

Theoretical Epidemiology

SPM/CIM, Hotel Quinta das Lágrimas, Coimbra, 16 January

No dia 16 de Janeiro de 2010 decorreu no Hotel Quinta das Lágrimas uma jornada de trabalho SPM/CIM em Epidemiologia Teórica. A organização esteve a cargo de Carlota Rebelo do Departamento de Matemática da Faculdade de Ciências e do Centro de Matemática e Aplicações Fundamentais da Universidade de Lisboa.

Estiveram presentes 25 participantes: matemáticos, biólogos, físicos, veterinários. Os participantes provinham de Braga (2), Viana do Castelo (1), Porto (4), Aveiro(1), Coimbra (3), Lisboa (12), Évora (2). Mais de um terço dos participantes eram alunos de doutoramento ou de mestrado.

O programa foi o seguinte:

11h30 **Integrative epidemiology**, Gabriela Gomes (Instituto Gulbenkian da Ciência)

12h15 **Stochastic models of infection dynamics**, Ana Nunes (Centro de Física Teórica e Computacional)

13h00 Lunch

14h30 **Age-dependent immune response and antigenic drift in influenza**, Andrea Parisi (Centro de Física Teórica e Computacional)

15h00 **High rates of reinfection tuberculosis: the selection hypothesis**, Paula Rodrigues (Dep. de Matemática da Fac. Ciências e Tecnologia da Universidade Nova de Lisboa e CMA)

15h30 Coffee Break

16h00 **Deciding between doing something or nothing to prevent rare and highly uncertain events**, Cláudia Codeço (Oswaldo Cruz Foundation and Visiting scientist at Instituto Gulbenkian da Ciência)

16h30 **Prospects for malaria elimination**, Ricardo Águas (Instituto Gulbenkian da Ciência)

17h00 **Discussion**, moderator: Gabriela Gomes (IGC)

Durante o debate, moderado por Gabriela Gomes, foram levantadas várias questões. Começou por se fazer um balanço da jornada concluindo-se que se gerou potencial para futuras colaborações. Sugeriu-se que num futuro evento de epidemiologia teórica estivessem também presentes modelos discretos. Referiu-se o problema enorme que é ter acesso a dados para validar os modelos em Portugal. Mencionou-se que seria importante fazer divulgação de assuntos ligados à epidemiologia teórica. Por fim, vários participantes pediram para que fossem colocados no site do evento os slides mostrados nas conferências e que fosse distribuída entre os participantes uma lista com os contactos de todos.

Agradecimentos

A organizadora agradece à SPM e ao CIM e em especial ao Professor Peter Gothen o convite para organizar esta sessão. Também agradece à Gabriela Gomes a ajuda na organização científica da jornada.

Um agradecimento especial à S.D. Helena Gonçalves do CIM por todo o apoio na organização.

Aos oradores e todos os participantes um sincero obrigado.

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Maria Carlota Rebelo Gonçalves

ABSTRACTS

Integrative Epidemiology

Gabriela Gomes

While biological experimentation unravels the molecular basis of living organisms in controlled settings, epidemiological observation collects evidence for factors associated with disease in natural environments. The effective transfer of knowledge between these two branches of biomedical sciences is critical to the definition of research priorities in terms of expected impact on human health. I will discuss the role of mathematical models in bridging biology and epidemiology.

Stochastic models of infection dynamics

Ana Nunes

During the last decade, more sophisticated approaches building on the traditional SIR and SEIR models have brought considerable advances in understanding and selecting some of the fundamental ingredients of the complex dynamics of infectious diseases [1]. This body of work belongs to an essentially deterministic framework, where demographic stochasticity plays a secondary role, that of sustaining small amplitude fluctuations around the deterministic system's equilibrium that follow the natural frequency given by the local linear approximation [2].

In population biology, stochasticity comes from the discrete interactions and the disordered interaction networks, and fluctuations and finite size effects in general are much more important than in typical physical systems. Indeed, recent results show that for realistic population sizes, the behaviour of predator-prey and of epidemic or endemic infections may be driven by the combined effect of fluctuations and correlations.

In [3], a general mechanism of resonant amplification of demographic stochasticity was proposed to describe the cycling behaviour of prey-predator systems. This resonant mechanism is generic for a class of stochastic systems that includes the majority of the classical models of diseases that confer either lifelong or temporary

total immunity, and it was shown in [4] that it plays a major role in describing the patterns of recurrent epidemics of childhood infectious diseases. In [5], that approach was extended by adding an ingredient which is missing in standard epidemic models, the 'mixing network' through which infection may propagate. It was shown that correlations have a major effect in the enhancement of the amplitude and the coherence of the resonant stochastic fluctuations, providing ordered patterns of recurrent epidemics, whose period may differ significantly from that of the small oscillations around the deterministic equilibrium.

We shall review the main results of [1-5], and then explore analytic models where the assumptions of random mixing of the population and/or of constant recovery rate during the infectious period are relaxed, and see how this implies important corrections to the amplitude and dominant frequency of the stochastic fluctuations [6-8]. The finding that in finite, discrete populations internal noise together with correlations produces sustained incidence oscillations of significant amplitude all over the parameter region that includes childhood infectious diseases is of importance for the long-standing controversy in epidemiology and ecology as to the driving mechanisms of the pervasive noisy oscillations observed in these systems.

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[2] C. T. Bauch and D. J. D. Earn, Transients and attractors in epidemics, *Proc. R. Soc. Lond. B* 270, 1573-1578 (2003)

[3] A.J. McKane, T.J. Newman, "Predator-Prey Cycles from Resonant Amplification of Demographic Stochasticity", *Physical Review Letters*, 94, 218102 (2005);

[4] D. Alonso, A. J. McKane, M. Pascual, "Stochastic amplification in epidemics", *J R Soc Interface* 4, 575-82 (2007).

[5] M. Simões, M. Telo da Gama and A. Nunes, "Stochastic fluctuations in epidemics on networks", *J R Soc Interface* 5, 555-66 (2008).

[6] Ganna Rozhnova & Ana Nunes, "Fluctuations and oscillations in a simple epidemic model", *Phys. Rev. E* 79, 041922 (2009) & *Virtual Journal of Biological Physics Research* 17 (9), May-1 (2009)

[7] Andrew J. Black, Alan J. McKane, Ana Nunes & Andrea Parisi, "Stochastic fluctuations in the susceptible-infective-recovered model with distributed infectious periods", *Phys. Rev. E* 80, 021922 (2009).

[8] Ganna Rozhnova & Ana Nunes, "Cluster approximations for infection dynamics on random networks", Phys. Rev. E 80, 051915 (2009).

Age-dependent immune response and antigenic drift in influenza

Andrea Parisi

Human Influenza A is characterized by different subtypes, defined by the antigenicity of the corresponding Hemmagglutinin protein which is recognized by the host immune system. When a human host immunized by a certain strain of influenza is infected by a new influenza virus, the immune system is able to promptly respond to the aggression provided the virus presents only a few mutations with respect to the previous immunizing strain. In general a number of mutations is necessary in more than one antigenic site in order for the immune system not to be able to recognize the virus. So, on the one hand immune escape is possible when a number of mutations occurs; on the other hand, any new mutation of an infecting virus will still be recognized by the immune system and will hardly survive in the host. Hence the mechanism through which new influenza strains can escape the immune response and spread, leading to the occurrence of an antigenic drift is still not understood. Here we propose a possible origin for such mechanism. Some studies have underlined the fact that the immune response of adult individuals is more developed than that of young individuals. In particular, young humans with age up to a few years, show a high degree of specificity in their immune response. We explore how an age-dependent immune response in humans can lead to interesting epidemic dynamics with synchronized subsequent epidemics of mutants in both the adults and children populations.

High rates of reinfection tuberculosis: the selection hypothesis

Paula Rodrigues

Recent molecular epidemiology studies indicate that rates of reinfection tuberculosis are higher than rates of new tuberculosis. We propose the selection hypothesis to

reconcile these observations with the consensual view that infection confers some degree of protection that reduces the individual susceptibility to reinfection. We postulate that some individuals are a priori more likely to develop the disease because they are more exposed or have some form of innate susceptibility. As infection tends to affect individuals at higher risk, the distribution of recovered individuals is skewed towards higher susceptibility inating the rates of reinfection. The hypothesis is formulated mathematically and confronted with data from six regions representing distinct transmission intensities distributed worldwide. We retrieve natural history parameters in agreement with previous estimates and propose a criterion for further validation.

Deciding between doing something or nothing to prevent rare and highly uncertain events

Cláudia Codeço

Concerns regarding natural or induced emergence of infectious diseases have raised a debate on the pros and cons of pre-emptive vaccination of populations under uncertain risk. In the absence of immediate risk, ethical issues arise because even smaller risks associated with the vaccine are greater than the immediate disease risk (which is zero). The model proposed here seeks to formalize the vaccination decision process looking from the perspective of the susceptible individual, and results are shown in the context of the emergence of urban yellow fever in Brazil.

Prospects for malaria elimination

Ricardo Águas

A characteristic of *Plasmodium falciparum* infections is the gradual acquisition of clinical immunity resulting from repeated exposures to the parasite. While the molecular basis of protection against clinical malaria remains unresolved, its effects on epidemiological patterns are well recognized. Accumulating epidemiological data constitute a valuable resource that must be intensively explored and interpreted as to effectively inform control planning. Here we apply a mathematical model to clinical data from eight endemic regions in sub-Saharan Africa. The model provides a quantitative framework within which differences in age distribution of clinical disease are assessed in terms of the parameters underlying transmission. The shorter infectious periods estimated for clinical infections induce a regime of bistability of endemic and malaria-free states in regions of mesoendemic transmission. The two epidemiological states are separated by a threshold that provides a convenient measure for intervention design. Scenarios of eradication and resurgence are

simulated. In regions that support mesoendemic transmission, intervention success depends critically on reducing prevalence below a threshold which separates endemic and malaria-free regimes.