Information and Communication Technologies

Developing the Framework for an Epidemic Forecast Infrastructure

Work Package 1.

Deliverable 1.4

Models of spread, impact and evolution of vector-borne pathogens, including the demography and ecology of host species.

Annual Progress Report

2011.02.01 to 2012.01.31

CONTENTS

Introduction

The project objectives of WP1 for the third period of the project were concerning the modeling of population contact networks, the structure of interacting populations and the effect of seasonality. In particular, WP1 was expected to study the spread, impact and evolution of vector-borne pathogens. The work carried in this third period produced many major publications that represent the state-of-the-art in the field. WP1 activities have produced a wealth of scientific results that are reaching toward future deliverables and bridging the activities of other Work Packages. Results on how the hosts demographics, different pathogen strains, non linear transmission processes etc. affect the host population are providing inputs to the computational modelling platform in WP4 and at the same time are triggered by the data collected in WP3.

In this deliverable, the several contributions of partners involved in the WP1 are reported: Gulbenkian Institute (FGC-IGC), London School of Hygiene and Tropical Medicine (LSHTM), Tel Aviv University (TAU), University of Lisbon (CMAF).

Gulbenkian Institute

This work has been inspired mainly by malaria and dengue although some of the results are more generally applicable. We first studied aspects of the dynamics of malaria infection and immunity in the human host, specific to the two most important human malaria parasites: *Plasmodium falciparum* and *P. vivax*. We have then proceeded to study the dynamics of the vector.

A major challenge in theoretical studies with *P. falciparum* is posed by the expression pattern of variant surface antigen (VSA) families that allow pathogens to evade immune responses and establish chronic and repeated infections. We have used the available molecular and serological evidence regarding VSAs to formulate a mathematical model of the evolutionary mechanisms shaping VSA organization and expression patterns (1). We have constructed a two-level selection model integrating the transmission dynamics of specific VSA subsets between hosts with their competitive interactions within hosts. The model includes so-called dominance blocks that characterise the competitive potential of specific VSA subsets. It predicts an evolutionary stable balance between inter-clonally conserved dominance blocks that are highly competitive within-host and diverse blocks that are favoured by immune selection at the population level (Figure 1). The application of a monotonic dominance profile to VSAs encoded by a gene family generates two opposing selective forces and, consequently, two distinct groups of genes emerge in adaptation to naïve and partially immune hosts, respectively.

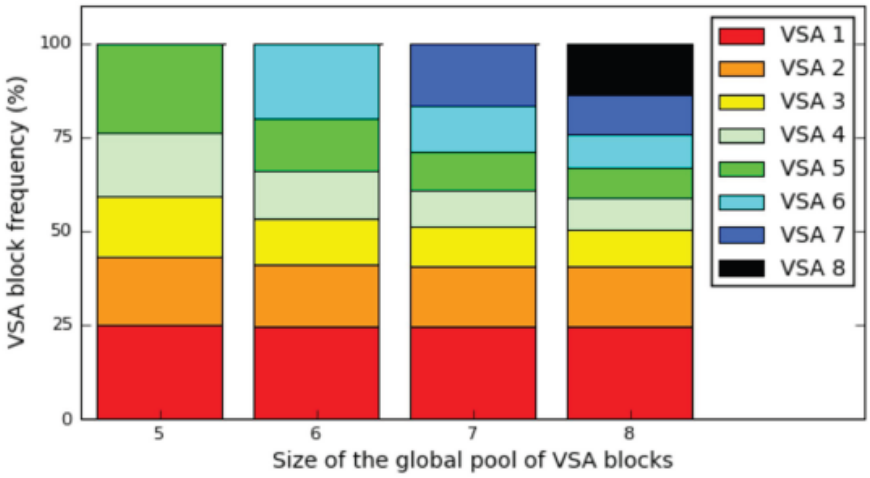


Figure 1: VSA prevalence in the parasite population at endemic equilibrium for increasing sizes of the VSA pool. Increasing the size of the VSA pool, diversity accumulates in the low-dominance VSAs (by reducing the frequency of each such VSA) while the frequency of specific high-dominance VSAs remains unchanged. With more VSAs available there is a disproportionately increase in the diversity of low-dominance VSAs.

Although *P. falciparum* is the main cause of malaria deaths, *P. vivax* is a significant cause of morbidity whose importance is increasing with the realization that current interventions have much more impact on *P. falciparum* than on *P. vivax*. We developed a mathematical model representing the transmission dynamics of *P. vivax* (2) by adding new elements to the foundation laid by previous work in *P. falciparum*. Our simulations confirm that therapy can reduce *P. falciparum* prevalence to a much greater extent than *P. vivax* prevalence. *P. vivax* elimination is predicted to be unstable, meaning that any perturbation in the system would drive it back to the endemic state. Differences in age profiles of clinical malaria can be explained solely by *P. vivax*'s ability to relapse, which accelerates the acquisition of clinical immunity (Figure 1). Relapse also serves as an immunity boosting mechanism that prevents onsets of malaria episodes in older ages. *P. vivax* transmission can subsist in areas of low mosquito abundance and is robust to drug administration initiatives due to its relapsing ability, making it inconvenient and cumbersome, yet less lethal than *P. falciparum*.

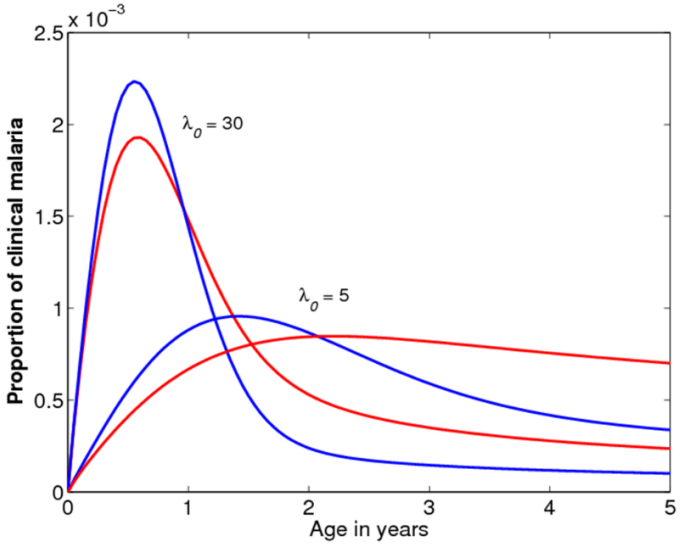


Figure 2: Age profiles for two transmission settings. Clinical *P. vivax* malaria age profiles (blue lines) compared with *P. falciparum* profiles (red lines) for equal risks of infection.

The models described above have greatly simplified the dynamics of the vector, which we now elaborate. Malaria is transmitted among humans by *Anopheles mosquitos, while dengue is transmitted by Aedes mosquitos.* In both cases, successful development of the microparasite in the mosquito depends on environmental factors, such as temperature and humidity, and biological factors that determine whether the mosquito becomes infected and survives long enough to allow the parasite to complete its cycle and transmit to the next human host. While the treatment of environmental factors overlaps with the deliverable "Models of disease transmission under seasonality and other external drivers", here we focus on biological factors.

Recent research is showing that insects maintain many symbiotic interactions with microorganisms that protect them against natural microparasites. These findings have inspired the development of biological control interventions whereby mosquitoes artificially adapted to carry symbionts that block infection by human pathogens would be released in the field to replace natural vector populations. We have developed mathematical models to inform the design of these interventions (3). In particular, we have addressed the control of dengue transmission by releasing *Aedes aegypti* mosquitoes carrying the symbiont bacterium *Wolbachia* (4). Possible scenarios are illustrated in Figure 3.

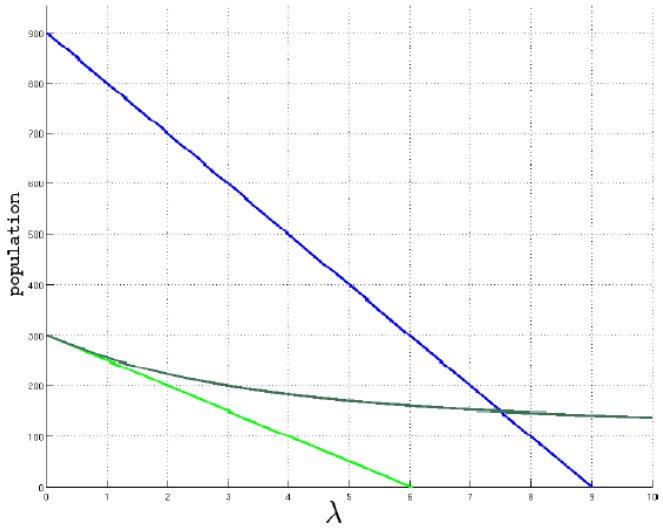


Figure 3: Equilibrium population of wild type insects (blue), and of *Wolbachia*-carrying insects with either homogeneous (light green), or heterogeneous susceptibility reduction (dark green).

This work has been supported by the Epiwork project for the 50% of the effort.

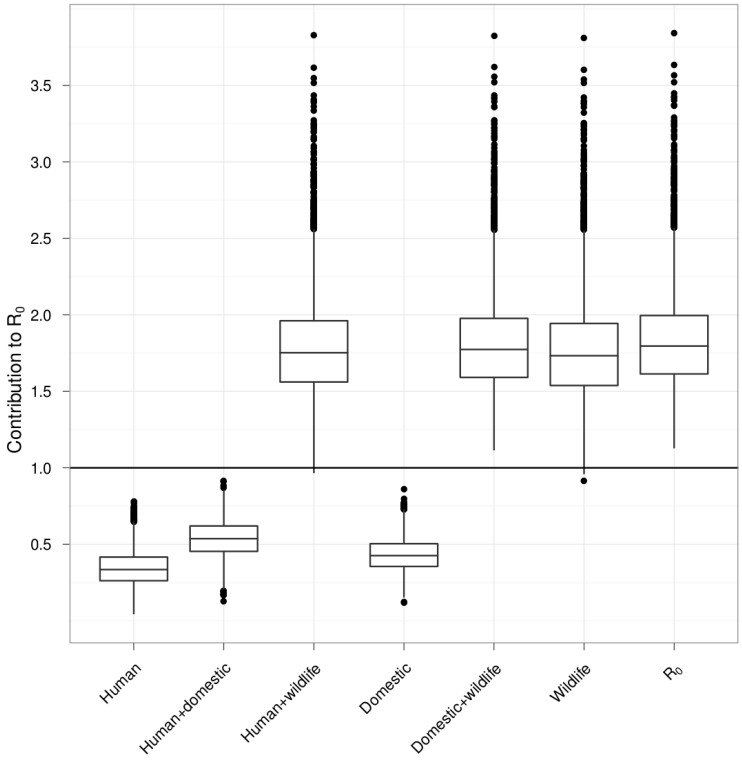
Publications:

1. van Noort SP, Nunes MC, Weedall GD, Hviid L, Gomes MGM (2010) Immune selection and within-host competition can structure the repertoire of variant surface antigens in Plasmodium falciparum - A mathematical model. *PLoS ONE* **5**(3):e9778.
2. Aguas R, Ferreira MU, Gomes MGM (2012) Modeling the effects of relapse in the transmission dynamics of malaria parasites. *J Parasitol Res*:921715.
3. Gomes MGM, Ceña B, Pessoa D, Lopes JS, Rebelo C, Codeço C, Struchiner CJ, Marialva M, Teixeira L. Measures and impacts of intervention effects in host-pathogen systems. (In preparation 2012).
4. Mendes C, Gomes MGM. Effect of heterogeneity in invasions by Wolbachia. (In preparation 2012)

London School of Hygiene and Tropical Medicine

Human African Trypanosomiasis is a deadly neglected tropical disease, spread by the bite of the Tsetse fly. The West African form of the disease has traditionally been regarded as a human disease, whereas the rarer East African form is thought to be a zoonosis. We developed and fitted a parsimonious mathematical model to detailed prevalence data from vectors and multiple potential hosts from rural Cameroon, with the aim of determining the contribution of different hosts to the overall basic reproduction number (the average number of secondary cases arising from a case in the absence of any constraints). The findings were striking: transmission amongst humans alone would not be sufficient to maintain transmission (basic reproduction number less than 1 – Fig 3), and the wildlife reservoir, particularly certain wild primates, seems essential to maintain transmission. Extensive sensitivity analysis confirmed these results, and suggest that, contrary to prior beliefs, HAT may also be predominantly a zoonosis. This has profound implications for public health, as it suggests that targeting humans alone (which is the current strategy) will not be sufficient to control the disease. The paper is in review at *Science* [2]. This work was largely funded by EPIWORK.

Fig 3. Contribution of different host species to overall basic reproduction number (R_0) for HAT.



Tel Aviv University

Modelling transmission of vector-borne pathogens shows complex dynamics when vector feeding sites are limited

Kershenbaum,A, Stone,L., Kotler,B. and Blaustein L.

The relationship between species richness and the prevalence of vector-borne disease has been widely studied with a range of outcomes. Increasing the number of host species for a pathogen may decrease infection prevalence (dilution effect), increase it (amplification), or have no effect. We derive a general model, and a specific implementation, which shows that when the number of vector feeding sites on each host are limiting, the effects on pathogen dynamics of host population size are more complex than previously thought. The model examines vector-borne disease in the presence of different host species that are either competent or incompetent (i.e. that cannot transmit the pathogen to vectors) as reservoirs for the pathogen. With a single host species present, the basic reproductive ratio R_0 is a non-monotonic function of the population size of host individuals (H), i.e. a value $\hat{H}$ exists that maximises R_0. Surprisingly, if $H > \hat{H}$, a reduction in host population size may actually increase R_0. Extending this model to a two-host species system, incompetent individuals from the second host species can alter the value of $\hat{H}$, which may reverse the effect on pathogen prevalence of host population reduction. We argue that when vector-feeding sites on hosts are limiting, the net effect of increasing host diversity might not be correctly predicted using simple frequency-dependent epidemiological models.

Our analysis shows how the presence of additional, reservoir-incompetent, host animals can affect the basic reproductive ratio R_0 both by dilution and amplification. Surprisingly, R_0 varies nonmonotonically under a wide range of conditions. First, we considered a system with only a single host, and no incompetent alternatives for the vectors to feed upon. In this system, R_0 peaks at the boundary between saturated feeding sites (more vectors than sites) and excess feeding sites (more sites than vectors). This has important and counter-intuitive applications for the popular, but not always successful pest control methods of reducing the number of disease host animals. This strategy can reduce R_0 only if the initial host population is below this boundary level. However, if the number of host animals is higher than this boundary level, reducing their numbers is likely to increase the risk of disease outbreak. While this result may at first seem counterintuitive, the explanation is straightforward; at high host population levels, vector loads are small, and so an infected individual will pass on the infection only to a small number of vectors. If feeding sites are saturated, the same infected individual will pass the infection to the maximum possible number of vectors each feeding session. This difference in the number of vectors infected by a host will be translated directly into a change in R_0.

The results we have shown here demonstrate the importance of incorporating specific details of disease ecology into predictive models. Vector transmission is far from the approximation of mass action [35] and predictions made on the basis of more simplistic models may be misleading. In particular, we predict a potential detrimental effect of naïve host-control techniques at certain levels of host abundance. Specific
34predictions of when host-control will produce the desired reductions in disease risk, and validation of those predictions, will be major future challenges.

Predation risk can drive cycles in zoonotic disease prevalence

The recent increase in human cases of leishmaniasis in northern Israel has been accompanied by dramatic anthropogenic changes in the landscape that affect the behavioral ecology of one of its mammalian reservoirs, the rock hyrax, *Procavia capensis*. Hyraxes migrate from refuge to refuge, presumably following forage availability, but their migration patterns are strongly affected by the availability and spacing of the rock piles that form their den sites and give them protection from predators. We therefore expect changes in predation risk to influence the ability of hyrax groups to migrate from site to site. We combine mathematical metapopulation models of hyrax behavioral ecology, as well as compartmental models of disease dynamics, to investigate the effect of microhabitat alteration and varying perceived predation risk on disease incidence. Our models indicate that such fine-scale alterations in predation risk can have surprising effects on pathogen prevalence, leading to the emergence of epizootic cycles. Regular (predictable) cycles and chaotic (unpredictable) cycles may occur as predation risk is reduced. Under some conditions, cycles may result from very small changes in predation risk or environmental conditions. Our models show regions of sensitive dependence on environmental and predatory conditions, leading us to predict the possibility of the emergence of chaotic disease cycles as the result of small environmental disturbances.

In the underlying resource model, the availability of food at location x and at time t, is specified by the function $F(x,t)$ describing resource growth and consumption, where:

[redacted]

Here resource growth is taken to follow an appropriate model such as logistic or exponential (defined by parameters θ and ϕ) and the animal consumption is specified by ε.

We consider foraging location choice to be re-evaluated by the animals every morning, so the natural time unit for t is measured in days. Consider three potential refuges from which the animals must choose where to forage as shown in Figure 2.

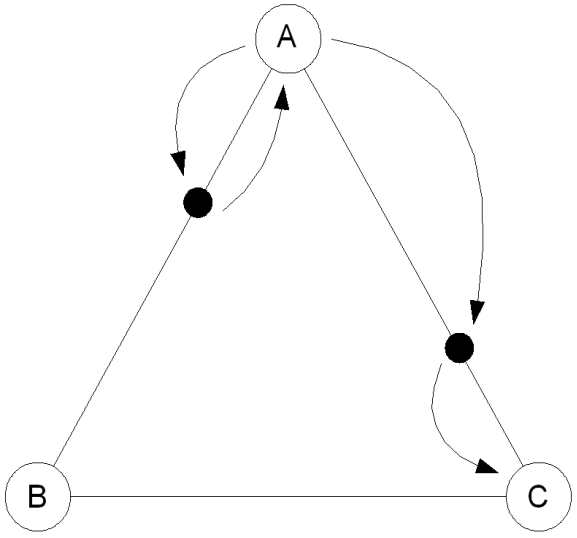


Figure. Foraging choices with three potential dens. Central place foragers will choose the optimum foraging location from the perspective of their current den. If they choose a point closer to their current den (as shown here between A and B), they will return to the same refuge. However, if the optimal foraging point is far from their current den (as shown here between A and C), the animals will choose to return to the alternative refuge.

We assume that the animals will return to the nearest refuge once they have finished foraging – this will often, but not always, be the refuge from which they departed. As the hyraxes leave their refuge and move about to find and exploit resources, the optimal feeding point may at some time become one that is closer to a different refuge than it is to the initial home refuge. Thus, we can expect that under certain conditions, the animals will move from one refuge to another, i.e. migrate. This is a key feature of multiple central-place foragers: they are prepared to move from one den to another, using the new den as a base for future foraging forays. Solving for Q for a variety of parameter values for γ and δ, we find four possible behaviours exist: (a) the animals stay in the same location, (b) they alternate between two locations, (c) they migrate between different locations in a cyclic manner, and (d) they migrate between different locations in an aperiodic manner. The distribution of these behaviours in γ-δ parameter space is shown in Figure 3.

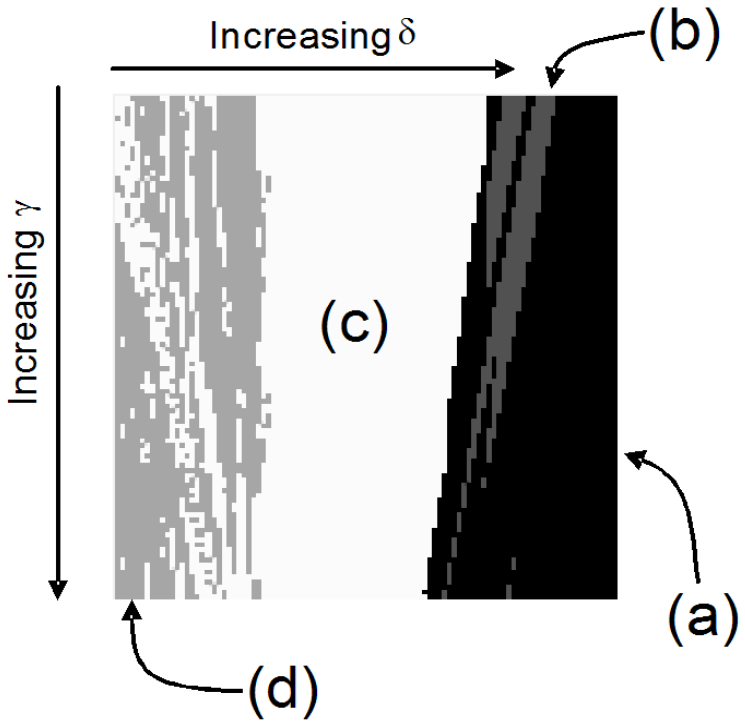


Figure 3. Four different possible behaviours in γ–δ parameter space. As the animals become less fearful (moving from right to left), the behaviour changes from remaining in a single den (a), through a small region where they alternate between two dens (b), and into a behaviour of cyclic use of three dens, periodically (c) and aperiodically (d). The chart shows γ and δ varying from 0 to 1.

In some regions of parameter space (e.g. Region a), the animals behave in a conservative manner where they are unwilling to stray far from their dens and therefore unlikely to move from one den to another. However, if the animals show more willingness to forage at a distance, or if suitable dens are closer together, migration more often takes place (Regions b & c). Additionally, there are regions of parameter space (Region d) where the model is highly unstable, and a small change in the response to predation risk or refuge spacing may produce sudden and unexpected changes in movement patterns. These unstable regions indicate chaotic behaviour, within which accurate predictions are impossible. Such changes in migratory behaviour as demonstrated in the model will also affect the distribution of hyraxes across the landscape and the connectivity among subpopulations.

Our second model considers how migration affects infection dynamics. Two populations with enzootic infection may infect each other providing they are located close to each other physically, within the range of the disease vector. By combining the population migration model with a pathogen transmission model, we generate a set of patch populations with migration between them, thus generating a metapopulation system where the subpopulations can infect each other. Adapting a simple SIR (Susceptible-Infected-Recovered) model of infection within a reservoir population, we add a term for infection between the two populations that depends on the vector transmission between them:

Here, S, I and R represent the compartments of susceptible, infected and recovered individuals respectively, b is the birth rate, d the death rate, g the recovery rate, and β is the infection rate. In addition, we add the cross-infection term $\zeta\psi SI'$ where ζ is a coefficient of infection between the two populations, I' is the number of infected individuals in the other population, and ψ a measure of the distance between them as a barrier to cross infection. In the case of leishmaniasis, where infection is transmitted by a vector species, the nature of the infection term $\zeta\psi SI'$ may be complex. We assume that transmission is caused by vector or host movement between den sites, and not by infected vectors remaining in a vacated site. This is consistent with what is known of the sandfly life cycle, in which the period from blood meal to oviposition, and the life expectancy of females, is short. Since the sandfly is a poor flyer, we assume that the probability of transmission via an infected sandfly is proportional to the inverse square of the distance r between the infected den and the non-infected one.

The infection rate can be approximated as being proportional to SI since the sandfly vector is unlikely to show preference for individuals amongst the hyrax hosts. Each population is defined by the same set of equations and parameter values, since the cross-infection between them is symmetrical. However, we introduce a small amount of infection ($I_0<<1$) to just one population at the start of the simulation. The values used in these simulations were: $b=d=0.01$, $\beta=0.3$, $g=0.2$, $\zeta=0.2$. The birth rate b of 1% per day, or 3.65 offspring per year corresponds to a single annual litter size of ~7, rather higher than, but still in line with, the estimate of 3-4 given by Mendelssohn (1965). While the values for β and ζ used for this part of the simulation are arbitrary, we later vary these parameters through their entire range (0-1) to explore their effect on the infection dynamics.

By combining the SIR model with the migratory model given above, we can see what happens when two reservoir populations move from den to den - we use the first (migration) model to generate the movement patterns that are used as an input to the second (disease) model. We emphasise that our focal species forages and migrates as a unified group, so the flow of individuals can be treated in a simple manner. The distance between the populations varies with time, as we allow each population to move between den sites.

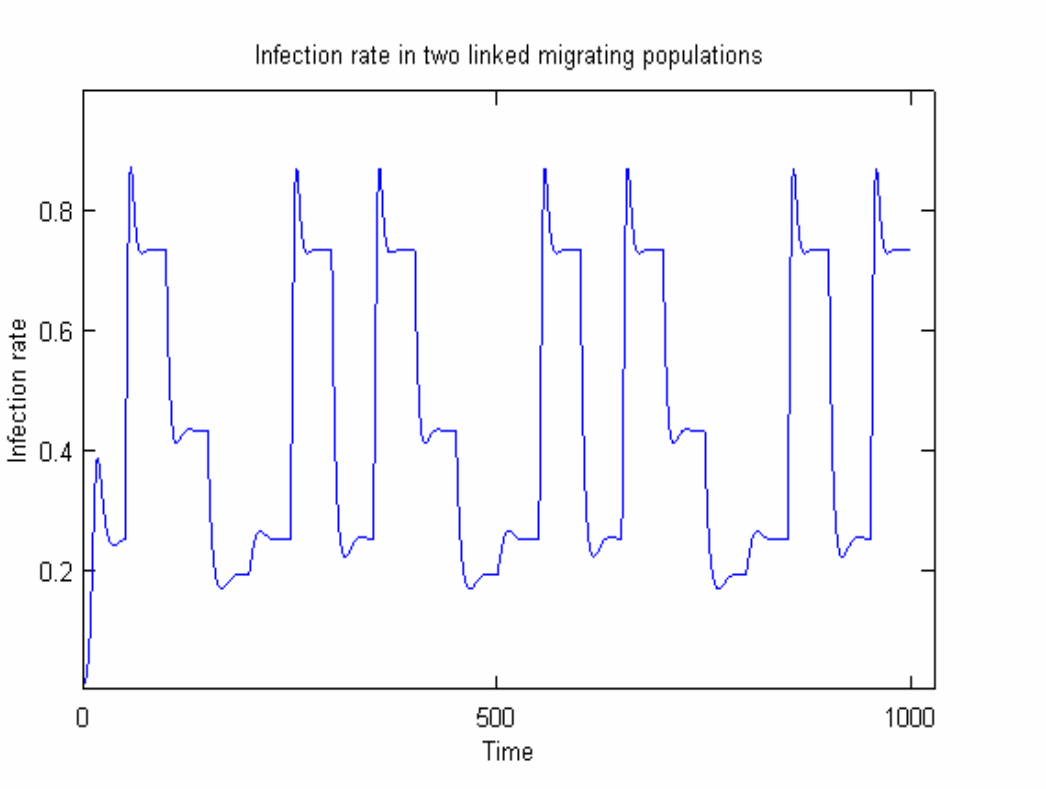


Figure 4 Epidemic behaviour of model with time, in region "c". When the distance between the two dens varies regularly, the resulting pathogen prevalence dynamics show epidemic peaks when the populations approach each other.

These models demonstrate how small variations in the predator-prey balance, and fine-scale habitat disruption, can lead to a wide variety of possible outcomes of the disease dynamics. In particular, the opening of migratory corridors for the reservoir species by the inadvertent construction of suitable habitats between existing populations, or the enabling of existing corridors by the reduction in perceived predation risk, can result in striking epidemic cycles, where a stable enzootic infection was previously observed. We used the models to explore two qualitative properties of this system. First, we showed that migration of the animals is sensitive to the spacing of suitable refuges, and to the willingness of animals to venture far from the refuges. At some spacing, migratory behaviour may become complex, or even chaotic. Second, we showed that the complex migratory behaviours of two subpopulations are likely to produce epidemic peaks in each one due to the varying infective load from one population to the other.

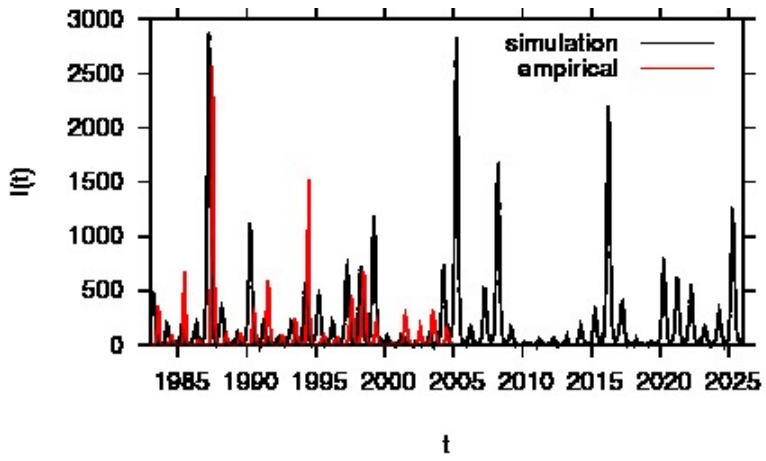
The importance of metapopulation modelling for the understanding of disease dynamics has long been emphasised, and the mathematical basis of such systems has been closely examined. However, these treatments place an emphasis on disease invasion thresholds, and rarely consider the factors behind the existence of disease cycles. In addition, the specific behavioural features of migration patterns are not usually incorporated into such models. We have shown that behavioural modifications can have a profound effect on disease dynamics, and should be incorporated into such metapopulation models, particularly where migration behaviour may be strongly influenced by community dynamics. Our chosen focal species, the rock hyrax, shows particularly complex movement patterns because of its nature as a multiple central-place forager. While central-place foraging is commonplace, only a few species have so far been identified as foraging from multiple den sites; examples include the spider monkey *Ateles geoffroyi*, and Atlantic salmon *Salmo salar* (Steingrimsson & Grant, 2008). For this reason, our model has importance beyond the specific instance of the hyrax-leishmaniasis system, and raises relevant issues where host species migratory behaviour is a complex result of multiple environmental influences.

Kershenbaum,A, Stone,L., Kotler,B. and Blaustein L. ISRAEL JOURNAL OF ECOLOGY & EVOLUTION, Vol. 56, 2010, pp. 281–295

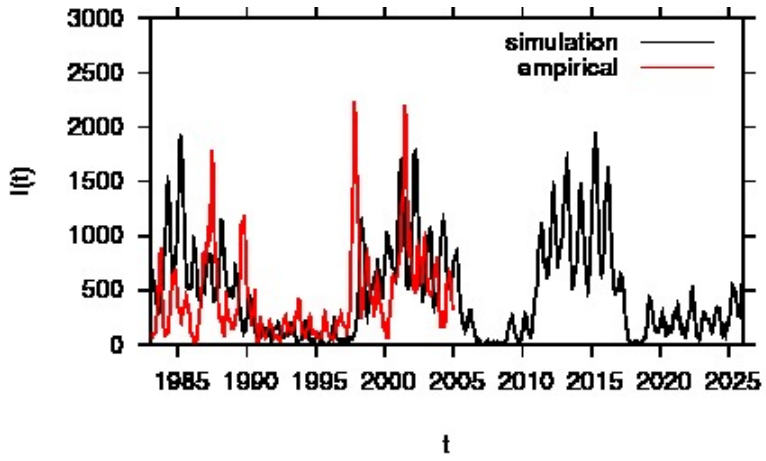
University of Lisbon

The influence of seasonality and import on multi-strain models, based on dengue fever as a test case, has been investigated. The dynamics of Northern Thailand shows good agreement with deterministic models, whereas the large area of the capital, Bangkok, has a much noisier dynamics, seasonality playing less of a role, but import is more important than in the North (Aguiar, Ballesteros, Kooi, Stollenwerk, JTB 2011). Since dengue hemorhagic fever (DHF) is a clear clinical picture, the present modelling and data analysis gives a better picture than for example influenza, for which notification data have turned out to be much less reliable.

Chiang Mai:

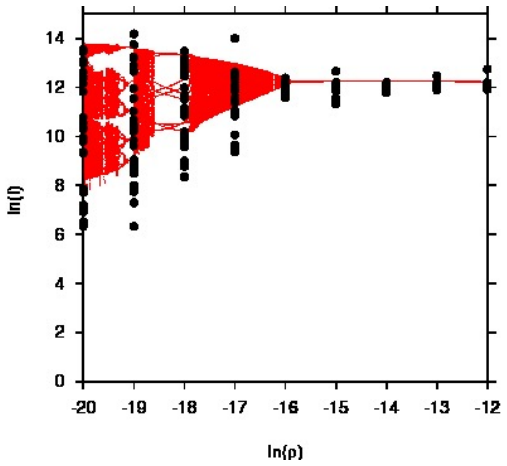


Bangkok:



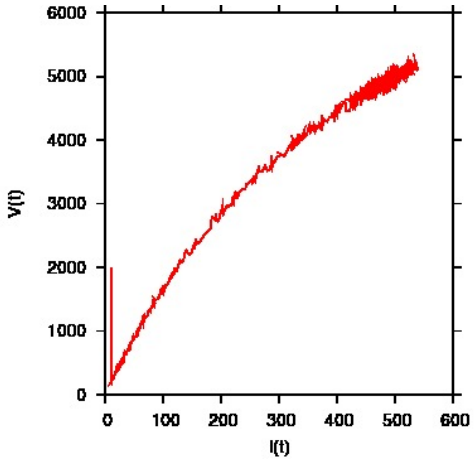
When comparing data and models, again for the test case of dengue fever in Thailand and surrounding countries, the deterministic skeleton and its bifurcation structure describes well the dynamics of data time series, especially in the North of Thailand and the province of Chiang Mai, but the corresponding stochastic versions blure this deterministic skeleton for population sizes of a single province or several

provinces lumped. Only for as large systems as the population of Thailand and surrounding coutries (of approximately 200 Mio inhabitants) avoids the collision of the noisy version of the attractor structure with the absorbing boundary. In this situation deterministic skeleton and stochastic system compare well, import becoming less of a driving force of the dynamics and in case of data availablity will have good chances of successful formal model evaluation and selection analysis (Aguiar et al. 2012, forthcoming article in MMNP).



Stochastic and deterministic bifurcation diagram East Asia

For an explicit model of coupled dynamics of hosts with vectors we find a typical slow fast dynamics, most pronounced in the stochastic version. The infected hosts I determine the long term dynamics as well as the fluctuations in stationarity, whereas from arbitrary initial conditions the infected vectors V move rapidly towards the centermanifold of the I dynamics (forthcomming manuscript, to be presented at CMMSE 2012 in Murcia, Spain).



Aguiar, M., Ballesteros, S., Kooi, B. W., Stollenwerk, N. (2011).The role of seasonality and import in a minimalistic multi-strain dengue model capturing differences between primary and secondary infections: complex dynamics and its implications for data analysis. Journal of Theoretical Biology, 289, 181–196.