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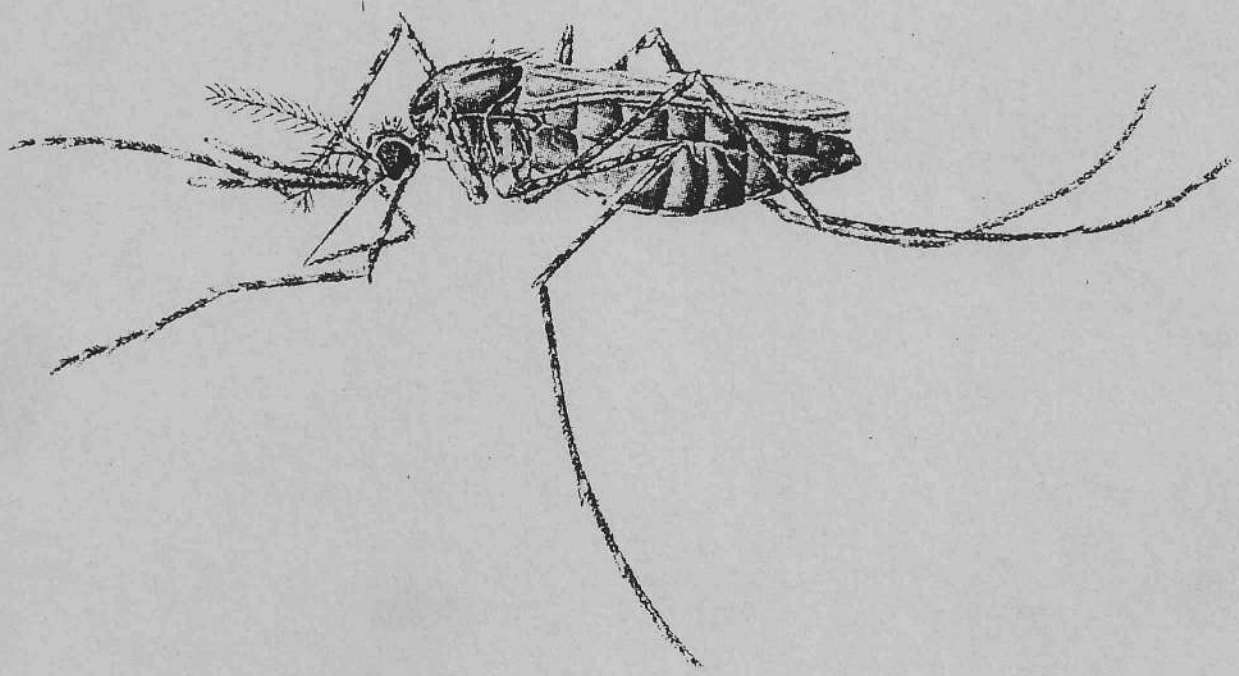

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SEX, DRUGS AND CLIMATE CHANGE:
Modelling malaria as a complex adaptive system

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abstract

As the resistance of the malaria parasite to antimalarial drugs continues to intensify, as does that of the malarial mosquito to insecticides, efforts to adequately control the malaria situation in many tropical countries are coming under strain. This, together with a projected climate change may substantially increase malaria risks in the coming decades. In this paper we introduce genetic algorithms to simulate the adaptation (development of resistance) of mosquitoes and parasites. By coupling genetic algorithms with a dynamic malaria-epidemiological model we derive a complex adaptive system which is used to analyze strategies of malaria management for high and low endemic regions. Our results show that control programs can be used successfully in low endemic regions although increased effort will be necessary in case of a climate change. However, in high endemic regions the inefficient use of insecticides and antimalarial drugs may eventually increase the incidence of malaria by decreasing the high levels of natural immunity of the population in these regions.

key words: malaria, climate change, genetic algorithms, adaptation

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1. Introduction

When forecasting the future one should always take a general law into account: 'The unexpected always happens'. Social and biological systems interact continuously with their environment and they are subject to changes over time. In assessing the impact of global and local changes, the modelling of adaptation to changes and evolutionary processes is a crucial tool for scanning the future. The aim of this paper is to apply evolutionary modelling tools in order to scan the future risks of the occurrence of malaria and the possibilities for controlling those risks.

Malaria is, one of the world's most important vector-borne diseases, and there are few infectious diseases which have as great an impact on the social and economic development of societies. Out of a world population of approximately 5,300 million people in 1990, some 2,200 million are regarded as being at risk of contracting malaria. Roughly 270 million people are actually infected with the malaria parasite. At present, the distribution of malaria is mainly restricted to the tropics and sub-tropics, although before the Second World War malaria was a common disease in many temperate areas of the world.

The effective use of DDT and other insecticides after 1945 led to a significant global decrease in the prevalence of malaria and to its eradication or near-eradication in temperate zones and in some tropical areas. The rate of decrease has now slowed down considerably and a resurgence of malaria has occurred in many countries. The development of resistance to insecticides is considered to be one of the main obstacles to using insecticides for vector control in the strategy of malaria control/eradication. The regions in which resistance to insecticides is most pronounced are to be found in Africa, Central America and in West and South-East Asia (Pant, 1988).

Another obstacle is the development of drugs resistance in *P.falciparum*, the malaria parasite responsible for most deaths (Figure 1). In the last few years there has been an increased selection and progressive dispersal of parasites resistant to antimalarial drugs, as these drugs are used increasingly as prophylactics and for self-medication, usually in insufficient doses. The problem of drug resistance has been particularly alarming in Africa, and its continual intensification hampers efforts to provide adequate treatment of the disease (Nájera *et al.*, 1992).

It is therefore clear that past malaria patterns have to a large extent depended on the effectiveness of control efforts, together with socio economic development. Although new drugs are being investigated and work is progressing on various potential malaria vaccines, given the increasing resistance of the malaria mosquito and the parasite to insecticides and antimalarial drugs, respectively, the treatment of malaria will be more difficult in the future. Another factor which may influence future malaria trends, and to which attention has been paid only recently, is the effect of a human-induced climate change on the transmission dynamics of malaria (Bradley, 1993; Matsuoka & Kai, 1994). Anthropogenic climate change may directly effect the behaviour and geographical distribution of the malaria mosquito and the life cycle of the parasite, and thus change the incidence of the disease.

A model to improve the quantitative projections of climate-related changes in the potential distribution of malaria has recently been developed by Martens *et al.* (1994, 1995 a+b). Although this model does take account of how climate change directly affects the mosquito population, i.e., mosquito development, feeding-frequency and longevity of the mosquito and how it affects the incubation period of the malarial parasite (plasmodium) inside the mosquito, it fails to adequately address artificial interventions by humans and how this may affect malaria risk due to climate changes. To allow for anti-malarial control measures *and* the adaptation of mosquitos and parasites on these malaria control policies, we have combined a systems dynamic model (which describes the transmission dynamics between human and mosquito populations) with genetic algorithms. A genetic algorithm is a general and robust evolutionary modelling approach which is based on the mechanics of the survival of the fittest. The inclusion of the notion of variability within the population makes the genetic algorithm a suitable tool for simulating the adaptive behaviour of a population within a changing environment. In this paper we present a simplistic, idealized model of the resistance cycles resulting from insecticide and drugs use, and the interaction with climate changes, solely for heuristic purposes. However, the approach does elucidate the mechanism of resistance development, interactions with climate, and consequences for the implementation of strategies for malaria management.

2. Malaria

2.1 Introduction

Malaria is caused by one or more of four species of parasites of the genus *Plasmodium*, and the vector responsible for malaria transmission is the mosquito of the genus *Anopheles*. The life cycle of the malaria parasite involves transmission both from mosquito to man and from man to mosquito, effected by the bite of a female mosquito (see Figure 2). The parasite multiplies within the mosquito by means of sexual reproduction, and, following an incubation period of several days (depending on the temperature and the species of parasite), malarial parasites can be found in the salivary glands of the insect. When an infected mosquito bites a human host, saliva is also injected and parasites are thus transferred to (hitherto uninfected) people. Asexual multiplication takes place in the human host. Having received an infective bite, there is an incubation period in the patient which varies between 10 and 40 days, depending on the species of parasite. The incubation period culminates in a severe attack which is caused by the destruction of infected blood cells and the release of toxins into the bloodstream. Infections involving *P.falciparum* are often associated with fatal complications (e.g. anaemia and cerebral malaria).
Although malaria may manifest itself throughout the world, the incidence shows marked regional variations, depending on four groups of interacting factors, namely: the human host, the malaria parasite, the mosquito as vector, and the environment, whereby the latter is understood to subsume physical, biological, and socio economic elements (Clyde, 1987). These factors will be discussed in the sections which follow.

2.2. The human host

Two main factors determine an individuals' propensity to succumb to malarial infection: on the one hand, genetic factors affect the ability of the parasite to penetrate and maintain itself within the erythrocyte; on the other, some degree of immunity may have been acquired by virtue of a previous history of infection. Among the genetic factors associated with protection against malarial infection are the sickle-cell trait and the Duffy factor (Molineaux, 1988). Those who have survived an attack of malaria acquire some degree of immunity to the disease. The number of parasites in the blood is lower and the infection may present few, if any, clinical symptoms. Consequently, in areas where malaria is rife, deaths from the disease occur mainly in the category of children aged between six months and five years. The high collective levels of acquired immunity of populations in these stable endemic areas reduce the likelihood that malaria epidemics will occur.

2.3. The parasite

There are four species of the malaria parasite of the genus *Plasmodium*, namely: *P.falciparum*, the most common species in tropical areas and the most dangerous clinically; *P.vivax*, which has the broadest geographic range including many temperate zones; and *P.ovale* and *P.malariae*, which are less prevalent (Clyde, 1987). Virulence varies greatly from species to species. The ranking in decreasing order of virulence is as follows: *P.falciparum, P.vivax, P.malaria* and *P.ovale*. When left untreated *P.falciparum*

does not survive in the human body for longer than two to three years, whereas infection by *P.vivax* may last between two and more than 11 years. The duration of infection by *P.ovale* and *P.malariae* may last 1 year and up to 53 years, respectively.

2.4. The mosquito

Malaria is transmitted to humans by female mosquitoes of the genus *Anopheles*. This mosquito belongs to a very large genus which includes hundreds of species throughout the world, although only 60 of these are actual or potential malarial vectors.
There are four distinct stages in the life cycle of the mosquito: the egg, larval, pupal and the adult stage. In order to produce eggs a female mosquito must take a blood meal, and the eggs are normally laid after the blood meal has been digested. Development and survival during the larval and adult stages of the *Anophelines* depends on favourable climatic temperature, humidity and rainfall. Temperature governs the growth rate of a mosquito population by determining the time needed for one generation to develop. The optimum temperature for most malaria vectors is found in the range 20-30°C. Relative humidities in excess of 60% are preferred by vectors. Moderate rain may prove beneficial to mosquito breeding, but excessive rainfall may flush out the mosquito larvae.

2.5. The environment

The physical, biological, and socio economic environment plays an essential part in the epidemiology of malaria, and some of the physical factors have already been mentioned above. Among the biological factors which play a role in malaria transmission are the presence of predators and the presence of domestic animals. Cattle may be employed as sources of blood and hence divert mosquitoes from feeding on people. When considering the connections between malaria and socio economic variables, two apparently contradictory relations can be identified. Firstly, in the long run, social and economic development is associated with a downward trend in malaria. This is partly due to the effects of socio economic development on the provision of health services, both curative and preventive. Socio economic development can also suppress malarial prevalence independently of deliberate control measures (e.g. the enhancement of public hygiene, drainage and housing) as the cases of Europe and North America would suggest (Bruce-Chwatt, 1980). On the other hand, in the short run, development projects may lead to an increased incidence of malaria, in particular when such projects are divorced from social development (e.g. when they involve deforestation, irrigation, colonization of new territory etc.). It is important to bear in mind that there is a direct feedback from the incidence of malaria to the socio economic development of a country. The social and economic damage caused by malaria morbidity and mortality - e.g, falls in the productivity of labour, pressure on health services- may prevent many low-income countries from achieving an efficient level of malaria control and/or an eradication programme.

2.6 Climate change impacts

Direct effects of the anticipated changes in global and regional temperature, precipitation, humidity and wind patterns resulting from anthropogenic climate change are factors which have an impact on the mosquito reproduction habits and on their longevity, and are thus associated with changes in annual vector density. In general, the rate of development of a

parasite accelerates as the temperature rises. An increase in temperature may therefore result in the completion of the life cycle of a parasite in areas in which previous temperatures were too low for the parasite to reach maturity. Indirect effects of climate change include changes in vegetation and agricultural practices which are mainly caused by temperature changes and trends in rainfall patterns. Another indirect effect of climate change is associated with the rise in sea level and the resulting coastal flooding. The proliferation of brackish water lagoons influences the availability of habitat and either encourages or discourages vector species, depending on whether or not they prefer brackish water. Generally speaking, drought and desertification, including a migration or extension of global desert belts, could be expected to decrease malaria transmission. It is thus evident that major changes in the incidence of this vector-borne disease might be expected to be associated with a climate change.

2.7 The evolution of malaria models

The history of a mathematical approach to malaria is nearly as old as the discovery of its transmission dynamics. The earliest attempt to provide a quantitative understanding of the dynamics of malaria transmission was that of Ross (1911). His models consist of a few differential equations to describe changes in the densities of susceptible and infected people and mosquitoes. In the 1950s, MacDonald (1957) added a layer of biological realism to these early models by his careful attention to the interpretation and estimation of parameters. Although these basic models give a good overview of the dynamics of malarial infection, many of their predictions are strikingly different from reality.

An obvious modification to the basic model is the incorporation of latent periods during which hosts are infected but not yet capable of transmitting the disease. Also, models for the transmission dynamics of malaria have begun to take account of the phenomenon of acquired immunity.

The reason for this late attention to immunity development is in part a consequence of the early focus in malaria models on the vector component in transmission, deriving from the initial aim of global eradication of malaria based on the application of DDT. Aron and May (1982) have described a simple way to incorporate the observed mechanism of the maintenance of immunity with continuous exposure. Although their model represents an advance over the simple models, it is still a very crude description of the true complexities of immunity to malarial infection.

With respect to resistance dynamics, a number of simulation models have contributed to our general understanding of this phenomenon and the development of strategies to reduce the development of resistance (a review is given in Glass *et al.* (1984)). Most of them have postulated that resistance is determined by a single gene. These models are generally not applicable when resistance is a quantitative trait (polygenic), in which the underlying genes are not identified individually. Because insecticide and anti-malarial drugs are agents of selection, insecticide and drugs resistance can be studied by using the same theoretical frameworks as have been applied to other types of evolutionary change. In the sections which follow, resistance development is studied by means of using genetic algorithms.

3. Complex Adaptive Systems

3.1 Introduction

Simple deterministic systems are the classical tools of 'Newtonian' science. The pseudo-mechanistic approach studies an object in isolation from its environment and is time-independent, which appears to be a useful approach for studying, for example, the orbits of planets or the functioning of machines. To study social and biological processes, however, such an approach is of limited use since humans, societies and organisms live in continuous interaction with their environment and change in time. Furthermore, each biological or social agent has specific characteristics, which means that individuals are not all equally successful in the survival of the fittest.
The last decade has seen the emergence a new stream of modelling approaches, the so-called complex adaptive systems approach. Complex adaptive systems are systems of many agents which interact with their environment and can adapt to changes. These kinds of systems organize themselves, learn and remember, evolve and adapt. This evolutionary modelling approach has been applied in various disciplines which study, for example, economies, ecologies, immune systems and nervous systems (e.g. Arthur, 1990; Kauffman, 1991; Holland, 1992; Waldrop, 1992; Ruthen, 1993). This modelling approach embraces a whole range of modelling tools such as genetic algorithms, cellular automata, artificial life and nonlinear dynamic systems. In the next session we will discuss genetic algorithms in more detail, since we have adapted this modelling tool to the simulation of the adaptation of malaria mosquitoes and malaria parasites to human interventions.

3.2 Genetic algorithm

Most organisms evolve by means of two primary processes: natural selection and sexual reproduction. The first determines which members of a population survive to reproduce, and the second ensures mixing and recombination among the genes of their offspring. A very obvious biological consequence of sexual reproduction is the generation of new combinations by mixing genetic information from different individuals. Without this mixing generated by sex, adaptive evolution would simply consist of the sequential selection of mutations in the genetic information. Selection takes place on the basis of the fitness of the organisms.

The genetic algorithm (GA) was developed by Holland (1975) in order to try to abstract and explain the adaptive processes of natural systems. The basic construction is to consider a population of individuals that each represent a potential solution to a problem. The relative success of each individual with this problem is considered to be its fitness, and is used to selectively reproduce the most fit individuals to produce similar but not identical offspring for the next generation. This survival of the fittest concept, as simulated by the genetic algorithm, is the main reason for using genetic algorithms to model the adaptation of mosquitoes and parasites in a changing environment.

A genetic algorithm works as follows: Consider a population of N mosquitoes, each represented by a chromosomal string of L allele values. An initial population is constructed at random on a specific range; call this generation g_0. Each individual is evaluated in terms of the life expectancy of the mosquito. The evolutionary algorithm then

performs two operations. First, its selection algorithm uses the population's N fitness measures to determine how many offspring each member of g_0 contributes to g_1. Second, some set of genetic operators are applied to this offspring to make them different from their parents. The resulting population is now g_1. These individuals are again evaluated in the next time step, in the new situation, and the cycle repeats itself.

We will now formulate the genetic algorithm in a more formal way:

(1) An individual can be characterized by a bit string of fixed length L, which is denoted as a, and $a \in B^L$ where B = {0,1}. The bit string can be separated into n segments of equal length l_x, thus implying $L = n * l_x$. Each segment is interpreted as the binary code of the object variable $x_i \in [u_i, v_i]$ which can be redecoded by

$$\Gamma_i(a_{i1}...a_{il_x}) = u_i + \frac{v_i - u_i}{2^{l_x} - 1} \cdot \left(\sum_{j=0}^{l_x - 1} a_{i(l_x - j)} \cdot 2^j \right) \qquad (1)$$

where $(a_{i1}...a_{il_x})$ denotes the i-th segment of an individual $a \in B^L$. Then $\Gamma = \Gamma_1 x..x \Gamma_n$ yields a vector of real values on the desired range $[u_i, v_i]$.

Example: a = 10011, u = 0, v = 1

$\Gamma = (1*2^4 + 0*2^3 + 0*2^2 + 1*2^1 + 1*2^0)/31 = 0.613$

(2) Mutation is a bit reversal event that occurs with small probability p_m per bit. This mutation can explore new genetic information and is a powerful operator in discovering ways to adapt to a changing environment.

Example: Suppose we have the following bitstring: 11111

At random, roughly one in every 1000 symbols flips from 0 to 1 or vice versa; in our example from 1 to 0: 11011

(3) The algorithm uses a crossover operator that arbitrarily exchanges substrings between two individuals with probability p_c. Both the length and position of these substrings are chosen at random, but are identical for both individuals.

Example: Suppose we have the following bit strings: 11111 and 00000

A point along the strings is selected at random and the offspring contain a mixture of the parents: 11000 and 00111

(4) The probabilistic selection operator forms the next generation by copying individuals on the basis of fitness-proportional probabilities

$$p_i = \frac{F(a_i)}{\sum_{j=1}^{N} F(a_j)} \qquad (2)$$

where $F: B^L \rightarrow \mathbf{R}$ is the fitness function. The less fit individuals therefore have a lower probability of reproducing its genetic information.

According to Goldberg (1989), genetic algorithms are successful robust algorithms in optimization because they are able to select strings with useful blocks of information, and concentrate their search (selection) on variations which include those blocks. The genetic algorithms test and exploit large numbers of regions in the search space, while manipulating relatively few strings, and without using specific information about the functional forms of the search space. Instead of using GA purely as an optimization routine, we shall illustrate the power of the algorithm as an optimizer within a changing environment. In Section 4.3 we describe in greater detail the application of GAs to mosquitoes and parasites.

4. Modelling Malaria: a Complex Adaptive Systems Approach

4.1 Introduction

The model described in this paper is an extended version of the systems approach of Martens *et al.* (1994; 1995a,b) and involves two general malaria control options: the use of insecticides to decrease mosquito densities, and the use of drugs to decrease the levels of parasites. The systems approach of Martens *et al.* was intended to derive a global model of the effects of an anthropogenically induced climate change on malaria risk, in contrast to the model presented here, which aims at including local dynamics in order to derive a generic local model with human intervention in terms of insecticide and drugs use and the development of resistance to these control measures.

4.2 The malarial system

The interaction between the human population and the mosquito population determines the transition rates between the susceptible, the infected and the immune respectively. The mosquito system is denoted by state variable $\mathbf{x}(t)$ and the human system by state variable $\mathbf{y}(t)$. The potential of the mosquito population to transmit *P.falciparum*[1] is influenced by temperature, $T(t)$, and the use of insecticides, $u_1(t)$. The dynamics within the human population are affected by the transmission potential of the mosquitoes and the use of anti-malarial drugs, $u_2(t)$.

$$\frac{d\boldsymbol{x}(t)}{dt} = f(\boldsymbol{x}, T, u_1)$$
$$\frac{d\boldsymbol{y}(t)}{dt} = g(\boldsymbol{y}, \boldsymbol{x}, u_2) \qquad (3)$$

To include adaptation to antimalarial drugs and insecticides, this dynamic system is coupled to two genetic algorithms, representing the genetic variety within the mosquito and the parasite population (Figure 3). The genetic algorithms determine parameters that determine the resistance of the mosquitoes and parasites and the optimum temperature for mosquito survival. The system can therefore be reformulated as

$$\frac{d\boldsymbol{x}(t)}{dt} = f(\boldsymbol{x}, T^{a}, u_1^{a}, T, u_1)$$
$$\frac{d\boldsymbol{y}(t)}{dt} = g(\boldsymbol{y}, \boldsymbol{x}, u_2^{a}, u_2) \qquad (4)$$

[1] In this paper we have focused on the transmission dynamics of *P.falciparum*, since this is the most lethal malaria parasite and because of the world-wide development of resistance of this parasite to anti-malarial drugs.

where T^a, u_1^a and u_2^a represent the fixed parameters in system (3). Now simulated by genetic algorithms, they are subject to adaptations caused by the changing system over time. In Section 4.3 and 4.4 we describe the original model representation (3), and in Section 4.5 we discuss the incorporation of the genetic algorithms.

4.2.1. Mosquito population

The dynamics of the mosquito population are much more rapid than human population dynamics, so the mosquito system can be considered to be in equilibrium with respect to changes in the human population. Therefore, the description of the mosquitoes is given in terms of an equilibrium instead of a set of differential equations. Following Garrett-Jones (1964), the entire mosquito population is incorporated in a single state variable, the vectorial capacity. The Garrett-Jones formulation is multiplied by the relative fitness of mosquitoes to insecticides, F_{ins}^m, which will be discussed in Section 4.3.1:

$$x_1 = \frac{p_1 \cdot x_2^2 \cdot x_3^{x_4}}{-\ln(x_3)} \cdot F_{ins}^m \tag{5}$$

where x_1 is the vectorial capacity, defined as the number of potentially infective contacts inflicted by the mosquito population per infectious person per day; p_1 incorporates variables assumed to be temperature independent (including the efficiency with which a mosquito infects a susceptible human; the propensity of the mosquito population to feed on humans; the recovery rate in humans; and the density of the mosquito population in relation to man); x_2 is the man-biting habit (number of blood meals taken from humans per mosquito per day); x_3 is the daily survival probability of the mosquito; and x_4 is the incubation period of the parasite in the vector (in days).

The man-biting habit depends on the frequency with which one vector takes a blood meal and the total number of these blood meals being taken from man. The frequency of feeding depends mainly on the rapidity of digestion of a blood-meal, which increases as temperature rises and, at the optimum temperature, results is one meal being taken every 48 hours (Muirhead-Thompson, 1954). The relation between temperature and the rapidity of blood digestion is given in Detinova (1963). The resulting equation for the man-biting habit (per day) is:

$$x_2 = \frac{T - p_3}{p_2} \tag{6}$$

where p_2 is the number of 'degree-days' required for the digestion of a portion of ingested blood at relative humidity 70-90%, (36.5 degree-days), p_3 is the minimum temperature required for the digestion of the blood meal (9.9 °C) and T is the actual average temperature (in °C).

The vector's longevity determines its ability to transmit a parasite, since the female mosquito has to live long enough for the parasite to complete its development. There is presumably an optimum temperature and an optimum humidity for each species of mosquito. Between certain limits, longevity decreases with rising temperature and increases with increasing relative humidity (Boyd, 1949; Molineaux, 1988). Data reported

by Boyd (1949) and Horsfall (1955) on mosquito longevity indicate an optimum temperature of about 20-25°C and an optimum relative humidity of 60-90%, and our assumption about the relation between the longevity of the *Anopheles* mosquito and temperature is based on these data. The maximum mean longevity is assumed to be 10 days (x_3 = 0.9) at temperatures of about 20°C. In the systems approach, the relative humidity is assumed to remain at a level favourable for mosquito development and is assumed not to change with changing precipitation. The assumed relationship between temperature and daily survival probability of the adult mosquito (Martens *et al.*, 1994) is:

$$x_3 = e^{\frac{-1}{-4.4+1.31 \cdot T - 0.03 \cdot T^2}} \quad (7)$$

The incubation period (duration of sporogeny) in the vector must have elapsed before the infected vector can transmit the parasite. This latent period depends on the critical factors of species of parasite and the ambient temperature. The parasites develop in the vector only within a certain temperature range, whereby the minimum temperature for parasite development lies between 16 and 19°C for *P.falciparum*, while the proportion of parasites surviving decreases rapidly at temperatures over 32-34°C (Horsfall, 1955; Macdonald, 1957; Detinova, 1963). The relation between the incubation period and temperature (if higher than 16°C) can be expressed in the following equation (Macdonald, 1957):

$$x_4 = \frac{p_4}{T - p_5} \quad (8)$$

where x_4 is the incubation period of the parasite inside the vector (in days), p_4 the number of 'degree-days' required for the development of the parasite (=111 degree-days for *P.falciparum* (Detinova, 1963)), T the actual average temperature (between p_5 and a maximum temperature of about 40°C; in °C), and p_5 the minimum temperature required for parasite development (16°C for *P.falciparum*).

4.2.2. Human population

The model used to describe the transition between the reservoirs of the human population at risk is based on a microparasite-epidemiological model as described in Aron and May (1982), Bailey (1982), Levin *et al.* (1989) and Anderson and May (1991). The human population subject to a risk of malaria is divided into three categories for each of two different age classes (people younger than 5 years and people 5 years and older): susceptible persons (y_1^i), infected persons (y_2^i) and immune persons (y_3^i). The latent reservoir is omitted, because the duration of a stay in this reservoir is usually very short in comparison to the residence time in the other reservoirs.

The number of susceptible persons may change over time, as they become members of the infected class at a rate y_5. Infected individuals either die from infection at a rate $b_7^{(i)}$ or recover to join the immune class (at a rate y_6). Immune persons lose their immunity at a rate y_7, and those who have lost their immunity return to the reservoir of susceptible persons. All newborn babies are assumed to be members of the class of susceptibles, and as they grow older they graduate from the younger age class to the older (at rate b_3). People die from other causes at rate b_2.

The dynamic behaviour of the human system can be described by:

$$\frac{d}{dt}\begin{bmatrix} y_1^{(1)} \\ y_1^{(2)} \\ y_2^{(1)} \\ y_2^{(2)} \\ y_3^{(1)} \\ y_3^{(2)} \\ y_4 \end{bmatrix} = \begin{bmatrix} -y_5-b_2-b_3 & 0 & 0 & 0 & y_7^{(1)} & 0 & b_1 \\ b_3 & -y_5-b_2 & 0 & 0 & 0 & y_7^{(2)} & 0 \\ y_5 & 0 & -b_2-b_6^{(1)}-b_3-y_6^{(1)} & 0 & 0 & 0 & 0 \\ 0 & y_5 & b_3 & -b_2-b_6^{(2)}-y_6^{(2)} & 0 & 0 & 0 \\ 0 & 0 & y_6^{(1)} & 0 & -y_7-b_2-b_3 & 0 & 0 \\ 0 & 0 & 0 & y_6^{(2)} & b_3 & -y_7-b_2 & 0 \\ 1 & 1 & 1 & 1 & 1 & 1 & 0 \end{bmatrix} \cdot \begin{bmatrix} y_1^{(1)} \\ y_1^{(2)} \\ y_2^{(1)} \\ y_2^{(2)} \\ y_3^{(1)} \\ y_3^{(2)} \\ y_4 \end{bmatrix} \quad (9)$$

where y_5 is the rate of infection, y_6 the rate of loss of infection and y_7 the rate of loss of immunity.

The rate at which individuals become infected (y_5) depends on the vectorial capacity (x_1), which represents the transmission potential of the mosquito population and on the proportion of infected people in the human population.

$$y_5 = 365 \cdot x_1 \cdot \frac{y_2^{(1)} + y_2^{(2)}}{y_4} \cdot F(u_2^a) \quad (10)$$

Rates of recovery from infection appear to increase with the longevity of people in endemic areas. Assuming that re-exposure does not occur, infection and immunity endure for a fixed period of time. However, if a person is further exposed before this period has elapsed, infection and immunity is sustained. The basic loss rate of infection, b_4, is defined as 1/average duration of infectiousness (average one year). The basic loss rate of immunity b_5 is 0.67/year, corresponding with a mean duration of immunity of 1.5 years (Aron and May, 1982). If infection occurs at a per capita rate y_5, the average per capita rate of loss of infection (y_6) and loss of immunity (y_7) as a function of y_5 is expressed as described in expressions 11 and 12.

$$\text{if } y_5 = 0 \text{ then } y_6^{(i)} = b_4^{(i)} \text{ else } y_6^{(i)} = \frac{y_5}{e^{y_5/b_4^{(i)}} - 1} \text{ for } i = 1,2 \quad (11)$$

$$\text{if } y_5 = 0 \text{ then } y_7 = \frac{1}{b_5} \text{ else } y_7 = \frac{y_5}{e^{y_5/b_5} - 1} \quad (12)$$

4.3 Adaptation

In this session we will describe how genetic algorithms are used to simulate the adaptive evolution of the mosquito and the parasite population. For each population a genetic algorithm is used to model the sexual transmission of genetic information. We use genetic algorithms containing a rather arbitrary number of 100 individuals to simulate the variety within a population. Experiments have shown that a population of fewer than 100 individuals is not sufficient to simulate the adaptation to control programs, while higher values are not chosen in order to keep the model suitable as a interactive learning tool. In the following session we discuss one of the most crucial items of the genetic algorithm: the fitness function, used to simulate the fitness of individual mosquitoes and parasites.

The output of the genetic algorithm is the individual values of $u_{1,i}^{a}$, $u_{2,i}^{a}$ and z_i^{a}. In the system dynamic framework, as described in Section 4.2, the average values of the parameter values are used.

4.3.1 Mosquitoes

Within the genetic algorithm sexual reproduction is implemented using two crucial parameters: the crossover probability (p_c) and the mutation probability (p_m). Within the simulation model we use a time step of 0.1 year although the average lifetime of mosquitos lies around 10 days, which would suggest a time step in terms of days. However, the model should be seen as an aggregation of the behaviour of mosquitoes in order to simulate long term dynamics in an interactive way. Therefore the crossover probability and the mutation rate which are used have no physical meaning, but seem to be suitable to simulate the observed behaviour of expected and historical adaptation patterns of mosquitoes (for adaptation to insecticides see Table 1). We have assumed a crossover probability of 0.5 and a mutation rate of 0.001, which are parameter values usually used in GA applications.
The fitness of a (biological) population is related to the chance of getting descendants (Hofbauer and Sigmund, 1988). We assume that the expected lifetime of a mosquito is a measure of the individual fitness since life expectancy is directly related to the production of offspring. The general fitness function of a mosquito is therefore equal to the expected lifetime which is formulated as (MacDonald, 1957):

$$F_i(t) = \frac{-1}{\ln(x_3)} = -4.4 + 1.31 \cdot T - 0.03 \cdot T^2 \qquad (13)$$

Within this approach we distinguish two pressures on the mosquito population: temperature change and insecticides.

Adaptation to temperature change

We assume that for every mosquito there is a temperature at which its expected lifetime is a maximum (Figure 4). Within the mosquito population there is a variation of these optima. If the temperature increases over a longer time, mosquitoes for which the optimum is higher than average derive a higher fitness. Due to the mechanisms of the survival of the fittest the average optimum temperature will therefore rise. The implementation of this

process by means of a genetic algorithm is as follows.
Within the mosquito system the daily probability of survival is a function of temperature (see eq.7). Within the population, individual temperature likelihoods are spread around the mean temperature. Note that we do not distinguish seasonal temperature changes. The daily survival probability is therefore a function of the *local mean temperature*. We introduce the variable T_i^a which represents the individual adaptation to temperature. This results in a daily survival probability such that the fitness function of mosquito i becomes,

$$F_{T,i} = -4.4 - 1.31 \cdot (T - T_i^a) - 0.03 \cdot (T - T_i^a)^2 \qquad (14)$$

If temperature T changes, the value of T_i^a will also change in a survival of the fittest competition to keep the mosquitoes in the optimum temperature zone.
Furthermore, the daily survival probability of the adult mosquito becomes:

$$x_3 = e^{\frac{1}{-4.4 + 1.31 \cdot (T - T^a) - 0.03 \cdot (T - T^a)^2}} \qquad (15)$$

where T^a is the mean of T_i^a.

Adaptation to insecticides

A human-induced stress on the mosquito population is the use of insecticides. Several models have been developed to understand and manage the evolution of insecticide resistance, and nearly all of them assume that resistance is controlled by two alleles at one locale (Taylor, 1983; Tabashink, 1990; Anderson and May, 1991). We have based our fitness function on the study by Tabashink (1990), who has investigated three- and four - allele models.

We simulate a three-allele model by distinguishing three kinds of mosquitoes: susceptibles, moderately resistant and resistant, as three classes of individual sensitivity to insecticides. We assume that an imaginary dose of insecticide reduces fitness in the way depicted in Figure 5, where we assume that the same dose has a higher impact on susceptible mosquitoes than on (moderately) resistant mosquitoes. Furthermore, there is a biotic fitness component measuring the relative fitness of the mosquito in case no insecticides are used. A lower biotic fitness of the more resistant genes explains the lower density of these genes. Given an initial random distribution the following design for the fitness of mosquitoes, F_{ins}^m, in the face of an imaginary dose of insecticides u_1 is derived, where we assume that 99% of the mosquitoes are susceptible, 0.9% are moderately resistant and 0.1% resistant in the initial situation.

	$u_{1,i}^a$	relative biotic fitness	relative fitness to insecticides
susceptible	[0.0, 0.99)	1.0	$1-u_1/(0.002+u_1)$
moderate resistant	[0.99, 0.999)	0.95	$1-u_1/(0.05+u_1)$
resistant	[0.999, 1.0]	0.9	$1-u_1/(0.15+u_1)$

The average fitness of the individual mosquitoes $F_{ins}^m(u_{1,i}^a)$, $F_{ins}^m(u_1^a)$, is used in the equation of the vectorial capacity x_1.

4.3.2 Parasites

The dynamics of the gene pool of parasites differ from those of the mosquitoes. Actually, the population of parasites is spread over the human population and the mosquito population. Within a host the local parasite population may adapt rather rapidly to the use of drugs. However, the transmission of resistant parasites to vector populations within other hosts limits the adaptation of the parasite population at large. Note that we assume one gene pole for parasites, although local concentrations exist (in the hosts). Therefore, the adaptation of parasites over the population at large is assumed to occur somewhat more slowly than that resulting in a lower crossover probability of 0.1 in addition to the mutation probability of 0.001.

Adaptation to drugs

In line with our modelling of the resistance of mosquitoes to the use of insecticides, we have modelled the adaptation of parasites to the use of antimalarial drugs. We simulate a three-allele model by distinguishing three kinds of parasites: susceptibles, moderately resistant and resistant, as three classes of individual sensitivity to drugs. Given an initial random distribution, the following design for the fitness of parasites to an imaginary doses of drugs u_2 is derived assuming that 99% of the population is susceptible, is 0.9% moderately resistant and 0.1% resistant in the initial situation:

	$u_{2,i}^a$	relative biotic fitness	relative fitness to drugs
susceptible	[0.0, 0.99)	1.0	$1-u_2/(0.002+u_2)$
moderate resistant	[0.99, 0.999)	0.95	$1-u_2/(0.05+u_2)$
resistant	[0.999, 1.0]	0.9	$1-u_2/(0.15+u_2)$

The fitness function for a parasite therefore becomes

$$F^p(u_2^a)_i = F^p_{bio,i} \cdot F^p_{u_2,i}$$

In equation (10) the mean value of $F^p(u_{2,i}^a)$, $F^p(u_2^a)$, is used to determine the impact of resistance on the transmission dynamic within the human population.

5. Results

5.1 Introduction

We analyze the consequences of the use of insecticides and anti-malarial drugs, and a climate change on the occurrence of malaria for a time horizon of two decades in two types of region: a low endemic region and a high endemic region. We assume that the initial force of infection (y_s) is 2.0 per annum in highly endemic regions and 0.1 in areas of lower endemicity (Martens *et al.*, 1995a). Although these values are chosen rather arbitrarily they lie within the range of the values found in several studies on the pristine force of infection in young children. The initial settings for these systems are given in Table 2. Low endemic regions can be characterised by low vectorial capacity resulting in a high percentage of susceptibles persons (≈80%), and low percentages of infected (≈ 8%) and immunes (≈12%). Low endemic *P. falciparum* regions can be found in South-East Asia and South America.
High endemic regions are characterised by a high vectorial capacity. The initial situation shows a high percentage of immune (≈68%) and infected persons (≈ 27%). The younger age class especially suffers from a high percentage of infected (≈ 45%). Highly endemic regions are mainly found in tropical Africa.
We now report a set of results derived using the complex adaptive system approach[2]. In the starting year a situation is assumed which is near equilibrium because we want to focus on the impact of control policies on the occurrence of malaria, including the adaptation of mosquitoes and parasites. We therefore did not include population growth and socio-economic development in the present version.

5.2 Low endemic regions

Suppose a program of insecticide use is initiated for a few of years (Figure 6). The results show that the vectorial capacity drops by more than 50%, resulting in a decrease in the numbers of infected and immune persons. The incidence, which is a function of the fraction of susceptibles multiplied by the infection rate, will drop almost to zero. During the years of insecticide use the mosquitoes become resistant and the vectorial capacity returns to the initial values. The impact on the incidence of the use of antimalarial drugs is similar, although the reintroduction of malaria becomes significant at the end of the period because of the remaining level of vectorial capacity (Figure 7).
If we now combine the use of insecticides and antimalarial drugs we see that the incidence remains at a low level (Figure 8). However, in the case that temperature will increase in the coming decades at a rate of 0.3 °C per decade, resulting in increasing levels of the vectorial capacity, a reintroduction of malaria will appear at the end of the period (Figure 9). Additional measures seem to be necessary to reduce the occurrence of malaria. The influence of adaptation to temperature change is minor. The vectorial capacity is only slightly higher in the case that mosquitoes adapt as compared to the case where no adaptation was included.

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[2] The results should be seen as illustrative examples of the model. Due to the stochastic characteristics of the model, it may produce different outcomes while using the same control programs.

Note that the findings do not all hold if we do not include the adaptation of mosquitoes and parasites to the control programs because, if no adaptation occurs the problem is already solved in a way (Figure 10).
Nevertheless, we need additional measures. Suppose we increase the control programs at the end of the period then we are able to reduce the occurrence of malaria to almost zero (Figure 11).
The central finding for low endemic regions is that the incidence of malaria can be reduced for a long time period, even in case of a climate change, provided adequate control programs are implemented.

5.3 High endemic regions

Using insecticides to reduce the vectorial capacity may result in an increase of the incidence of malaria which is in line with field observations (Figure 12). Because the number of immune people in the oldest age group decreases and the number of susceptibles increase due to a lower vectorial capacity, the population is at higher risk if the vectorial capacity returns to its historical values due to developing resistance of the mosquitoes to insecticides. After a small decrease of the incidence, an outbreak of malaria will occur during the time that insecticides are still used. In the long run the incidence returns to its historical values.
The use of antimalarial drugs causes a temporary decrease of the occurrence of malaria, which returns after parasites become resistant in line with the use of insecticides, an outbreak follows (Figure 13). Should both policies be combined, the incidence will stabilise at a level which is lower than the start value, after an outbreak of malaria (Figure 14).
Suppose now that a temperature increase of 0.3 °C per decade occurs due to a human induced climate change. In contrast to the low endemic regions, a temperature increase may cause more persons to become immune due to a higher vectorial capacity. If control programs are used a downward trend is disturbed although the incidence will stabilise at a lower level in case of no climate change (Figure 15).
If the same analysis is performed using a model which does not incorporate adaptation of mosquitoes and parasites we will get a completely different view of a sustainable malaria policy. While the control programs are more effective, such a model will project a successful decrease of malaria occurrence (Figure 16). But these programs should be permanently implemented, since otherwise an enormous outbreak will occur.

While a model which does not include adaptation leads us to the conclusion that one should use a single insecticide on a large scale to reduce the vectorial capacity, our complex adaptive systems approach suggests a situation in which the use of one type of insecticide, together with one antimalarial drug is not advisable (Figure 17). Successful malaria policy in these regions may lie in socio economic development leading to improved housing and other infrastructural implications.

5.4 Limitations and future developments

Among others, two of the limitations of the present model version are the non-inclusion of the impact of socio economic developments and land use changes on the occurrence of malaria.

We have not yet included the concept that control programs do not reach the whole population of mosquitoes and parasites; nor have we incorporate the immigration of susceptible mosquitoes from other regions. Tabashink (1990) showed the importance of migration for three- and four-allele models compared with two-allele models in case of insecticide resistance. Further, Comins (1977) and Georghiou and Taylor (1977) showed that migration is an important factor in slowing down the evolution of resistance. The immigration of susceptible mosquitoes and parasites might be simulated by generating a fraction of susceptibles in each generation, regardless of the use of insecticides. Furthermore, the generation time of mosquitoes and parasites may change, which might result in a more rapid adaptation to changes. However, we have not included this aspect in the present version.

Another limitation is the assumption of a near equilibrium situation in the starting year, which was used to focus on the forcing factors of temperature change, insecticide use and the use of drugs and the resulting adaptation, with no noise from other developments, such as population growth and socio economic development.

Finally, we include only one type of insecticide and antimalarial drug. In practice, new insecticides and antimalarial drugs are being used when older ones lose their impact.

6 Conclusions

To summarize, this paper has presented a malaria assessment model including evolutionary processes which affect the population of mosquitoes and parasites, and therefore influence future malaria risks. Before presenting the conclusions, we emphasize the fact that the results are only tentative. Further work will include migration of mosquitoes and socio economic development, changes in generation time, as well as an additional test of the robustness of the outcomes and uncertainty analyses. Subject to these reservations, the following major conclusions may be drawn.

First, the inclusion of adaptation leads to a more satisfying explanation of field observations than those obtained with a model which does not include adaptation. Furthermore, it gives us different guidelines for promising strategies for future malaria management.

Second, the results suggest that adequate use of insecticides and drugs may reduce the occurrence of malaria in low endemic regions, although increased efforts are necessary in case of a climate change.

Third, in high endemic regions, the inefficient use of insecticides and mosquitoes will not result in a reduction of the malaria occurrence: on the contrary it will probably lead to an increase of the incidence. Therefore, the use of a single kind of insecticide and a single antimalarial drug are not advisable for high endemic regions. A projected climate change, however, may lead to a limited reduction of the occurrence of malaria due to a higher percentage of immune persons in the older age class. However, children below the age of five will experience a higher risk of malaria. A sustainable antimalarial policy in high endemic regions will probably be found in a stimulation of socio economic development.

In summary, the results show the usefulness of including the notion of adaptation of mosquitoes and parasites to control programs and to global and local environmental change, and of modelling such adaptation using a genetic algorithm.

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Table 1: This Table gives the time before a majority (> 50 per cent) of the individuals in the population are resistant to the control agent (source Anderson and May, 1991).

Anopheline mosquitoes (different localities)	Control agent	Time to resistance (in Years)
An. sacharovi	DDT	4-6
	Dieldrin	8
An. maculipennis	DDT	5
An. stephansi	DDT	7
	Dieldrin	5
An. culicifacies	DDT	8-12
An. annuaris	DDT	3-4
An. sundaicus	DDT	3
	Dieldrin	1-3
An. quadrimaculatus	DDT	2-7
	Dieldrin	2-7
An. pseudopunctipennis	DDT	>20
	Dieldrin	18 weeks

Table 2: We constructed the initial situations as follows: for highly endemic regions we assume an infection rate, y_5, of 2.0 and for low endemic regions an infection rate of 0.1. We assume that the birth rate is equal to the natural death rate, although the additional death rates due to malaria cause a slightly declining population. The initial values for p_1, $y_1^{(i)}$, $y_2^{(i)}$ and $y_3^{(i)}$ are an equilibrium situation in case we do not include malaria related deaths.

	low endemic	high endemic	decryption
p_1	0.02226	0.13445	temperature independent parameter
p_2	36.5		degree days blood digestion
p_3	9.9		minimum temperature
p_4	111		degree days development parasites
p_5	16.0		minimum temperature development parasites
T	21.88		initial local mean temperature
x_1	0.00335	0.02018	vectorial capacity
b_1	0.02		birth rate
b_2	0.02		natural death rate
b_3	0.2		aging children
b_4^1	1		basic loss rate infection (0-5)
b_4^2	;		basic loss rate infection (>5)
b_5	1.5		basic loss rate immunity
b_6^1	0.04		fatality rate (0-5)
b_6^2	0.01		fatality rate (>5)
$y_1^1(0)$	0.077	0.011	susceptible persons (0-5)
$y_1^2(0)$	0.718	0.034	susceptible persons (>5)
$y_2^1(0)$	0.007	0.041	infected persons (0-5)
$y_2^2(0)$	0.076	0.231	infected persons (>5)
$y_3^1(0)$	0.008	0.039	immune persons (0-5)
$y_3^2(0)$	0.115	0.644	immune persons (>5)

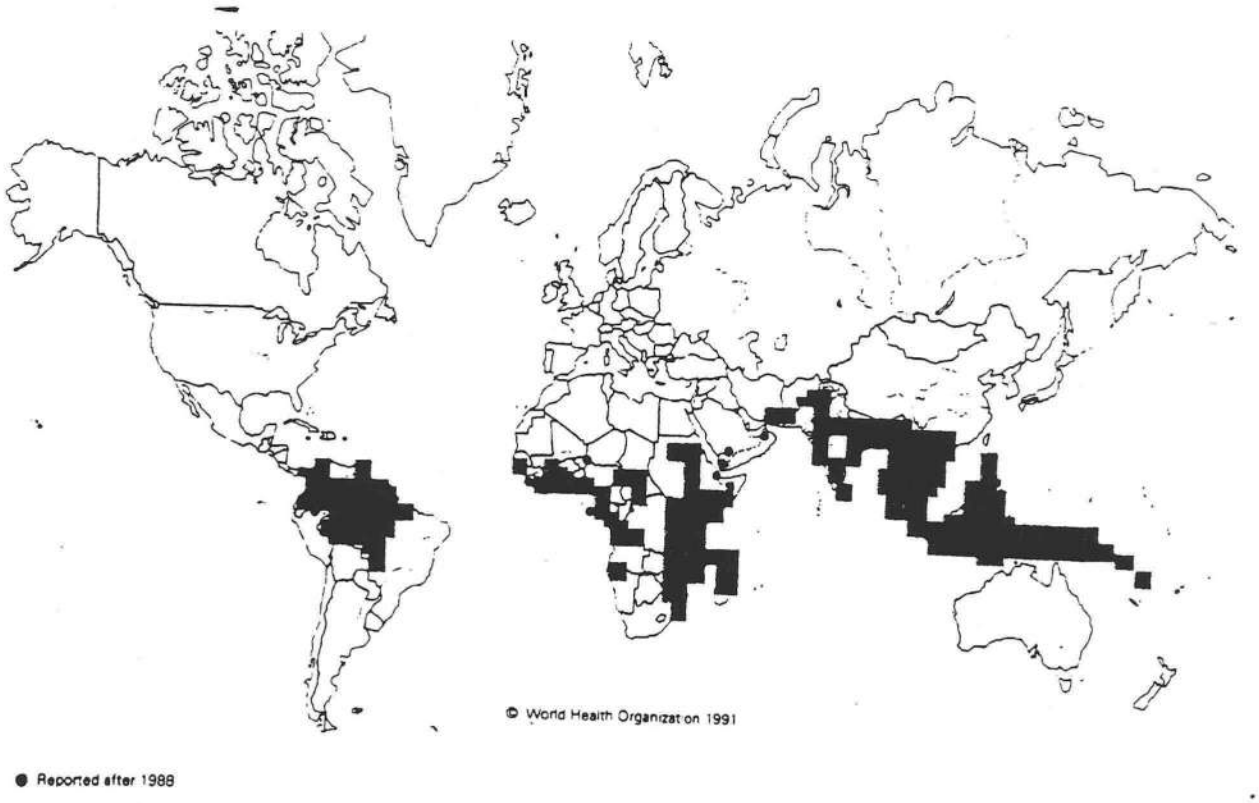

Figure 1: Current world-wide distribution where chloroquine-resistant *Plasmodium falciparum* has been reported.

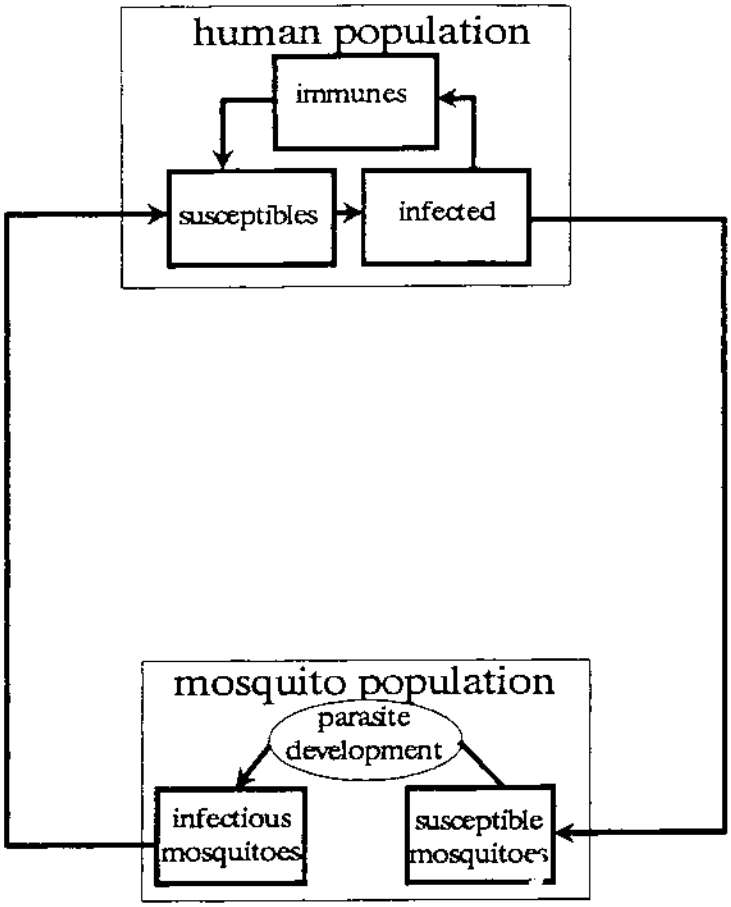

Figure 2: Transmission cycle of the malaria parasite.

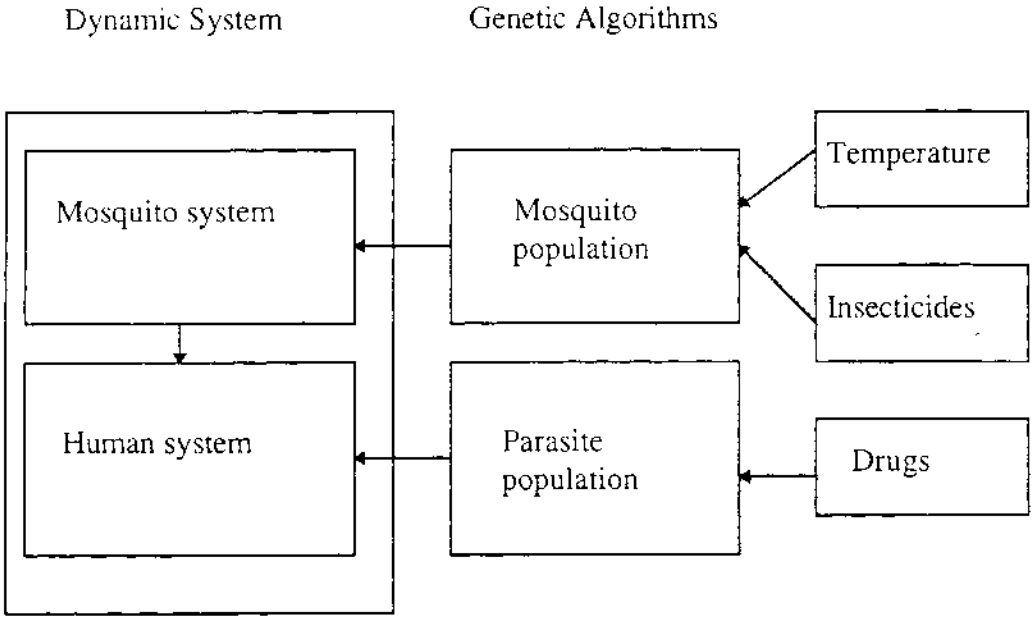

Figure 3: Simplified scheme of the integration of a system dynamic model and genetic algorithms.

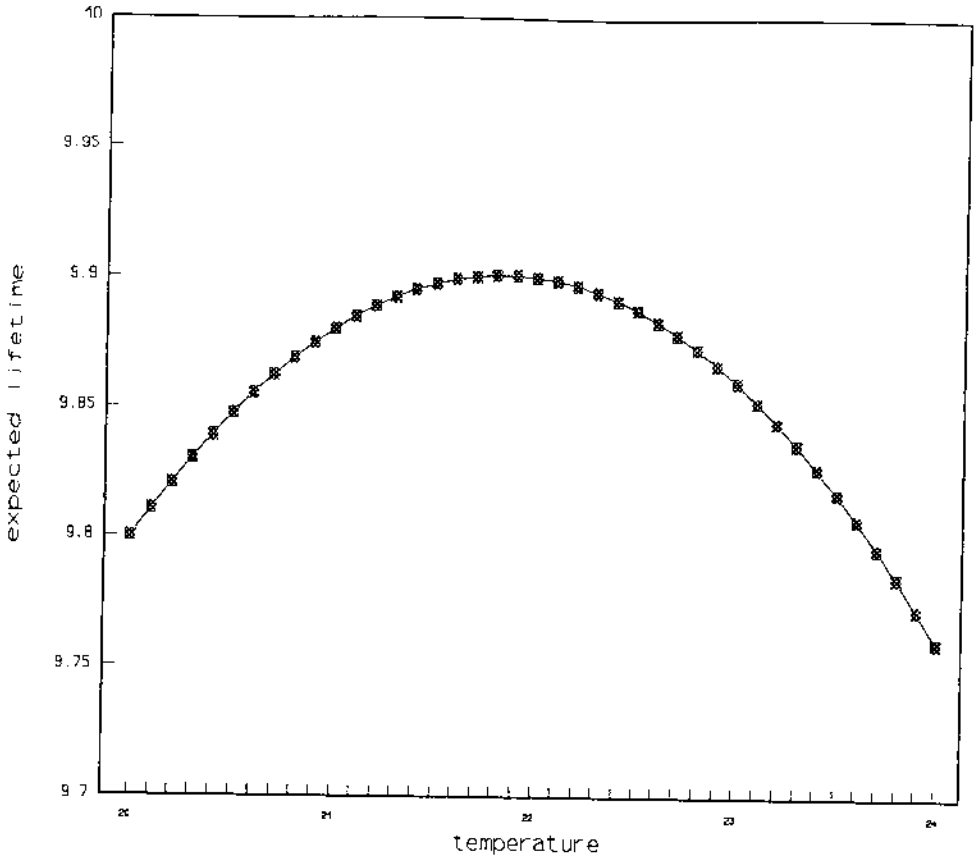

Figure 4: Expected lifetime (in days) as function of temperature (equation 13).

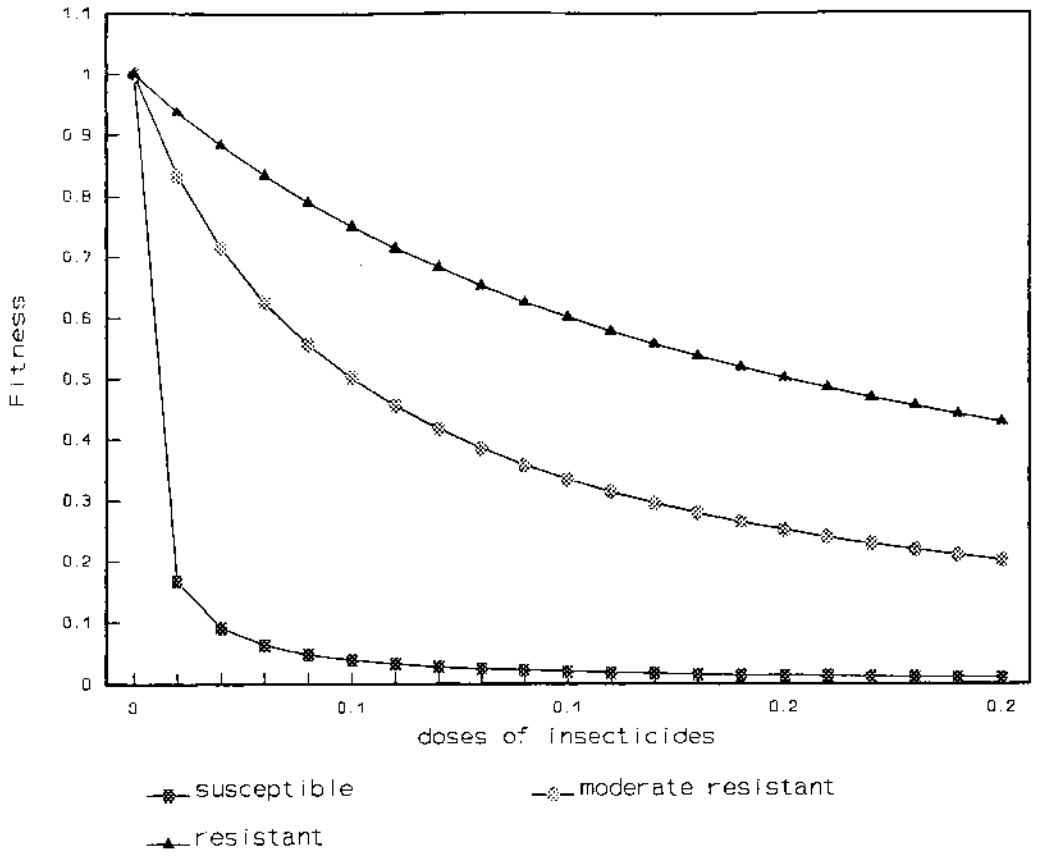

Figure 5: Relative fitness of mosquitoes related to the use of insecticides. An imaginary doses of insecticides lead to a reduction of the fitness, which is more severe for susceptible compared with the resistant ones.

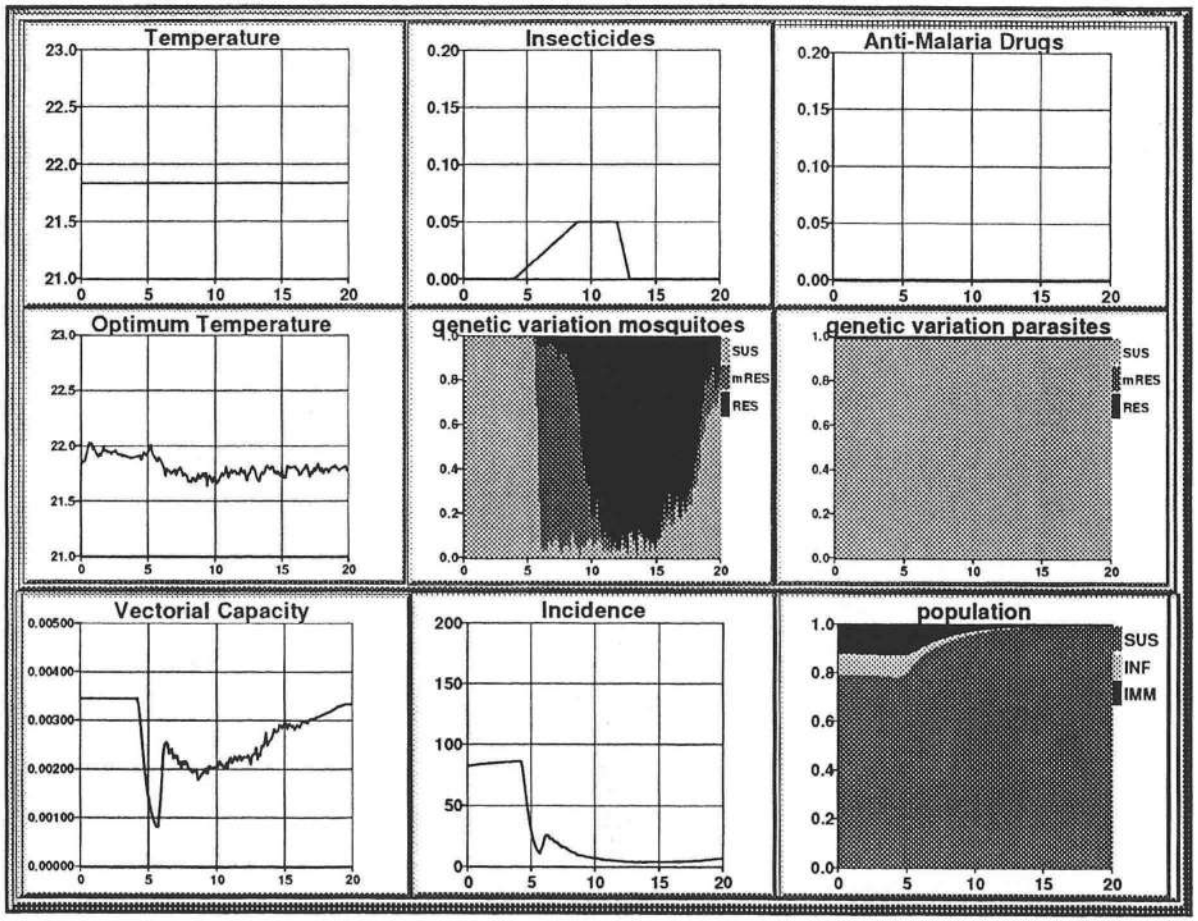

Figure 6: Results for a low endemic region if *insecticides* are used.

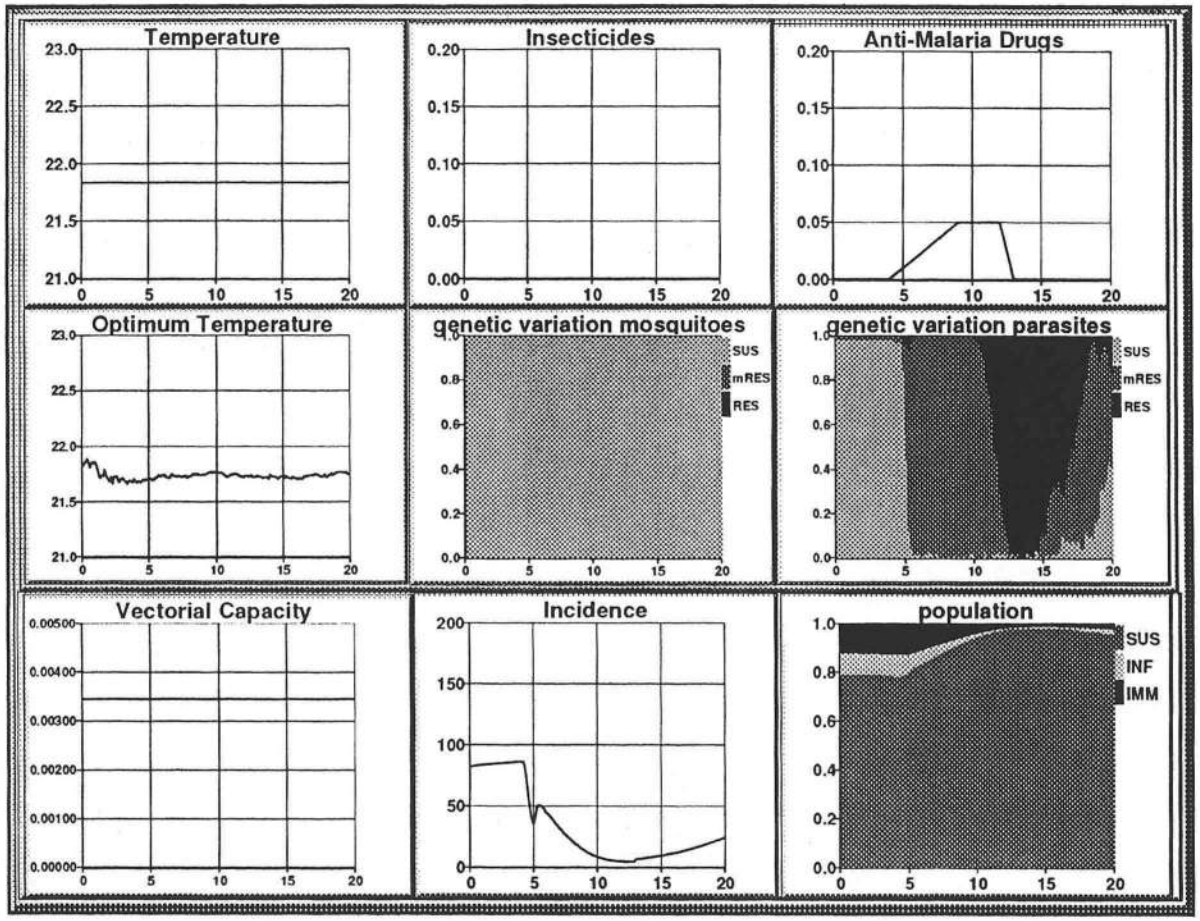

Figure 7: Results for a low endemic region if *anti-malaria drugs* are used.

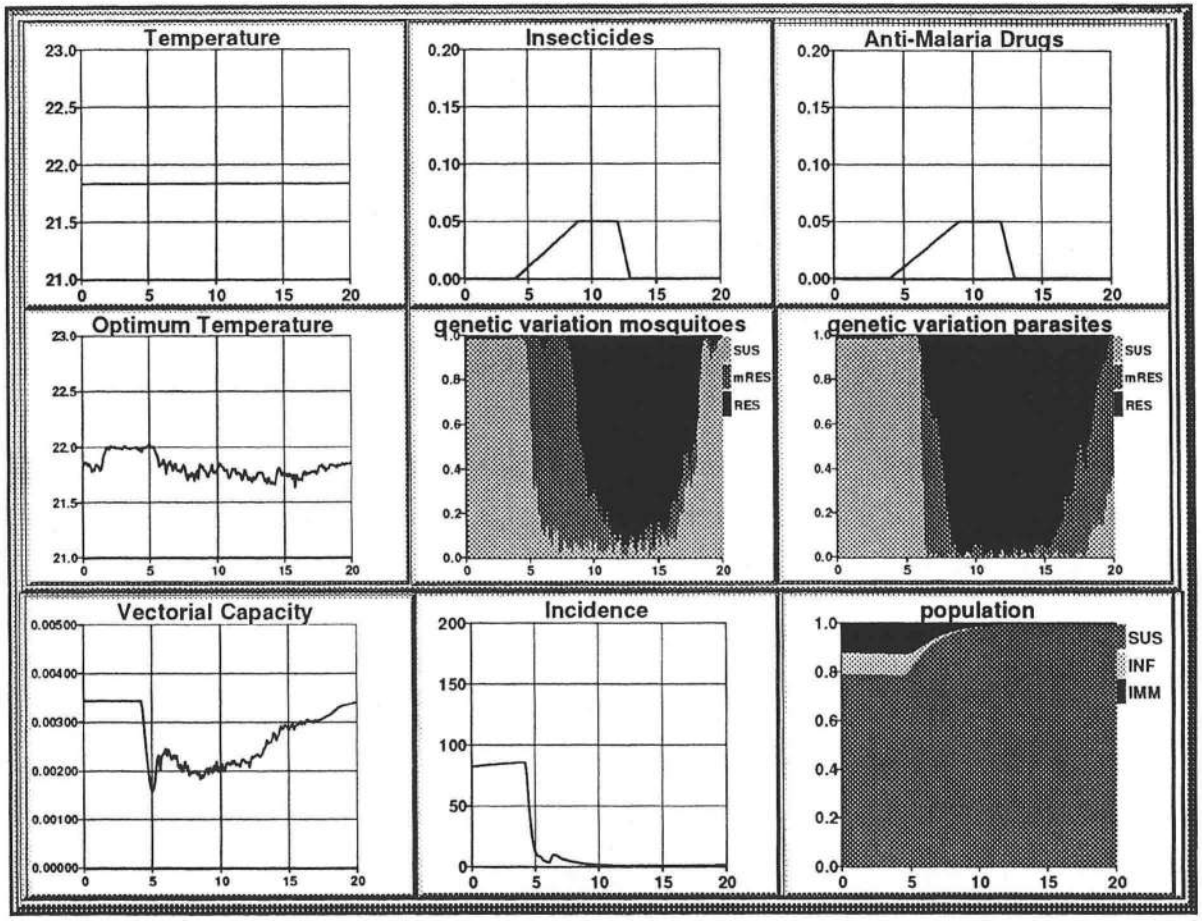

Figure 8: Results for a low endemic region if *insecticides and anti-malaria drugs* are used.

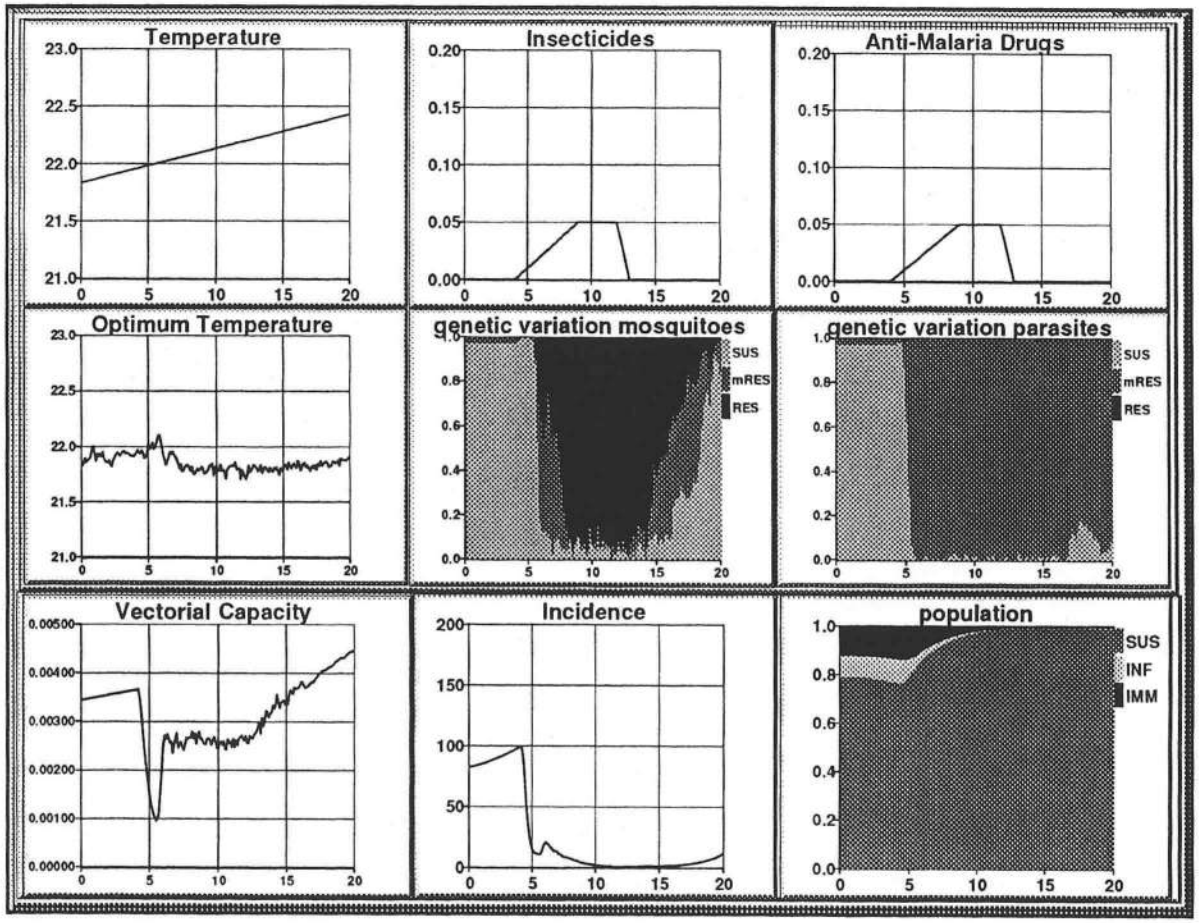

Figure 9: Results for a low endemic region if insecticides and anti-malaria drugs are used and if also a *temperature increase* occurs.

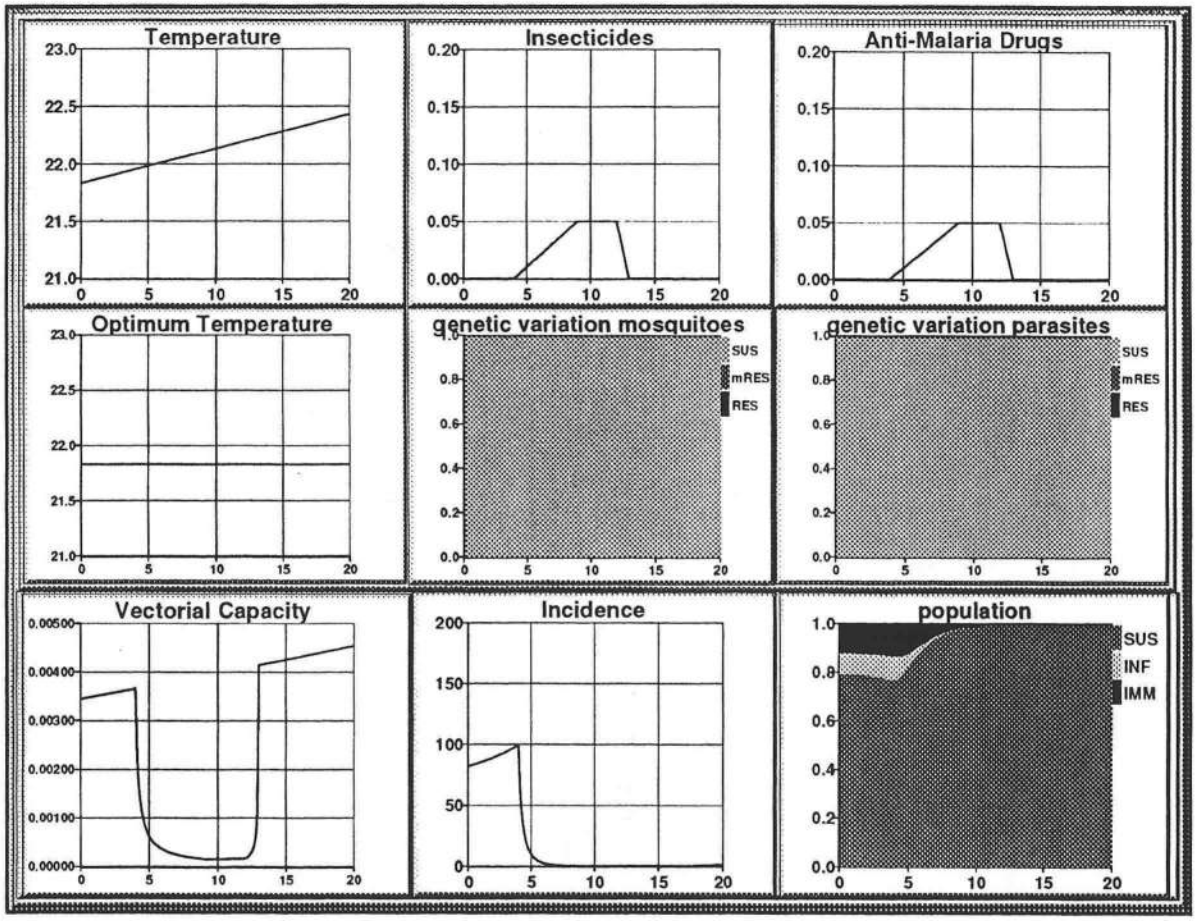

Figure 10: Results for a low endemic region if insecticides and anti-malaria drugs are used and if also a temperature increase occurs, but where the mosquitoes and parasites *do not adapt*.

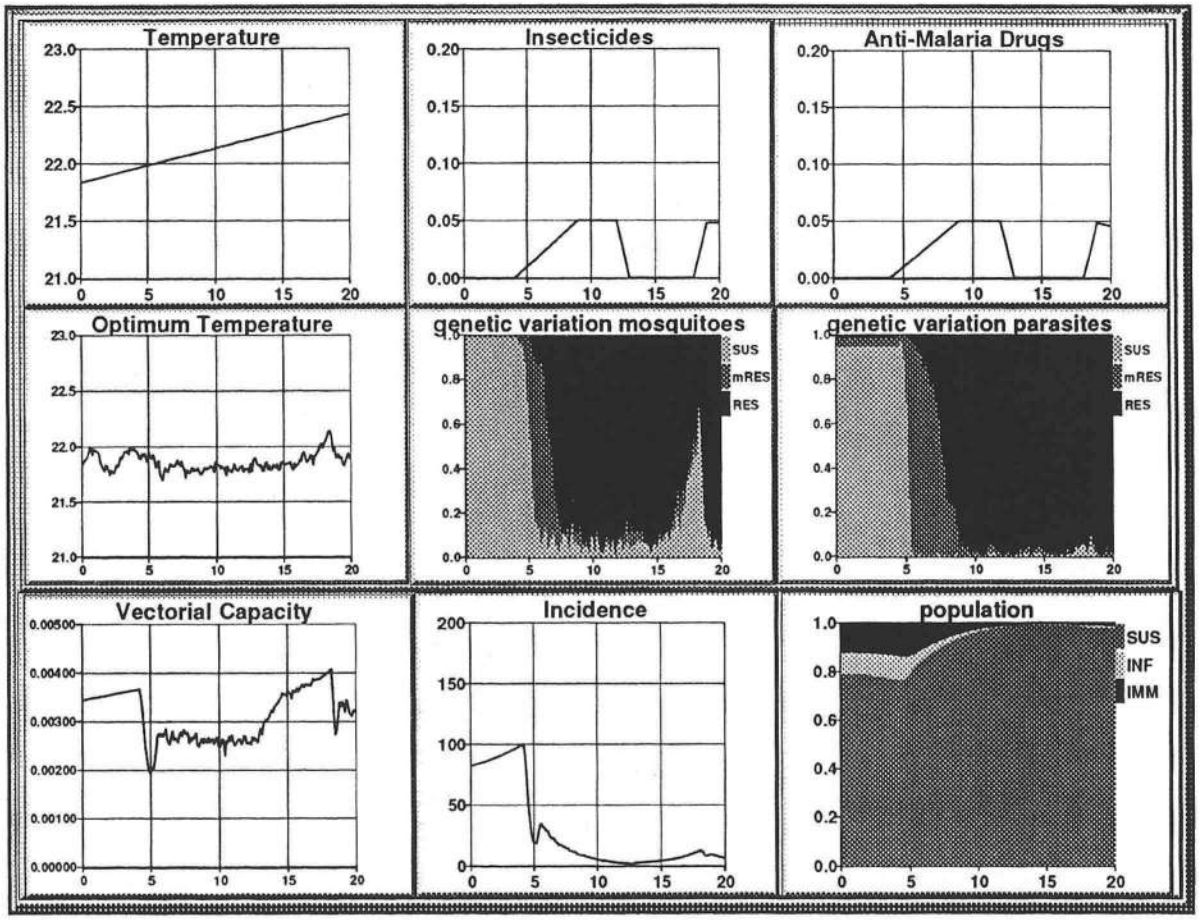

Figure 11: Results for a low endemic region if *additional* insecticides and anti-malaria drugs are used and if also a temperature increase occurs.

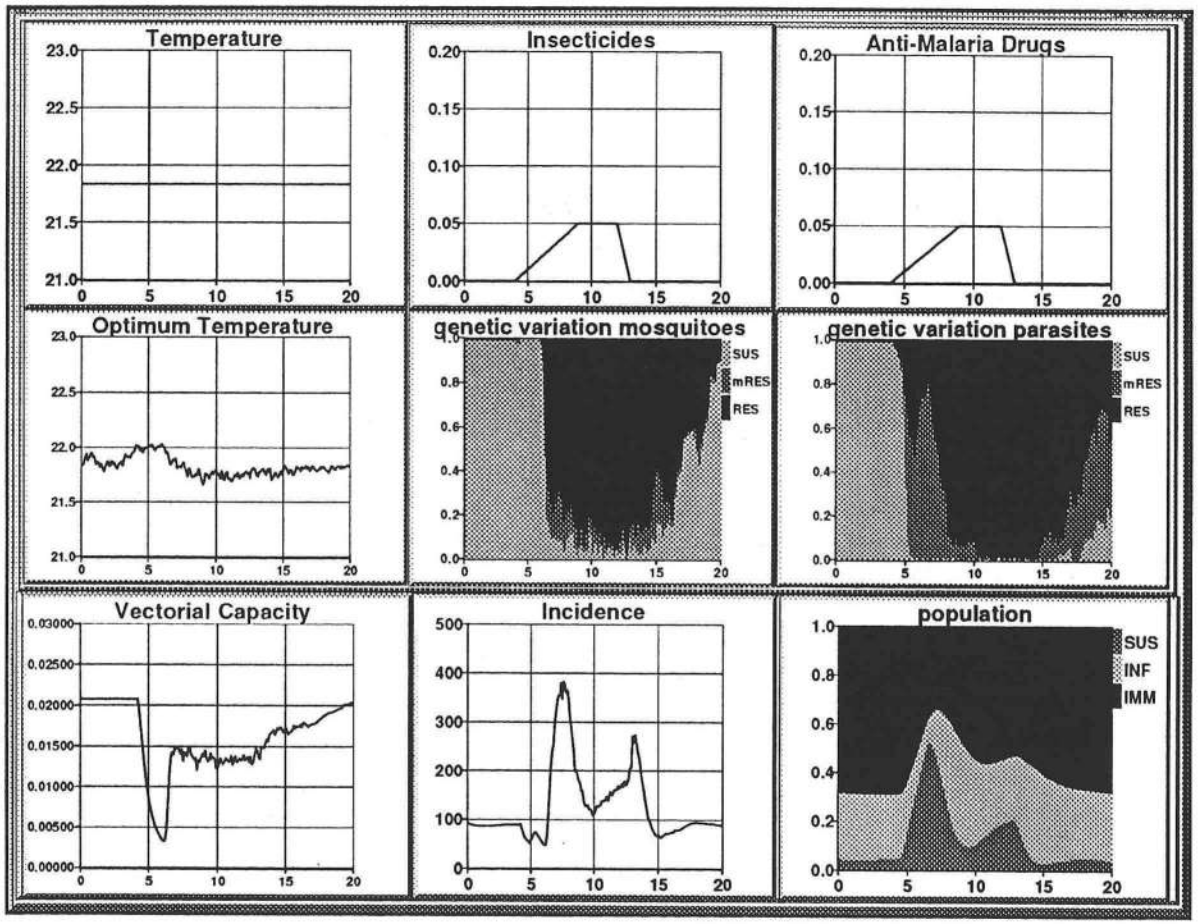

Figure 12: Results for a high endemic region if *insecticides* are used.

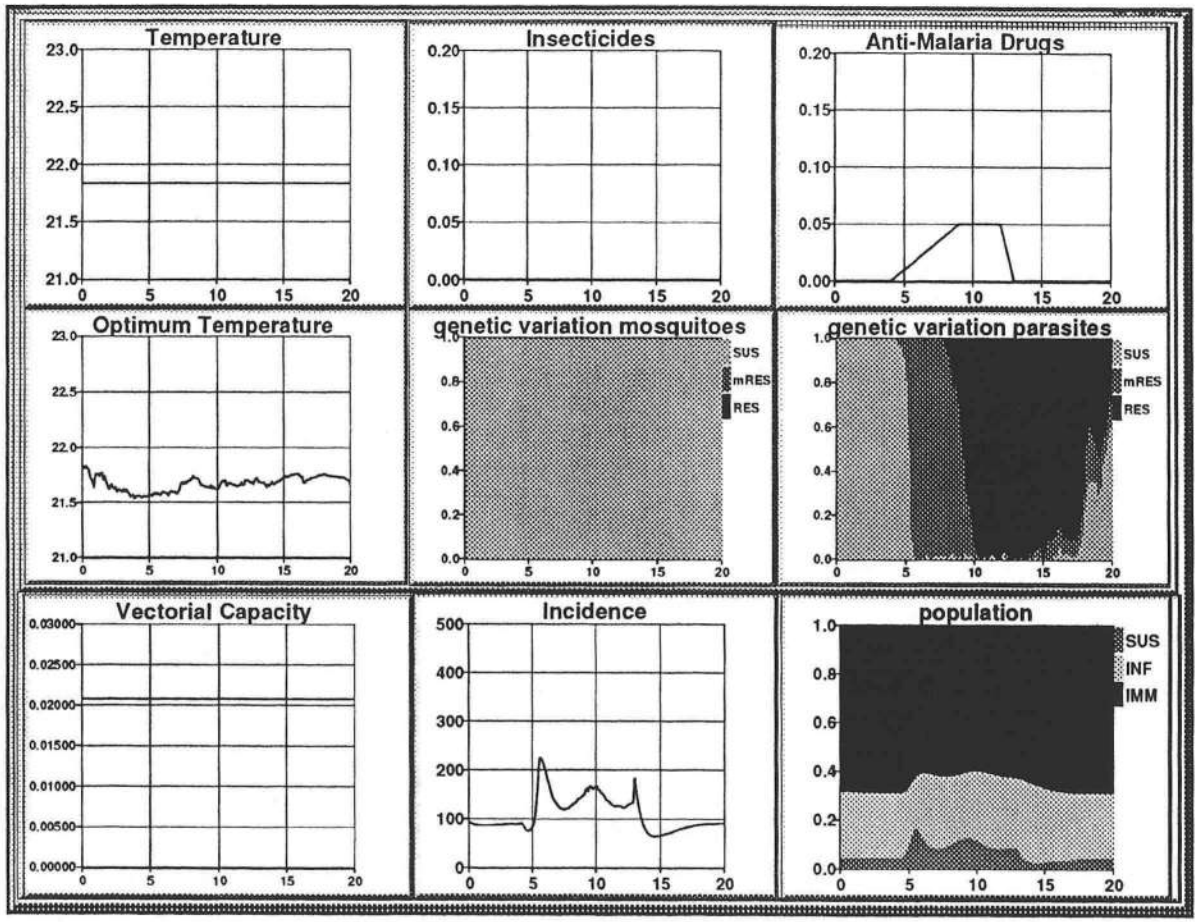

Figure 13: Results for a high endemic region if *anti-malaria drugs* are used.

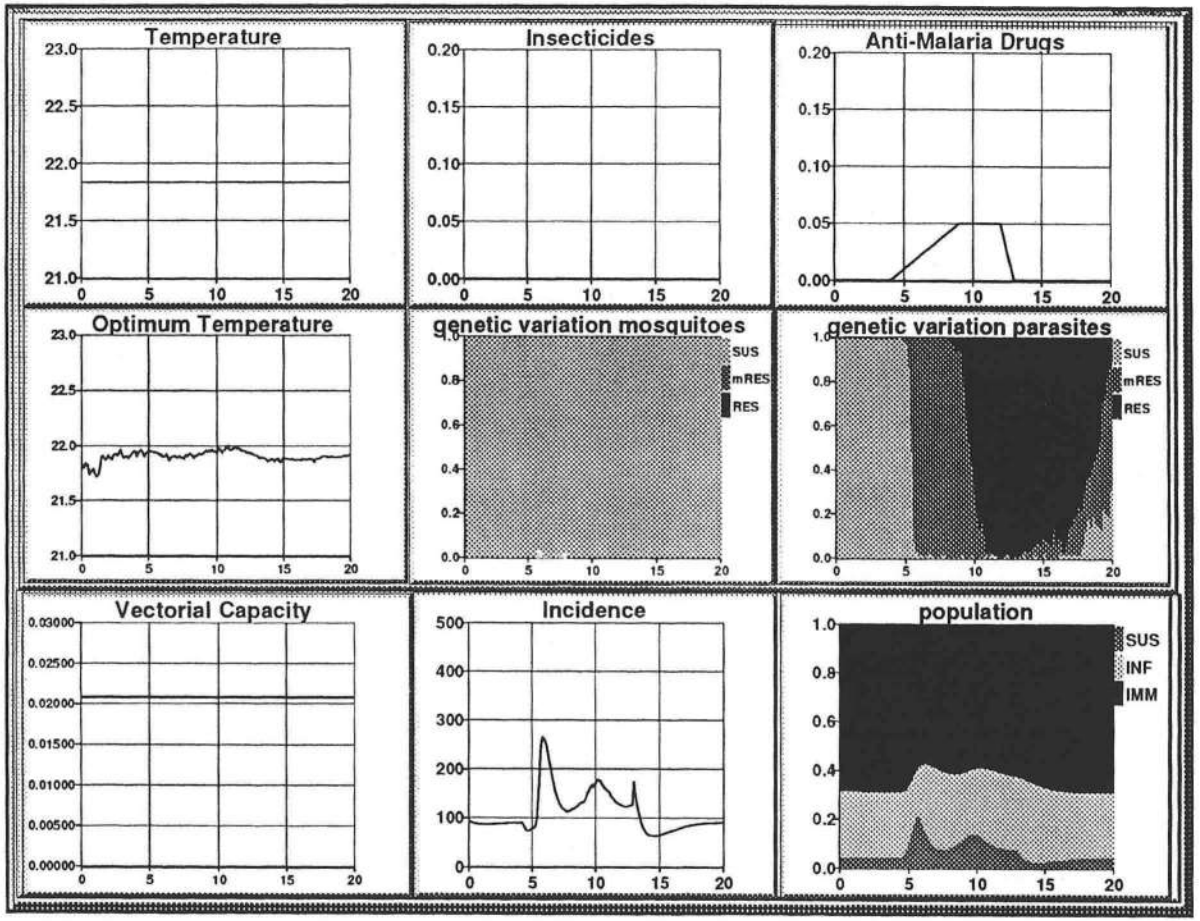

Figure 14: Results for a high endemic region if *insecticides and anti-malaria drugs* are used.

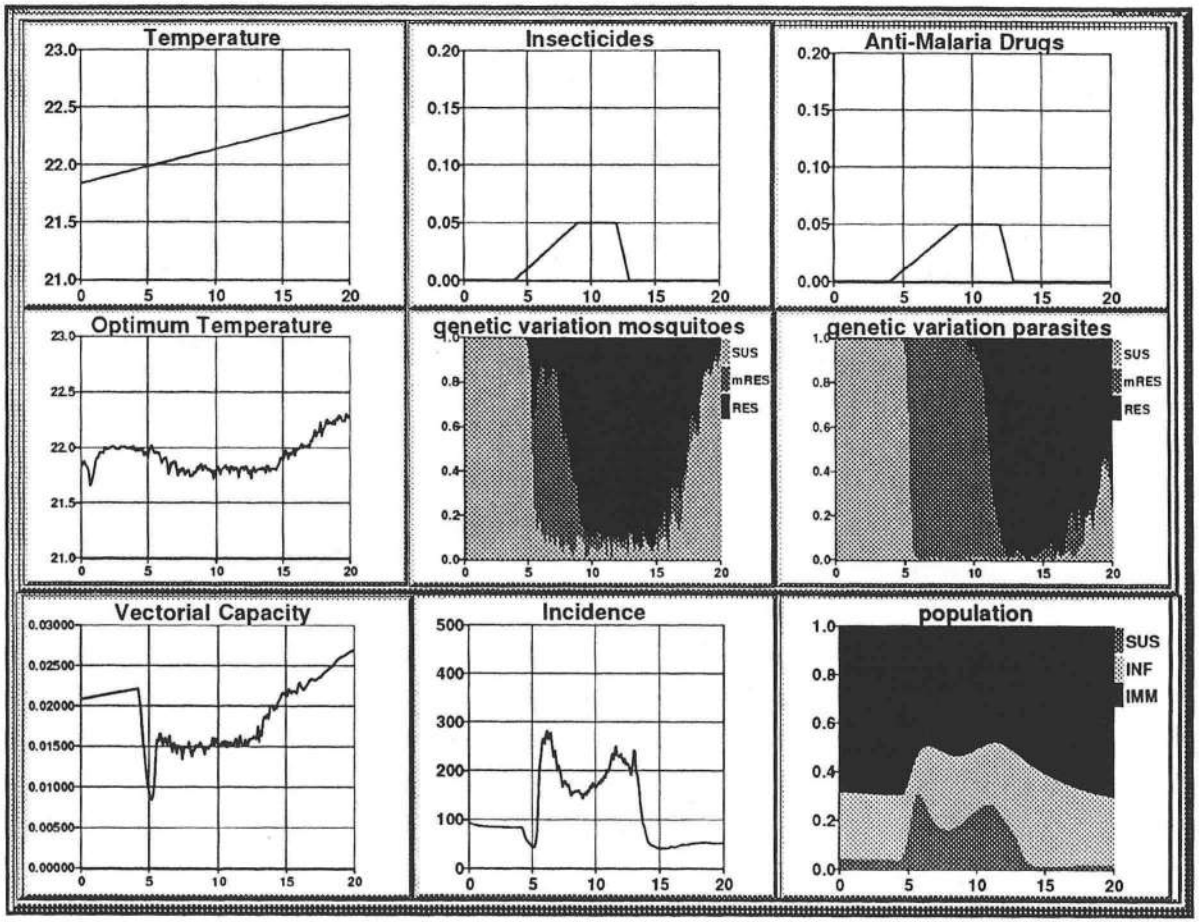

Figure 15: Results for a high endemic region if insecticides and anti-malaria drugs are used and if also a *temperature increase* occurs.

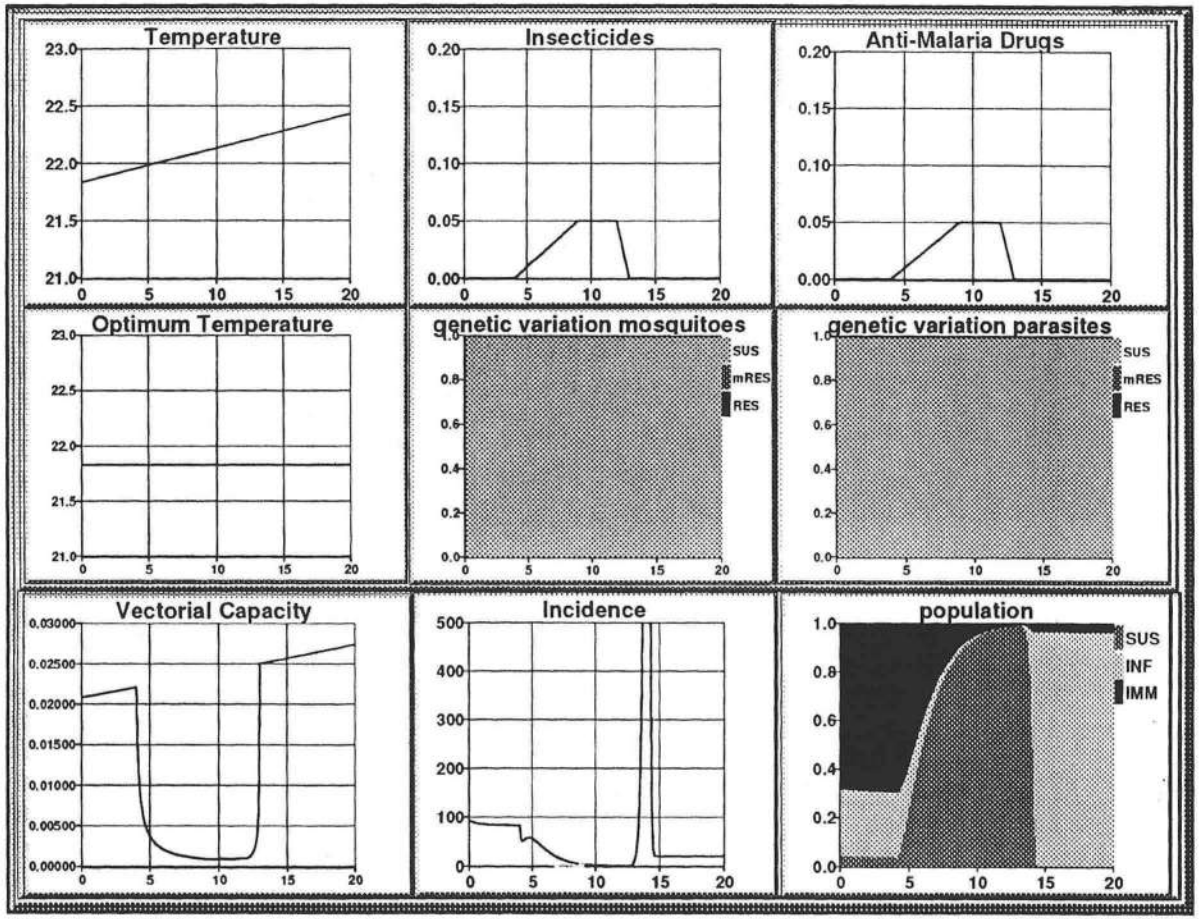

Figure 16: Results for a high endemic region if insecticides and anti-malaria drugs are used and if also a temperature increase occurs, but where the mosquitoes and parasites *do not adapt*.

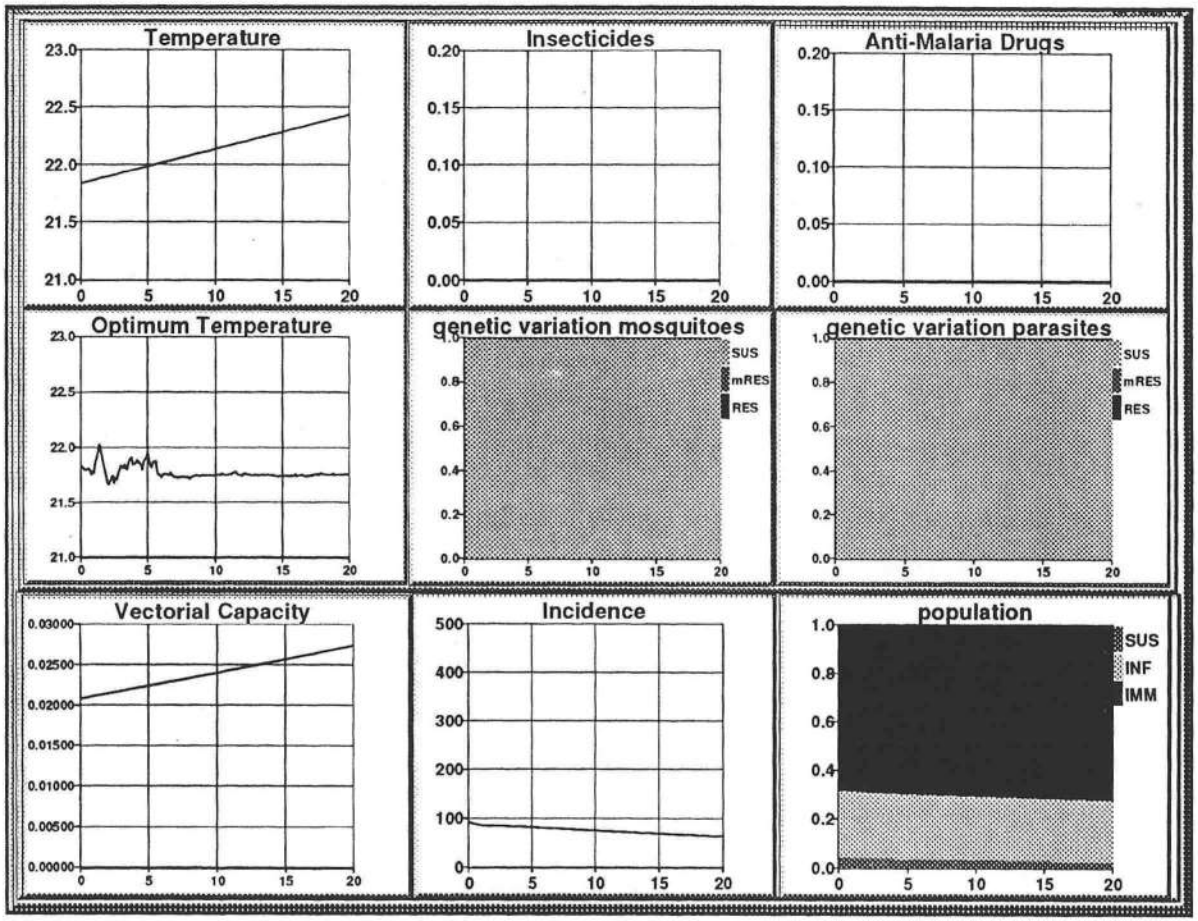

Figure 17: Results for a high endemic region if temperature increase but *no* insecticides and anti-malaria drugs are used.