotypes as opposed to immunity, in regulating their 'within-host' dynamics?
- What is the relevant time scale for the 'within-host' dynamics of a malaria infection?
- Which part of the infection is most critical for the parasite's survival and the patient's state of health?
- What is the role of antigenic variation in malaria parasites?

Barbara Hellriegel, University of Zürich, Switzerland

Herbert W. Hethcote

**Deterministic SIS models with variable population size**

The SIS models have disease-reduced reproduction, disease-related deaths and exponential, logistic or recruitment-death demographic structure. The incidence term is $\lambda(N)XY/N$ where the population size dependent contact rate $\lambda(N)$ is a non decreasing function. Thus it includes the standard incidence $cXY/N$ with $\lambda(N) = c$ and the simple mass action incidence $\beta XY$ with $\lambda(N) = \beta N$. The persistence of the disease combined with the disease-related deaths and disease-reduced reproduction can greatly affect the population dynamics. For example, it can cause the population size to decrease to zero, or to a new size below its carrying capacity or it can decrease the exponential growth of the population. In joint work with Jinshi Zhou on differential equation SIS models, we have determined thresholds, equilibria and global asymptotic behaviors. In joint work with Pauline van den Driessche on a delay-differential equation SIS model with incidence $\lambda XY/N$, we have determined thresholds and asymptotic behavior. For a small unrealistic parameter region there are periodic solutions, but above the threshold, the epidemic equilibrium is usually asymptotically stable. Linda Gao, Jaime Mena-Lorca and I have analyzed similar SEI models. For these SEI models there are periodic solutions for some parameter values with the simple mass action incidence $\beta XY$, but not with the corresponding models with the standard incidence $\lambda XY/N$. Thus SEIS, SEIR and SEIRS models with incidence $\beta XY$ can also have periodic solutions. Thus the

choice of $\lambda XY/N$ or $\beta XY$ as the incidence strongly influences the asymptotic behaviors in these models.

Herbert W. Hethcote, University of Iowa, Iowa City, USA

Mimmo Iannelli

**Some results on the AIDS epidemic in Italy**

A mathematical model for the HIV/AIDS epidemic has been compared to the AIDS cases, up to the year 1992, among intra-venous drug users in Latina (Italy). We tested several hypotheses about the dynamics of the epidemic. In the simplest model the population is assumed to be homogeneous and the contact rate constant in time, moreover infectiousness is assumed to be variable during the incubation period. This model fits incidence data up to the year 1989 very well, but is not adequate to describe the epidemic after this year. Thus we tested different mechanisms like a decrease of the contact rate, the existence of two subgroups with different rates, a decrease of infectiousness due to therapies. Though the models show different predictions they cannot be distinguished on the basis of present data.

Mimmo Iannelli, University of Trento, Italy

Valerie Isham

**Stochastic models of host-macroparasite interaction**

A simple non-linear stochastic model for the parasite load within a single host on the lifetime of the host is investigated. By concentrating on a model incorporating only parasite-induced excess host mortality, exact algebraic results are possible, providing insight into the effects of this interaction mechanism. Methods of approximating the moments of parasite load based on the normal and negative binomial distributions are explored and compared under a range of parametric assumptions. Extensions of the model to allow for heterogeneity between hosts and to incorporate acquired immunity within the host via a density dependent mechanism and via an additional stochastic variable are discussed.

Valerie Isham, University College London, Great Britain

John A. Jacquez

**Role of the primary infection in epidemics of HIV infection in gay cohorts**

A review of HIV infectivities in the stages of the disease provides evidence that the infectivity in the primary infection is very high and that the primary infection is followed by a long period of very low infectivity. Eventually infectivity increases as individuals pass into the pre-AIDS and AIDS stages. That means that the primary infection has much the dynamics of an SIR disease. That explains the appearance of the epidemic curves for HIV infection quite well. In addition evidence on behavioral changes stronger suggests that the behavioral changes came too late to have much effect on the initial arise of the epidemic but that it considerably decreased the subsequent rise after the initial plateau of the epidemic curve.
Finally, data on heterogeneity of contact rates show that the plateau levels for epidemic curves in a number of cohorts were well above the sizes of the high activity groups. The conclusion is that the primary infection is practically the sole source of infection in the rising phase of the epidemic and that it continues to play an important role up on the quasi-plateau.

John A. Jacquez, Univ. of Michigan, MI, USA

Mirjam Kretzschmar

**Measures of concurrency in networks and the spread of infectious disease**

We investigate the impact of concurrent partnerships on epidemic spread. Starting from a definition of concurrency on the level of individuals we define ways to quantify concurrency on the population level. We introduce an index of concurrency based on graph theoretical considerations and show how it is related to the degree distribution of the contact graph. Next we investigate the spread of an infectious disease on a dynamic partnership network. The model is based on a stochastic process of pair formation and separation and a process of disease transmission within partnerships of susceptible and infected individuals. Using Monte Carlo simulation we compare the spread of the epidemic for different contact patterns ranging from serial monogamy to situations where individuals can have many partners simultaneously. We find that for a fixed mean number of partners per individual the distribution of these partnerships over the population has a major influence on the speed of the epidemic in its initial phase and consequently in the number of individuals that are infected after a certain time period.

Mirjam Kretzschmar, RIVM (Bilthoven), The Netherlands
(with Martina Morris, Columbia University, New York, NY, USA)

Claude Lefèvre

**Poisson approximation for the final state of a generalized epidemic process**

A so-called generalized epidemic model is considered that describes the spread of an infectious disease of the SIR type with any given distribution for the infectious period. A necessary and sufficient condition is derived that guarantees a Poisson-like behavior for the ultimate number of susceptibles, when the population is large. The proof relies on two ideas, namely the building of an equivalent markovian representation of the model and the use of a suitable coupling via a random walk.

Claude Lefèvre, Univ. Libre de Bruxelles, Belgium

Simon Levin

**Scaling from individuals to populations**

In recent years, the analogies between ecology and epidemiology have been made more explicit: variable population sizes, evolution of disease dynamics and host-parasite co-evolution, the community theory of multiple hosts and interacting diseases. Perhaps the central such problem, and one inadequately developed to date, involves heterogeneous mixing and the issue of how the parasitism term or the incidence function should be "closed". Phenomenological approaches abound, but little has been done in the direction of relating these functional forms to individual or local dynamics. The objective of my lecture is to relate aggregate behavior to that of individuals.

I begin by considering standard S-I-R and S-I-S models in a spatial framework, and show how mean–field equations need to be modified by higher-order terms reflecting correlations. The system now is no longer closed, and so closure rules or explicit dynamics of the correlations must be introduced, in the latter case simply displacing the closure problem to another level. This approach is applied explicitly to the contact process, showing how better approximations result.

Renormalization approaches provide another alternative. Next, an S-I-S model is placed within the context of interacting particle systems, in which it is shown that persistence at endemic levels many result, through spatio-temporal fluctuation, for a system that must become extinct in a well-mixed (mean-field) formulation.

It is also shown how to derive diffusion limits (all of this joint work with Richard Durrett at Cornell). Finally, methods are introduced for Lagrangian models of individual movement in continuous environments and examples shown for how ensemble and Eulerian limits may be derived.

Simon Levin, Princeton University, NJ, USA

Fabio A. Milner

**Models of host-parasite systems in marine environment**

First a description of the interaction of a sea-bass (host) with Diplectanum (a helminth parasite) was presented as a direct cycle with three stages of development of the parasite: egg, larva, parasite. Then, a discrete stochastic model due to Langlais & Silan was described, concentrating on the important specific features of this interaction, especially a nonlinear parasite induced additional mortality of hosts and a differential recruitment of larvae by the hosts, Poisson distributed. Next, a differential model (due to Langlais, Milner, and Patton) was described. It consists of an age-structured linear differential system for the dynamics of eggs and larvae, coupled with a parasite density-structured one for the host population and a continuum of first-order ODE's corresponding to the parasite dynamics within individual hosts. Steady states of the system were discussed, as well as their interpretations. Finally, the model was compared and contrasted with several others found in the literature and some numerical simulation results were presented.

Fabio A. Milner, Purdue University (West Lafayette), IN, USA

Denis Mollison

**Epidemics in populations divided into groups or households**

We consider epidemics with removal ('SIR epidemics') in populations which mix at two levels, analyzing the conditions under which a large outbreak is possible, and the size of such outbreaks when they can occur; in each case comparing our results with the simpler homogeneous mixing case. More precisely, we first consider models in which each infectious individual has a probability $p$ of infecting each other individual within its local group or household, and has a different, typically much smaller, probability $q$ for infecting individuals in other groups. [Our approach also applies to spatial models with a mixture of local (e.g. nearest-neighbour) and global contacts.] We show that, compared with the homogeneous mixing model in which individuals make contacts simply with probability $q$, the local groups have an 'amplification' effect on the basic reproductive ratio $R_T$ of the epidemic: $R_T = b\mu$, where $b$ is proportional to the total number of susceptibles, and $\mu$ depends monotonically on group size. Where the groups are large, and the within-group epidemics above threshold, this amplification can permit an outbreak in the whole population at very low levels of $q$, for instance for $q = O(1/Nn)$ in a population of $N$ divided into groups of size $n$. Conversely, the implication for control strategies is that vaccination should be directed preferentially to the groups with the largest numbers of susceptibles. Finally, we discuss the estimation of our threshold parameter $R_T$ from data on epidemics among households.

Denis Mollison, Heriot–Watt University (Edinburgh), Great Britain
(with Frank Ball (Nottingham) and Gianpaolo Scalia-Tomba (Roma))

Johannes Müller

**Vaccination: individual versus population**

Within the framework of a SIRS-Model vaccination with side effects is considered. These side effects are modeled in such a way that individuals have some risk of to get ill due to the vaccination. The interest of the population is to minimize the prevalence. The vaccination rate to do this is determined.
The aim of an individual is to reduce her/his own risk. This yields a vaccination rate that depends on the prevalence. Thus the bifurcations of the system with variable vaccination rate is analyzed and the prevalence corresponding to the best individual vaccination coverage is determined.
Comparing the two vaccination coverages it turns out that they disagree for some parameter sets. This is important for the design of optimalization problems for vaccination.

Johannes Müller, University of Tübingen, Germany

Ingemar Nåsell

**Stochastic models for endemic infections**

The quasi-stationary distribution, the time to extinction, the invasion threshold, and the persistence threshold are described for the univariate SIS model and for the Ross malaria model. I deal with both numerical methods and results, and with analytical approximations. The thresholds are shown to depend on the population size.

Ingemar Nåsell, KTH, Stockholm, Sweden

Philippe Picard

**The S.I.R. model without martingales**

We consider a general Susceptible-Infected-Removed model for a closed population that satisfies the following conditions.
1. Susceptibles (respectively infectives) are exchangeable.
2. For arbitrary $k$ and $l$, it makes sense to define the probability $q(k,l)$ of the event "Infection is not transmitted from a given set of $l$ (initial or subsequent) infectives within a given set of $k$ susceptibles (i.e. susceptibles at time 0), the two sets being disjoint." For such a model that we call a collective epidemic model, we introduce a new argument, the argument BEFORE-AFTER, in which the state of the population is considered only at times 0 and $T$ ($T$ being the end of the epidemic). This argument leads easily to the construction of the distribution of the size of the epidemic and of

its severity. This argument works all the same for many generalizations of the initial unidimensional model.

Philippe Picard (Lyon, France), C. Lefèvre (Bruxelles, Belgique)

Sylvia Richardson

**Modelling a marker of HIV progression by a Hidden Markov process**

Markov chain models of the natural history of HIV play an important part in AIDS modelling. Transition rates can easily be evaluated when the classification of a subject into a "state" (discrete) is unambiguous; but in many cases the staging is defined on the basis of a discretization of values of (continuous) markers which are subject to measurement (or misclassification) errors and short-time-scale fluctuations.
This leads us to consider the framework of Hidden Markov models where a combined (hierarchical) model for both disease progression and measurement process is formulated that allows joint estimation of parameters of both processes. Estimation of the quantities of interest can be carried out via stochastic algorithms of the class of Markov Chain Monte Carlo methods (e.g. Gibbs sampling). By this approach, it is possible to simulate the joint posterior distribution of both measurement and disease parameters.
This approach was applied to the modelling of the progression of HIV in the San Francisco Mens' Health Study. Transition rates corresponding to Hidden Markov models with 7 states (both with and without backflows and direct transitions to AIDS) were estimated and the results were compared to previous analyzes of the same data set.

Sylvia Richardson, INSERM, Villejuif, France
in collaboration with C. Guihennenc, University of Paris V, France and I.M. Longini, Emory University, Atlanta, USA

Gianpaolo Scalia-Tomba

**Obtaining asymptotic results for final size of household epidemics by embedding constructions**

Consider a population composed of many small households. Let infection spread in this population according to standard SIR dynamics with a typically high infection probability for internal household contacts and a much smaller probability for contacts with individuals outside the household. At this meeting, Denis Mollison has presented the intuitive, largely graph theoretical arguments that yield the probability of large outbreaks and the final size possibilities, with extensions to situations where also the households grow large or where their sizes are determined by chance ("pigs on the line"). In my talk,

embedding constructions (see e.p. Scalia Tomba (1988) LNBM 86, 189-196) are presented, that allow the derivation of normal approximations for the final size distribution. These constructions require the definition of a family history process, that describes the effects, in terms of numbers of infectives and total infectious time, of "external" infection on a household, the representation of the population process as a sum of household processes and, finally, the construction of the epidemic generations as an infection where the infectivity produced by the population is used instead of the assumed "external" source. In this way, final size is achieved as the fixed point of the iteration. Various estimates and approximations now yield the derived asymptotic distribution. Similar constructions, based on processes counting various types of subgraphs, are available for the Reed Frost type formulations of the household model.

Gianpaolo Scalia Tomba, University "La Sapienza", Roma, Italy

Dieter Schenzle

**How to describe the New York measles data?**

In a series of papers Schaffer, Olsen and Tidd claim:

1. Measles incidences in NYC from 1928-1964 were chaotic.
2. The simple SIR model with seasonal contact rate provides a better description of these data than a more detailed age-structured model.

However, the nonlinear forecasting algorithm (adopted from Fugihara & May) only reveals that the first half of the final series is different from the second one. And the seasonal SIR model yields chaotic incidence patterns only if importation of infection into NYC is assumed to be less than 50 per year. Moreover this model does not fit the monthly data and it implies unrealistically that by age 1.9 years half of all children should have had measles. In these respects much better results are obtained with an age-structured model considering increased measles transmission within schools. So far this is also the only model that can explain why the observed "seasonal" contact rate has a different time course in years with low and high measles incidence. Therefore, rather than looking for chaos, one should try to explain the changing measles incidence pattern in NYC by the massive demographic changes during 1928-1964.

Dieter Schenzle, University of Tübingen, Germany

Birgitt Schönfisch

**Cellular Automata as Epidemic models**

We investigated the effects of introducing migration (mixing) into the classical Greenberg-Hastings automata. The time patterns, i.e. the proportion of infectious, show large

amplitude oscillations. These amplitudes and the periods are studied in detail with and without migration. To investigate the spatial patterns measures are introduced that distinguish between wavelike, structured patterns (without migration) and apparently 'diffusive', not ordered patterns (with migration). Simulations with short- and long-range migration of different strength are carried out. Conclusions are that even smallest perturbations from the deterministic state lead finally to the same pattern as those resulting with high migration. There seems to be almost no difference between the effects of short- and long range migration. If a high number of infectious neighbors is necessary for infection additional phenomena occur.

Birgitt Schönfisch, University of Tübingen, Germany

Hal Smith

**The SEIR epidemic model**

The deterministic SEIR model is considered with both constant and periodic contact rate. In the case of constant contact rates, the recent proof of M.Li & J. Muldowney that the endemic equilibrium is globally attracting is described. In the case of a seasonally varying contact rate, we show that there exist many simultaneously stable subharmonic solutions of different periods.

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**The implementation of standard theory of childhood diseases**

I shall try to describe the attempt being made in Denmark to use a model approach for epidemic childhood diseases, in the surveillance of the vaccination program. Data available, and the statistical analysis of it, is commented on, and the planned implementation of various models is described.

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