**PD Dr. John Shiner**
Bergacher 3
3325 Hettiswil
shiner@alumni.duke.edu

4049-063267
01.07.2001-30.06.2004


**Prof. Dr. Dominik Uehlinger**
Klinik und Poliklinik für
Nephrologie und Hypertonie,
Inselspital, Universität Bern
uehlinger@mph.unibe.ch


**Dr. Matt Davison**
Department of Applied
Mathematics, University
of Western Ontario, Western
Science Centre
CDN-London, Ontario N6A 5B7
mdavison@julian.uwo.ca

## *Prediction and predictability of resistance to antibiotics: Studies based on coupled map lattices*

**Objectives**  Population control and antibiotic usage strategies for reducing the appearance of antibiotic resistance and preventing its spread should be based on the best possible understanding of the effects of control strategies. Mathematical studies can provide valuable insights into the effects of guidelines for the selection of strategies against increased antibiotic resistance.

**Conclusions**  When the dynamics of an epidemic are chaotic, detailed prediction is impossible, except perhaps in the short term. However, when only one effective population is involved, long term prediction of statistical measures such as the mean or the standard deviation is possible. Surprisingly, even when there are multiple populations between which the infection can disperse and the dispersal rate is to slow to merge populations into a single effective one, this global long-term predictability of statistical measures such as the mean or standard deviation is maintained. However, higher order statistics and the probability distribution underlying the motion are changed by the coupling, and global predictability is weakened. To conclude, if we can be satisfied with statistical properties in the long term − predictability − this is not only possible but even good.

### *Main results and findings*

**Global predictability of chaotic epidemiological dynamics in coupled populations**  During outbreaks of infectious diseases in a unique population detailed prediction in the long term is impossible, since the dynamics of epidemics are chaotic. To investigate a possible loss of predictability for two coupled logistic maps, a simple model for the dynamics of infections in coupled populations was examined. The results can be summarised as follows:
- As expected, a strong influence of the coupling was found on the probability distribution underlying the chaotic dynamics of the populations.
- Unexpectedly, the mean or the standard deviations were only negligibly influenced by the coupling.
- However, higher order moment statistics such skewness and kurtosis were strongly influenced by the coupling.
- Investigation of the degree of contact between populations revealed that even when there are multiple populations between which the infection can disperse and the dispersal rate is to slow to merge populations into a single effective one, the global long-term predictability of statistical measures such as the mean or standard deviation is maintained.

Therefore, at least for the simple case studied, it is legitimate to extrapolate the long-term, global behaviour of an infection in coupled populations from the dynamics in a single population, at least as long as one is satisfied with information on the mean and standard deviation only.

**Quantifying the connectivity of scale-free and biological network**  Another case in which predictability worries us in infections systems arises when the network of connections between potentially infected individuals or populations is scale-free (i.e. for sexually transmitted diseases). However, predictability can be achieved on the basis of studies on extended entropies and "disorders". The technique is as follows: a scale-free probability distribution is replaced with an "escort distribution" (with a parameter chosen so that escort distribution has a finite mean and a finite variance), which corresponds to predictable connectivity properties. These studies are highly mathematical; for exhaustive information, see Davison and Shiner (2003), "Many entropies, many disorders" and Davison and Shiner (2004), "Extended entropies and disorder" (references below).

**Peripheral versus central treatment of infections**  According to current understanding, use of antibiotics itself promotes bacterial resistance. Thus, a central tenet of current efforts to combat bacterial resistance to antibiotics is minimisation of the use of antibiotics, consistent, of course, with accepted health care practices. In this study we investigate the minimum antibiotic dose necessary

to eradicate an infection for a particular set of coupled populations with relevance to several imaginable situations. Considering a central population surrounded by a number of smaller peripheral populations, then, the infection is allowed in principle to spread from the central population to the peripheral populations, from the peripheral to the central population and among the peripheral populations. The optimal strategies to eradicate the infection within minimal total antibiotic use (the total dose used in all populations) are given in the following table:

|  | Central population smaller than peripheral population | Central population larger than peripheral population |
| --- | --- | --- |
| Spread of infection from centre to periphery | Prohibited | Fast |
| Spread of infection from periphery to centre | Fast | Prohibited |
| Spread of infection among peripheral populations | Limited | Not relevant |
| Antibiotic dose in centre | Same as for a single population | None |
| Antibiotic dose in periphery | None | Same as for a single population |

That is, if the population in an urban centre is larger than that of all surrounding communities, then one should treat the infection in the surrounding communities only, not the centre, and send infecteds from the centre to the surrounding communities, but not let any infecteds return from the surrounding communities to the centre.

If the population in an urban centre is smaller than that of all surrounding communities, then one should treat the infection in the centre only, not in the surrounding communities, and send infecteds from the surrounding communities to the centre, but not let any infecteds return from the centre to the surrounding communities. Furthermore, contact among the surrounding communities should be limited in order to limit the spread of infection in the periphery.

However, for human populations these proposals may well be controversial and difficult to implement in a political and social context. But in an agricultural setting, where for example the central population is a feed lot or farm, and the peripheral populations the surrounding pastures and ranges, this problem would be less severe. Nevertheless, in the case of a biological attack by terrorists or in some other emergency situation, these recommendations would be more acceptable for human populations.

## *Publications of the NRP 49 project*

Davison M, Shiner JS.
**Extended entropies and disorder.**
*Advances in Complex Systems.* 2005 Mar;8(1):125-158.

Shiner JS, Davison M.
**Quantifying the connectivity of scale-free and biological networks.**
*Chaos, Solitons & Fractals.* 2004 Jul;21(1):1-8.

Davison M, Essex C, Shiner JS.
**Global predictability of chaotic epidemiological dynamics in coupled populations.**
*Open Systems & Information Dynamics.* 2003 Dec;10(4):311-320.

Davison M, Shiner JS.
**Many entropies, many disorders.**
*Open Systems & Information Dynamics.* 2003 Sept;10(3):281-296.