Simulating malaria transmission dynamics in the pilot areas of the Colombian Integrated National Adaptation Pilot project

Research Group

Contributions

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1. MALARIA TRANSMISSION MODELS

The history of malaria mathematical modeling is reaching now more than a hundred years. In the first decade of the past century, Sir Ronald Ross, the British physician who first succeeded in demonstrating the life-cycle of malaria parasites in *Anopheles* mosquitoes, proposed the first mathematical approach for the study of malaria epidemiology. This tool, which was later revised and complemented by the British malariologist George Macdonald in the mid 1950s, provided valuable insights into the determinants of malaria transmission. The now referred to as the Ross-Macdonald model (see section 1.1, this chapter) is considered the basis of much of the epidemiological understanding of vector-borne diseases. A long list of dynamical models, each of them with a different level of complexity, can be cited in the recent history of malaria mathematical modeling. Most of them follow the traditional SIR (susceptible, infectious and recovered hosts) or SEIR (susceptible, infected, infectious, and recovered hosts) structures for the representation of malaria spread. Dynamical models can be used to analyze the general epidemiology of the disease (e.g. understand the role of climatic and non-climatic drivers); compare simulation outputs with actual malaria morbidity profiles observed in several endemic/epidemic-prone regions; simulate several changing epidemiological scenarios, to assess the effects of global warming and future changes in local climatic and socioeconomic conditions on malaria transmission; simulate the impact of control interventions; conduct stability analysis; and finally, stimulate an interactive learning environment.

The following mathematical tools, proposed to analyze malaria transmission dynamics, are discussed in this chapter: the Ross-Macdonald's model (MAC, 1957); the Martens' model (MAR, 1997); the classic differential-equation model discussed by McKenzie *et al.* (CDE-I, 1998); the differential-delay-equation 'compartment' model discussed by McKenzie *et al.* (CDE-II, 1998); the Yang's malaria transmission model (YANG, 2000) for different levels of acquired immunity and temperature-dependent parameters in the mosquito vector population; the tool for decision makers proposed by Githeko and Ndegwa (GNM, 2001); the dynamical model proposed by Ruiz *et al.* (SIMULMAL, 2002a, 2002b, 2003, 2006); the non-spatial malaria epidemiology model suggested by Ruiz and Yan (CDE-III, 2003) as a revision of the compartment models discussed by McKenzie *et al.* (1998); the weather-driven model of malaria transmission proposed by Hoshen and Morse (HM, 2004); the mathematical model proposed by Worrall, Connor, and Thomson (WCT, 2007); the transmission model of endemic human malaria proposed by Chiyaka, Garira and Dube (CHGD, 2007); and the Gomero's malaria-sickle-cell model (GOM, 2008). Level and exogenous variables considered by each model are presented in Tables 1.1 and 1.2, respectively. The summary of exogenous variables is presented in Table 1.3 for three different levels of understanding of malaria epidemiology (poor, partial and good) and for five major components

(community-based, parasite, human host, mosquito population, and environmental exogenous variables). Values for each epidemiological scenario can be gathered from published literature or local data, directly calculated from field records and mosquito life-table studies, or measured in laboratory experiments. Numerical simulations of these mathematical models are run using the computer software Powersim Constructor® Version 2.51.

1.1. THE ROSS-MACDONALD'S MODEL (MAC)

The Ross-Macdonald's model is expressed by the following system of two differential equations:

$$\frac{dX}{dt} = a\,b\,m\,Y - X\left(a\,b\,m\,Y + r\right), \text{ and}$$

$$\frac{dY}{dt} = a\,X - Y\left[\,a\,X - ln\left(p\right)\right],$$

where the dynamical variable *X* represents, according to Macdonald, 'the proportion of people affected', and the dynamical variable *Y* its (implicit) counterpart in the vector population. Parameter *m* denotes the *Anopheline* density in relation to man, *a* the average number of men bitten by one mosquito in one night, *b* the proportion of those *anophelines* with *sporozoites* in their salivary glands which are actually infective, *p* the probability of a mosquito surviving through one whole day, and *r* the proportion of affected people, who have received one infective inoculum only, who revert to the unaffected state in one day. The parameter *r* is reciprocal of the average duration of the "affected state", and is roughly equivalent to $\frac{1}{HD+WN}$ (McKenzie *et al.*, 1998), where HD denotes the host delay (length of the interval between infection or sporozoite inoculation, and the onset of infectivity or gametocyte maturation in a host) and WN represents the host window (duration of a host's infectivity to vectors, from the first to the final presence of infective gametocytes).

The crucial aspects of the Ross-Macdonald's model are summarized in the formula for Z_o, the Basic Reproduction Rate of malaria:

$$Z_0 = \frac{-\left(m\,a^2\,b\right)\,p^n}{r\left[\,ln\left(p\right)\right]} = \left(\frac{b}{r}\right)C\,,$$

where the parameter *n* represents 'the time taken for completion of the extrinsic cycle', and:

$$C = \frac{-\left(m\,a^2\right)\,p^n}{ln\left(p\right)},$$

summarizes the 'Vectorial Capacity' of malaria. The stock-flow model (created on Powersim Constructor® Version 2.51) is shown in Figure 1.1.

Macdonald derived the Basic Reproduction Rate Z_o as an estimate of the average number of secondary cases arising in a very large population at risk of completely susceptible humans following the introduction of a single primary case. $Z_o=1$ was defined as the transmission threshold: for values above, malaria cases will propagate; for values below, the disease will recede. The formula for Z_o holds that the influence of vector survivorship (p) is greater than the influence of the average number of men bitten by one mosquito in one day (a) or the sporogonic cycle (n), which are in turn greater than the influence of the proportion b, the density m, or the proportion r. Hence, Macdonald considered the vector survivorship as the single most important element in the Basic Reproduction Rate of malaria.

Macdonald's affected proportions do not distinguish between infected and infectious stages. His conclusion with respect to host infectivity was: 'transmission can be altered by reduction of the mean period of infectivity of a case of malaria. The influence is, however, relatively low; the reproduction rate varies directly with the mean duration of infectivity, very great changes in which would be necessary to reduce the high rates common in Africa and some other places below the critical level'. Macdonald's b is a measure of incidence (e.g. by its role in expressions for 'inoculation rate' and 'force of infection'), and r the reciprocal of the average duration of the 'affected' state. Macdonald wrote that 'in nature, the value of the reproduction rate is greatly influenced by immunity altering the values of r and b'. Some modeling results are shown in Figures 1.2 (a) and (b).

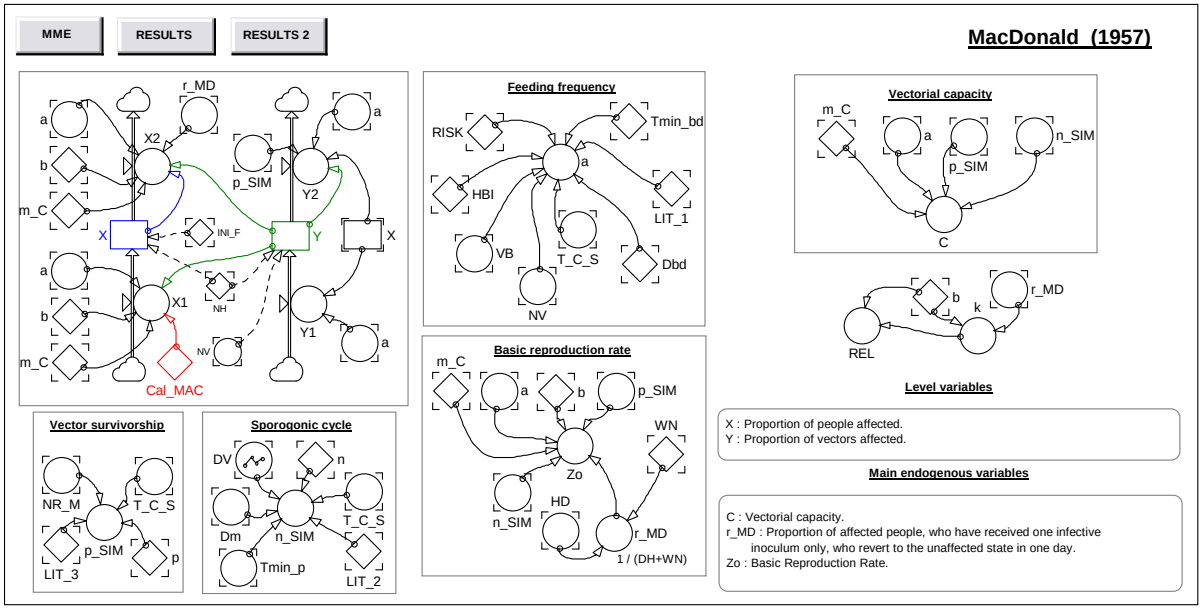
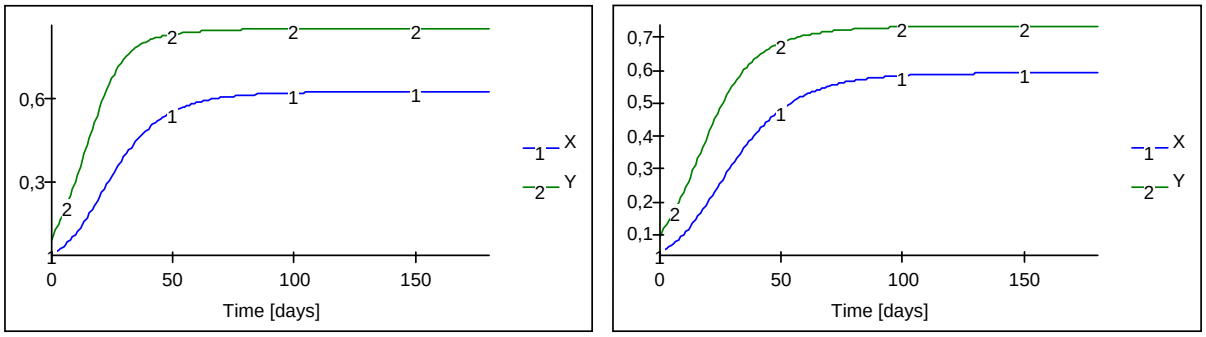


Figure 1.1. Ross-Macdonald's stock-flow model (1957)



(a) (b)

Figure 1.2. Time series of Ross-Macdonald's model results. (a) Level variables: X(0)=0.049, Y(0)=0.100; Exogenous variables: HD=20 days, WN=20 days, n=10 days, p=0.95, a=2,500/5,000, b=0.01, and m=10. The Basic Reproduction Rate and the Vectorial Capacity reached 11.67 and 29.18, respectively. (b) Level variables: X(0)=0.049, Y(0)=0.100; Exogenous variables: HD=20 days, WN=20 days, n=10 days, p=0.90, a=2,500/5,000, b=0.01, and m=10. For this case, Zo and C reached 3.31 and 8.27, respectively.

1.2. THE MARTENS' MODEL (MAR)

The mathematical model suggested by Martens (1997) is based on the epidemiological models proposed by Aron y May (1982), Bailey (1982), Levin *et al*. (1989), and Anderson and May (1991). The human population subject to a risk of malaria, for a given age a^*, is divided into three categories:

susceptible persons (X), infected persons (Y), and immune persons (Z). The latent reservoir is omitted because the duration of a stay in this reservoir is usually very short in comparison with the residence time in the other reservoirs. The proposed system of differential equations is the following:

$$\frac{\delta X}{\delta t} + \frac{\delta X}{\delta a^*} = \gamma(t)\, Z(a^*, t) - [\lambda(t) + \mu]\, X(a^*, t),$$

$$\frac{\delta Y}{\delta t} + \frac{\delta Y}{\delta a^*} = \lambda(t)\, X(a^*, t) - [v(t) + \mu] Y(a^*, t), \text{ and}$$

$$\frac{\delta Z}{\delta t} + \frac{\delta Z}{\delta a^*} = v(t) Y(a^*, t) - [\gamma(t) + \mu] Z(a^*, t),$$

where $\lambda(t) = VC \cdot Y'(t)$, $v(t) = \frac{\lambda(t)}{e^{\lambda(t)\upsilon} - 1}$, and $\gamma(t) = \frac{\lambda(t)}{e^{\lambda(t)\tau} - 1}$. Susceptible persons become members of the infected class at a rate $\lambda(t)$, which depends on the vectorial capacity VC and on the proportion of infected people in the human population $Y'(t)$. Infected individuals recover and join the immune class at a rate $v(t)$. Immune people lose their immunity and return to the reservoir of susceptible individuals at a rate $\gamma(t)$. μ denotes the natural death rate, υ and τ the fixed periods of time during which infection and immunity endure, respectively (assuming that re-exposure does not occur). The stock-flow model (created on Powersim Constructor® Version 2.51) and some modeling results are depicted in Figures 1.3 and 1.4.

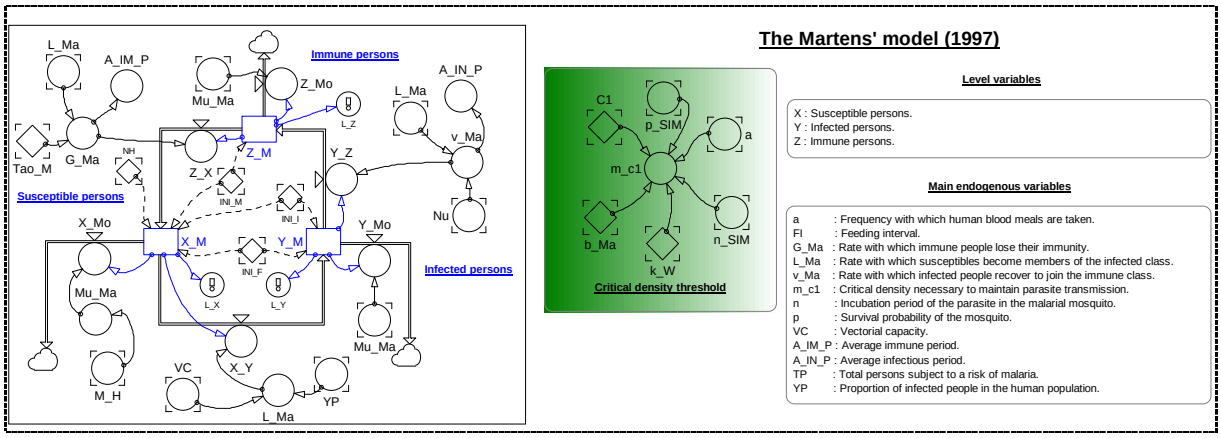


Figure 1.3. Stock-flow model of the Martens' malaria transmission model (1997)

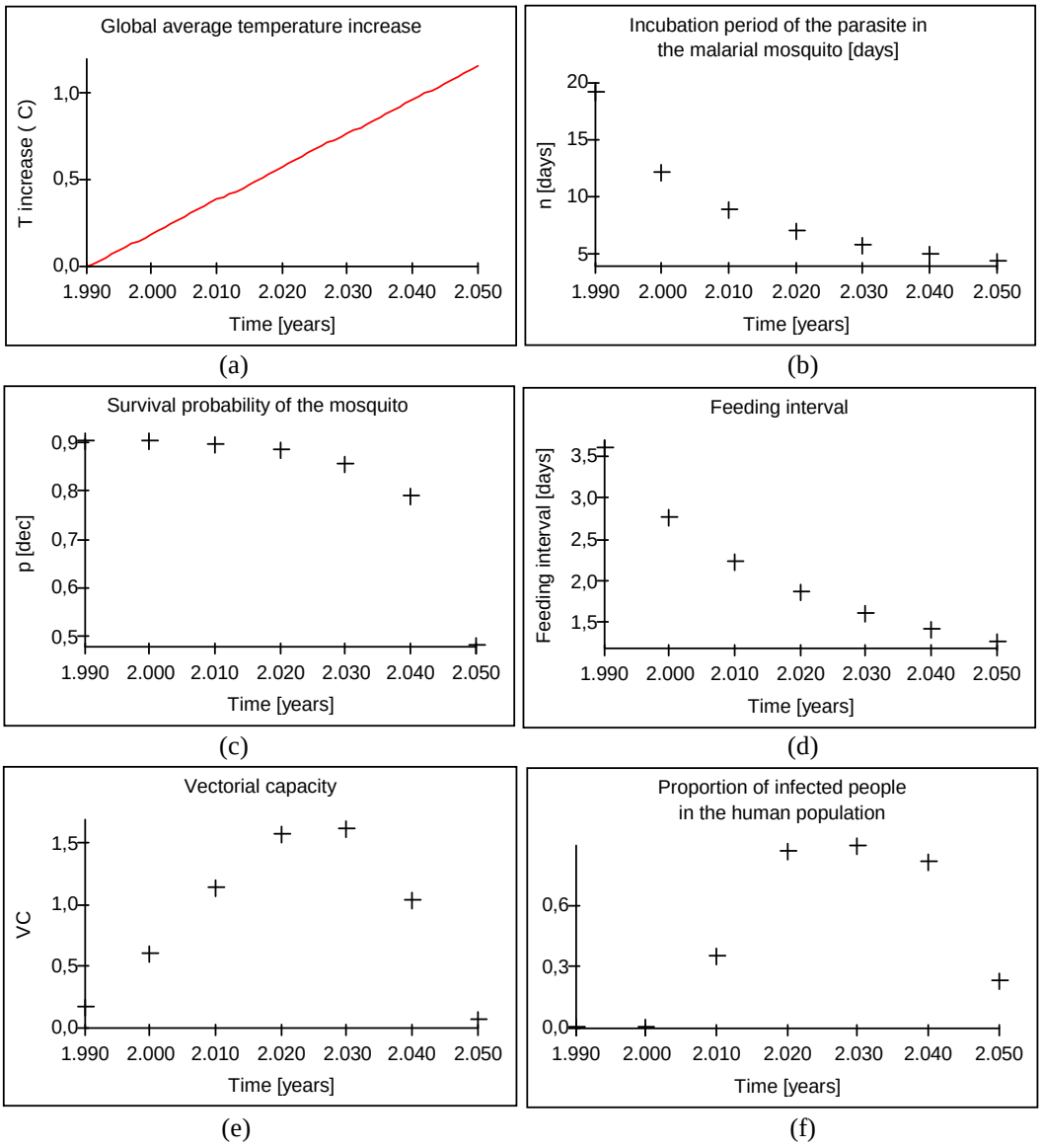


Figure 1.4. Time series of MAR model results for the simulation period 1990-2050 and assuming a time interval of 1 year. (a) Global temperature changes according to the IS92c scenario; (b) Mean duration of the extrinsic incubation period; (c) Mean daily survival probability of the mosquito vector; (d) Estimated feeding interval; (e) VC; and (f) proportion of infected individuals. The incubation period of malaria parasites and the vectorial capacity are estimated for *Plasmodium vivax* infection (defined by the exogenous variable PAR; (=1) for *P. vivax* and (=2) for *P. falciparum*). Level variables: X(0)=500, Y(0)=1, and Z(0)=10; Exogenous variables: υ=3 years (*P. vivax* infection), τ=1.5 years, μ=0.02/year, b=1.0 (efficiency with which an infective mosquito infects a susceptible human; Martens, 1997), c_l=1.0, D_m=105°C-day and $T_{min,p}$=14.5°C (for the estimation of the incubation period *n*; Martens, 1997), D_{bd}=36.5°C-day, $T_{min,bd}$=9.9°C and HBI=0.40 (for the estimation of the feeding frequency *a*; Martens, 1997), k_1=10 mosquitoes/human host, c=1.0 (recovery rate in humans; Martens, 1997), and k_W=1.0 (mosquito susceptibility or efficiency with which an infective human infects a susceptible mosquito; Martens, 1997).

1.3. THE CLASSIC DIFFERENTIAL-EQUATION MODEL (CDE-I)

The classic differential-equation model is given by the following system of seven differential equations:

$$\frac{dS}{dt} = q\,R - h\,F\,S\,,$$

$$\frac{dM}{dt} = h\,F\,S - k\,M\,,$$

$$\frac{dG}{dt} = k\,M - p\,G\,,$$

$$\frac{dR}{dt} = p\,G - q\,R\,,$$

$$\frac{dU}{dt} = b - h\,G\,U - d\,U\,,$$

$$\frac{dL}{dt} = h\,G\,U - c\,L - d\,L\,,\text{ and}$$

$$\frac{dF}{dt} = c\,L - d\,F\,,$$

where the dynamic variables *S*, *M*, *G* and *R* denote the proportions of susceptible, infected, infectious and immune humans, and *U*, *L* and *F* the proportions of susceptible, infected and infectious vectors, respectively. The parameters *h*, *b* (or *b_MK*) and *d* represent daily rates of vector biting, natality and mortality, respectively; *b/d* gives the ratio of vectors to human hosts *NV/NH* (*NV* represents the initial vector population size, and *NH* the host population size). Flow rates between human compartments are represented by the parameters *q* from immune to susceptible, *k* from infected to infectious and *p* from infectious to immune. Parameter *c* represents the flow rate between the infected and infectious mosquito compartments. The stock-flow model (created on Powersim Constructor® Version 2.51) is shown in Figure 1.5. Some modeling results are shown in Figure 1.6.

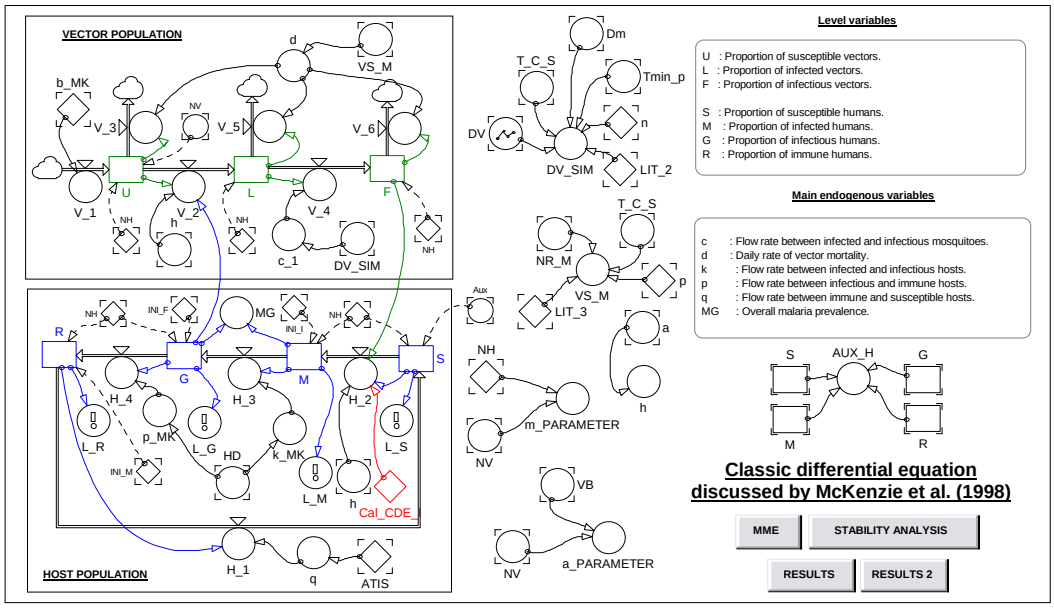


Figure 1.5. Stock-flow model of the classic differential-equation discussed by McKenzie *et al.* (1998)

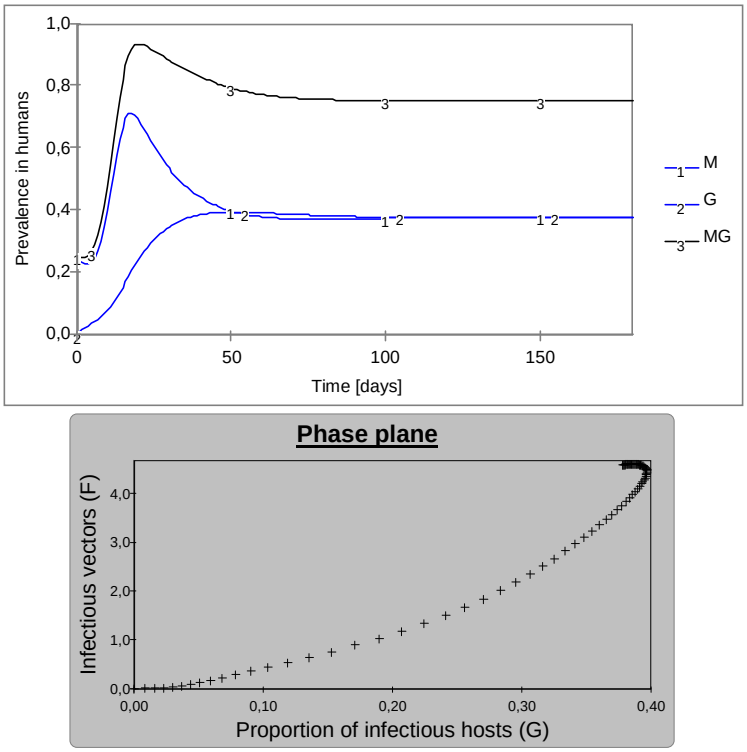


Figure 1.6. Time series of CDE-I model results (top) and phase plane (bottom). Level variables: S(0)=375/NH, M(0)=125/NH, G(0)=0/NH, R(0)=0/NH, U(0)=NV/NH, L(0)=0/NH, and F(0)=0/NH. Exogenous variables: NH=500, HD=20 days, ATIS=12.55 days (average time in immune state), b_MK=0.50, DV=10 days (vector delay between infection and the onset of infectivity), VS=0.95 (vector survivorship), h=0.50 day^{-1}, and NV=5,000 (vector population size).

1.4. THE DIFFERENTIAL-DELAY-EQUATION 'COMPARTMENT' MODEL (CDE-II)

The differential-delay-equation model replaces each of the parameters *k*, *p* and *c* of the classic differential-equation model with an explicit *time lag* corresponding to the host delay *HD* (length of the interval between infection or sporozoite inoculation, and the onset of infectivity or gametocyte maturation in a host), the host window *WN* (duration of a host's infectivity to vectors, from the first to the final presence of infective gametocytes) and the vector delay *DV* (length of the interval between infection or gametocyte ingestion, and the onset of infectivity or sporozoite migration in a vector), such that:

$$\frac{dS}{dt} = q\,R - h\,F\,S\,,$$

$$\frac{dM}{dt} = h\,F\,S - \left[\,h\,F\,S\,\right]_{t-k}\,,$$

$$\frac{dG}{dt} = \left[\,h\,F\,S\,\right]_{t-k} - \left[\,h\,F\,S\,\right]_{t-(k+p)}\,,$$

$$\frac{dR}{dt} = \left[\,h\,F\,S\,\right]_{t-(k+p)} - q\,R\,,$$

$$\frac{dU}{dt} = b - h\,G\,U - d\,U\,,$$

$$\frac{dL}{dt} = h\,G\,U - \left[1 - e^{-c\,d}\right]\left[\,h\,G\,U\,\right]_{t-c} - d\,L\,,\ \text{and}$$

$$\frac{dF}{dt} = \left[1 - e^{-c\,d}\right]\left[\,h\,G\,U\,\right]_{t-c} - d\,F\,,$$

where the dynamical variables and parameters were described above. No equilibrium can be calculated for this system, and its dynamics depends on the initial conditions. The stock-flow model (created on Powersim Constructor® Version 2.51) and some modeling results are shown in Figures 1.7 and 1.8, respectively.

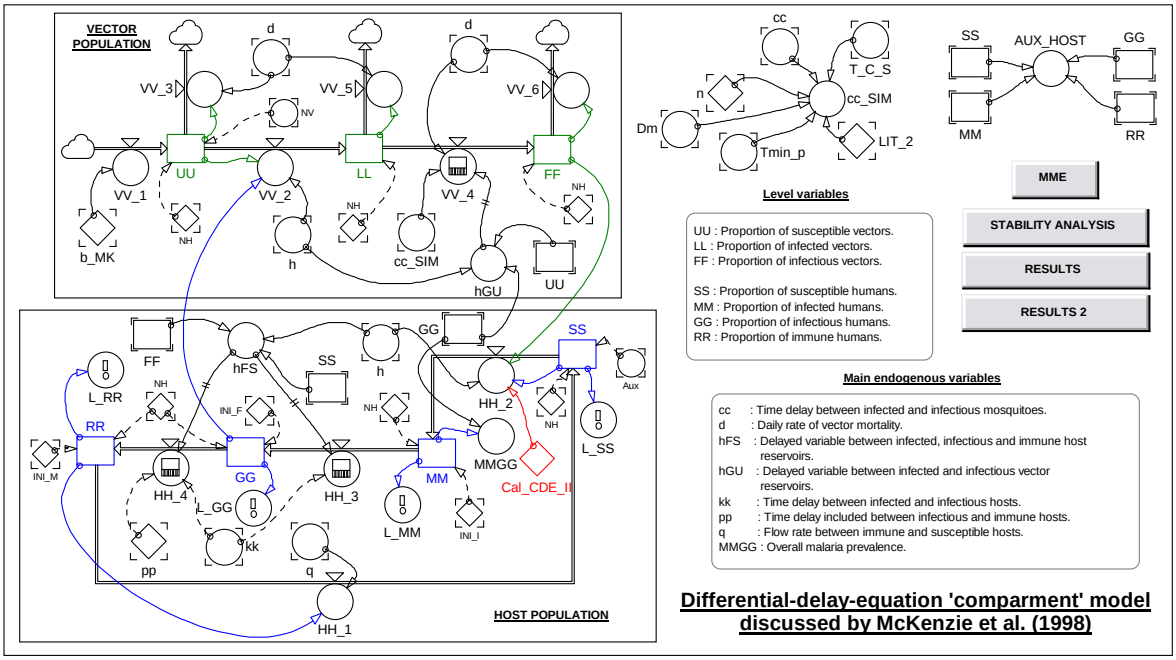


Figure 1.7. Stock-flow model of the differential-delay-equation 'compartment' model discussed by McKenzie *et al.* (1998)

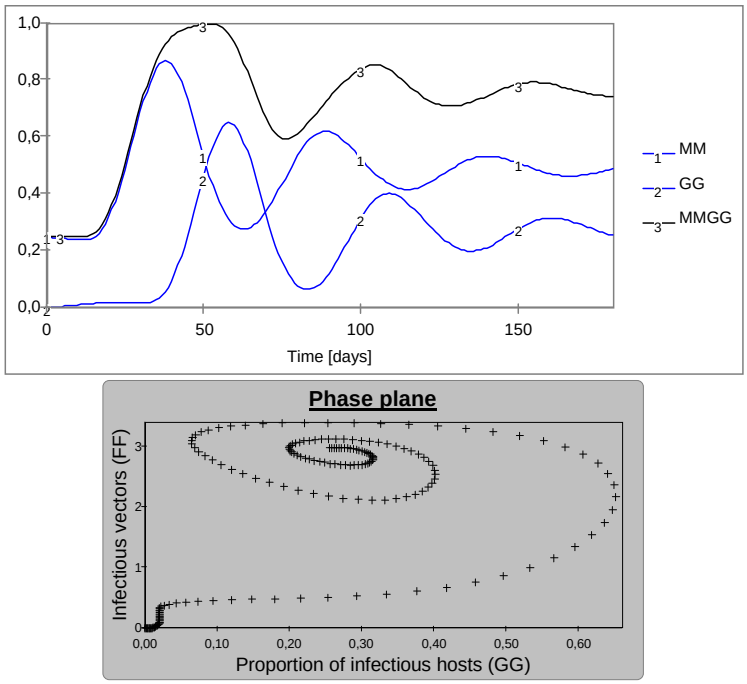


Figure 1.8. Time series of CDE-II model results (top) and phase plane (bottom). Level variables: SS(0)=375/NH, MM(0)=125/NH, GG(0)=0/NH, RR(0)=0/NH, UU(0)=NV/NH, LL(0)=0/NH, and FF(0)=0/NH. Exogenous variables: NH=500, kk=20 days (host delay from infected to infectious hosts), pp=20 days (host delay from infectious to immune hosts), b=0.50, cc=10 days (explicit time lag corresponding to the vector delay, from infected to infectious), VS=0.95, h=0.50 day^{-1}, and NV=5,000.

1.5. THE YANG'S MALARIA TRANSMISSION MODEL FOR DIFFERENT LEVELS OF ACQUIRED IMMUNITY AND TEMPERATURE-DEPENDENT PARAMETERS (YANG)

In this model the human host immunity is included by assuming the existence of acquired immunity and immunological memory, which boosts the protective response upon re-infection. The fractions of host population are described by the following system of seven differential equations:

$$\frac{dX_1(t)}{dt} = \mu + (\theta + \alpha) X_2(t) + \pi_3 X_6(t) - [h y_3(t) + \mu] X_1(t),$$

$$\frac{dX_2(t)}{dt} = h y_3(t) X_1(t) - (\theta + \gamma_1 + \mu + \alpha) X_2(t),$$

$$\frac{dX_3(t)}{dt} = \gamma_1 X_2(t) - (\gamma + \mu) X_3(t),$$

$$\frac{dX_4(t)}{dt} = \gamma X_3(t) + h y_3(t) X_5(t) - \gamma_1 X_7(t) - (\pi_1 + \mu) X_4(t),$$

$$\frac{dX_5(t)}{dt} = \pi_1 X_4(t) - [h y_3(t) + \pi_2 + \mu] X_5(t),$$

$$\frac{dX_6(t)}{dt} = \pi_2 X_5(t) + \theta X_7(t) - [h y_3(t) + \pi_3 + \mu] X_6(t), \text{ and}$$

$$\frac{dX_7(t)}{dt} = h y_3(t) X_6(t) - (\theta + \gamma_1 + \mu) X_7(t),$$

where $X_1(t)$ represents the fraction of individuals at a given time t who are susceptible, $X_2(t)$ the fraction of incubating individuals (those with asexual blood-stage infection but without infectious gametocytes), $X_3(t)$ the fraction of infectious people (those with circulating mature gametocytes), $X_4(t)$ the fraction of immune individuals (fully protected against new infections), $X_5(t)$ the fraction of partially immune hosts (still have some protective antibodies and other immune effectors but at low levels; if inoculated with *sporozoites*, however, effective immune responses will be elicited before asexual parasitemia develops), $X_6(t)$ the fraction of non-immune hosts but with immunologic memory (those who are susceptible to new inoculations, but asexual blood-stage parasitemia is cleared before infectious gametocytes are produced), and $X_7(t)$ the fraction of incubating people after re-infection.

μ and α are the natural and differential (disease-induced) mortality rates for the human host, respectively; θ is the natural resistance rate against malaria; $(1/\gamma_1)$ the average period of time delayed from the infection until the appearance of gametocytes in the human host (average period to initiate the production of gametocytes); and $(1/\gamma)$ the average period to build up an effective immune response in the human host. Parameters π_1, π_2, and π_3 represent the rates at which protective immunity, partial immunity

and immunologic memory decrease, respectively. Finally, *h* represents the inoculation rate (parameter dependent on the average number of mosquito's bites on humans, which measures the level of interaction between both populations).

The mosquito population is described by the following system of three differential equations:

$$\frac{dY_1(t)}{dt} = \phi\left[\frac{\sigma_1(T)}{\sigma_1(T)+\mu_e(T)}\right][Y_1(t)+Y_2(t)+Y_3(t)]-\left[f\ X_3(t)+\mu'+\alpha'\right]Y_1(t),$$

$$\frac{dY_2(t)}{dt} = f\ X_3(t)Y_1(t)-\left[\sigma_2(T)+\mu'+\alpha'\right]Y_2(t), \text{ and}$$

$$\frac{dY_3(t)}{dt} = \sigma_2(T)Y_2(t)-\left(\mu'+\alpha'\right)Y_3(t),$$

where $Y_1(t)$ represents the number of susceptible mosquitoes at time t, $Y_2(t)$ the number of incubating vectors (infected but non-infectious), and $Y_3(t)$ the total number of infectious mosquitoes. μ' and α' represent the natural and induced (for instance, by insecticides) mortality rates of mosquitoes, respectively, and ϕ the rate of oviposition. The parameters dependent on temperature *T* are the rate of eggs becoming non-viable ($\mu_e(T)$), the cycle duration from the egg to the mature adult or time elapsed since the oviposition until the development into an adult mosquito ($1/\sigma_1(T)$), and the duration of *sporogony* or development from the gametocyte to the infective *sporozoite*; that is, since the infection until the production of *sporozoites* in the mosquito vector ($1/\sigma_2(T)$). Finally, *f* represents the transmission rate (parameter dependent on the average number of mosquito's bites on humans, which measures the level of interaction between both populations). The ratio $\left[\frac{\sigma_1(T)}{\sigma_1(T)+\mu_e(T)}\right]$ denotes the probability of egg transformation into an adult mosquito during the period of time $1/\sigma_1(T)$ (all the viable eggs, given by the net oviposition $\phi[Y_1(t)+Y_2(t)+Y_3(t)]$, must survive during the period ($1/\sigma_1(T)$) and evolve into adult mosquitoes). The mosquito population can be set as fractions according to:

$$y_i(t) = \frac{Y_i(t)}{[Y_1(t)+Y_2(t)+Y_3(t)]}, \text{ for } i = 1, 2 \text{ and } 3.$$

Therefore, $y_3(t)$ is the fraction of infectious mosquitoes. The basic reproduction rate R_o is defined by:

$$R_o = \frac{f\ h}{r},$$

where *r* is given by:

$$r = \frac{\left[(\theta+\gamma_1+\mu+\alpha)(\gamma+\mu)\left(\mu'+\alpha'\right)\left(\sigma_2(T)+\mu'+\alpha'\right)\right]}{\gamma_1\,\sigma_2(T)}.$$

Yang's model does not include information from immunological, epidemiological, molecular and theoretical studies which demonstrate the need to subdivide the immunity to malaria into immunity against infection, (mild and severe) disease and, most important, transmission. The analysis of this model is restricted to the immunity against (severe) disease and transmission. Acquiring immunity is treated as something that has a finite duration and requires boosting. The expression for the basic reproduction rate can be re-written as:

$$R_o = \left[\frac{\gamma_1}{\theta+\gamma_1+\mu+\alpha}\right]\left[\frac{f}{\gamma+\mu}\right]\left[\frac{\sigma_2(T)}{\sigma_2(T)+\mu'+\alpha'}\right]\left[\frac{h}{\mu'+\alpha'}\right].$$

The first term is the probability that an individual will survive (and also recover naturally) during the latent period $1/\gamma_1$ and will be in the infective state. The second term is related to the number of susceptible mosquitoes infected with gametocytes by an infectious individual during his/her entire infective period. The third term is the probability that a mosquito will survive during the latent period $1/\sigma_2(T)$ and be in the infective state. Finally, the last term corresponds to the number of susceptible individuals infected with *sporozoites* by an infectious mosquito during its entire infective period. The gametocytes taken up by mosquitoes and the injection of *sporozoites* in the human host occur when female *Anopheles* mosquitoes bite humans. Hence, R_o is proportional to both the inoculation rate h and the transmission rate f. For this reason, the entomological parameter given by the ratio between human and mosquito population sizes appears quadratically.

Two terms of R_o are related to the infection of a susceptible mosquito; the other two terms are related to the infection of a susceptible individual. Thus, there should be a chain reaction to produce a new infection among mosquitoes. First, an infectious mosquito must inoculate *sporozoites* in susceptible individuals during its infective period. Then these *sporozoites* must evolve into gametocytes in the infected human host. Finally, during the infective period of these infectious individuals, susceptible mosquitoes must take up gametocytes. Therefore, the Basic Reproduction Rate measures the number of secondary infections produced by an infectious mosquito in a completely susceptible mosquito population. For that reason, areas with higher values of R_o require more efforts regarding malaria prevention measures.

The effect of the three types of human immune responses against malaria *delays* the recurrence of individuals, who already have had contact with parasite, to the susceptible category. The immunity boosting also avoids the flow into the susceptible compartment. Therefore, if a community is at high risk

of malaria (high value of R_o), then it will show a lower prevalence of individuals with asexual blood-stage infection but without infectious gametocytes. This community is also relatively free of severe infection due to the boosting of immunity by re-infection. The stock-flow models (created on Powersim Constructor® Version 2.51) for the human host and the mosquito vector components are depicted in Figures 1.9 and 1.10.

To focus on the effects on malaria transmission of social and economic conditions prevailing in a community at risk, as well as changes in ambient temperatures, parameters θ, γ_1, γ, π_1, π_2, π_3, μ, and ϕ are related to social and economic conditions, and parameters $\mu_E(T)$, $\sigma_1(T)$ and $\sigma_2(T)$ are related to temperature.

(a) Parameters related to social and economic conditions are used, for instance, as indicators of the health care system effectiveness in identifying promptly new malaria cases, their sanitation condition and economic activity. Lower values of these parameters in the model are representative of good social and economic conditions. Their values are given in terms of the periods of time (the inverse of the respective rates), which decrease as the rate increase. The lower bounded values of the parameters reveal a quick acquisition of immunity (represented by a large value of γ) and also a rapid natural recovery period (represented by a large value of θ). Both features can be associated to the effectiveness of the health care systems in identifying and treating malaria infected individuals (represented by an additional increase in θ), and providing the individuals some kind of protection (vaccine when available).

The quick immunity response and drug treatment can lead to the early differentiation of the *merozoites* to sexual gametocytes (represented by a large value of γ_1). Nevertheless, the quick immunity response can induce protection for a limited amount of antigens, which results in quick loss rates of acquired (fully and partially protective) immunity (represented by large values of π_1 and π_2) and immunological memory (represented by a large value of π_3). Finally, the surrounding environment can be adverse to the vector proliferation if the rate of oviposition is low (represented by low value of ϕ).

(b) Areas of low temperature (20°C), intermediate temperature (between 20 and 31°C but close to 21.5°C, because the shape of the curve of parameters as a function of the temperature follows a hyperbolic curve), and high temperature (31°C), are also considered.

Since socioeconomic conditions and temperature changes are both subdivided in three classes, there are 9 possible combinations of the model's parameters values (P_{ij}, i=1, 2 and 3; j=1, 2 and 3). The first subscript stands for the social and economic conditions (in the model, SEC=0 describes good conditions; SEC=1, intermediate conditions; and SEC=2, deteriorating conditions), and the second subscript for the temperature (j=1 for 20°C, j=2 for 21.5°C, and j=3 for 31°C).

Finally, the inoculation rate *h* and the transmission rate *f*, both being dependent on the average number of mosquitoes' bites on humans, measure the level of interaction between these populations. Three levels of human exposure to the mosquito (representative risk areas of malaria transmission) are analyzed, to reproduce low, intermediate and high contact of human hosts with mosquito's population. Both *h* and *f* can be dependent on temperature (vectorial capacity), social and economic conditions (bed-nets and deforestation), and climate anomalies (El Niño event). Modeling results for a disease-free community but potentially under low risk are shown in Figure 1.11.

1.6. THE TOOL FOR DECISION MAKERS PROPOSED BY GITHEKO AND NDEGWA (GNM)

Githeko and Ndegwa (2001) proposed a simple tool for decision-makers supported on the concept of Vectorial Capacity (in their tool, the daily survival probability of the mosquito vector is assumed function of the parity rate, *PR*, or the proportion of females that have laid eggs, and the feeding frequency *a*). In the development of the epidemic prediction model, these authors used two climatic variables (the monthly maximum temperature anomalies and the monthly rainfall amount) as key factors for malaria outbreaks. Temperature and rainfall data are proposed to be transformed into discrete values. The additive value of these two risk factors is expressed as a fraction of a predetermined maximum value. The mathematical expression representing the epidemic risk *ER*, expressed as percentage (*ER* above 50% indicates a high risk for an epidemic), is given by:

$$ER = \frac{T^i + R^i}{T^m + R^m} \times 100 ,$$

where T^i represents the transformed mean monthly maximum temperature anomaly, R^i the transformed mean monthly rainfall above a given monthly value threshold (for instance, a minimum of 150 mm/month is required for a significant increase in the population of *Anopheles gambiae*, the major vector of malaria in Kenyan highlands), T^m the maximum intensity index for the transformed mean monthly temperature anomaly, and R^m the maximum intensity index for the transformed mean monthly rainfall.

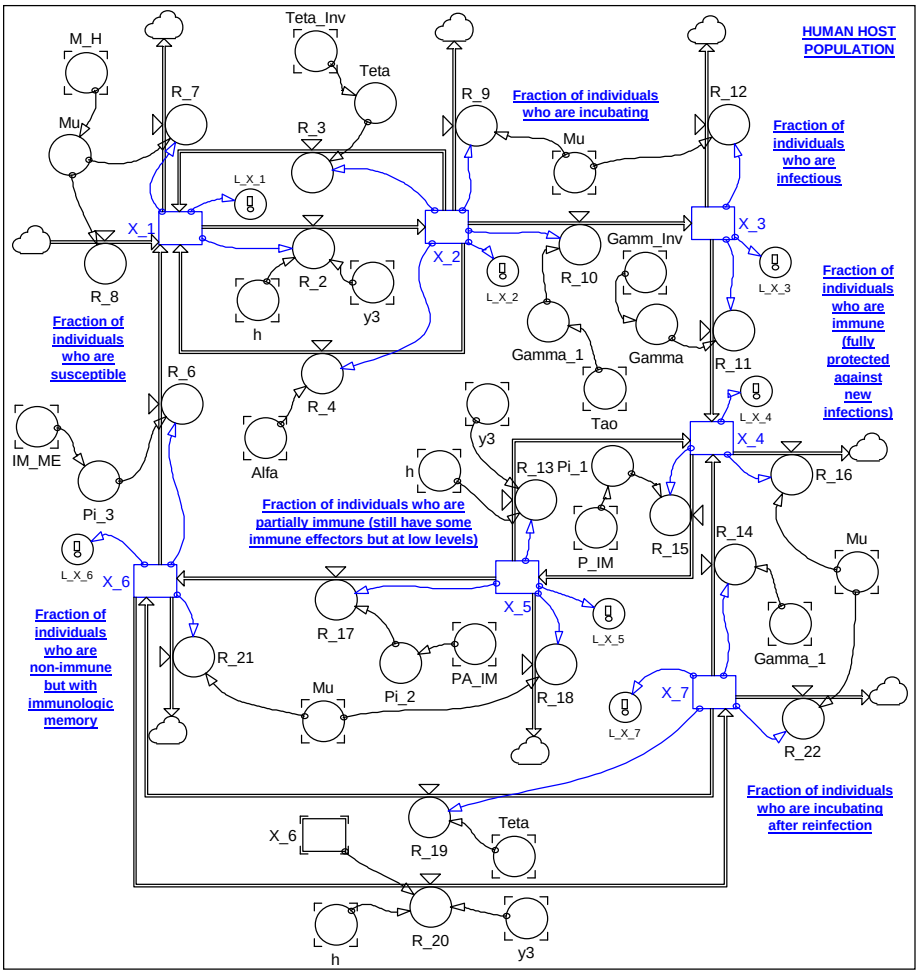


Figure 1.9. Stock-flow model of the human host component of the Yang's malaria transmission model (2000)

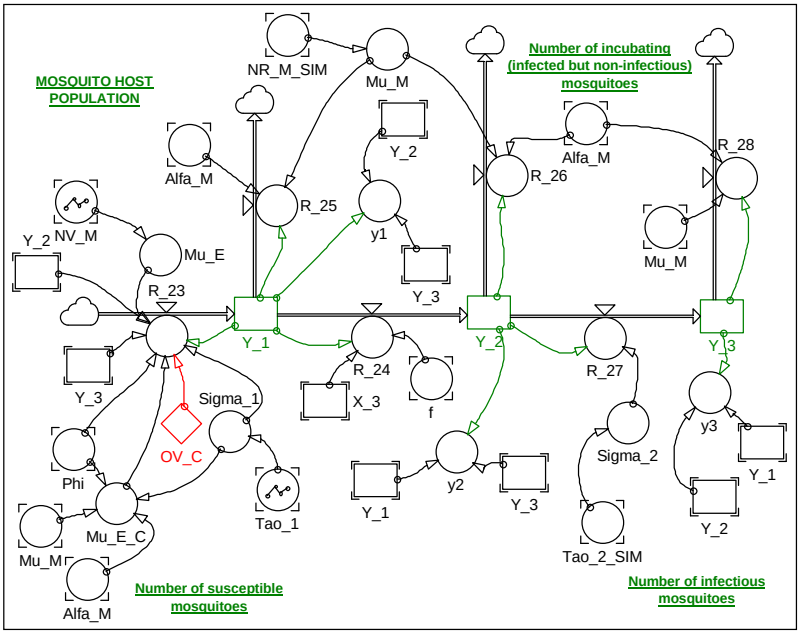


Figure 1.10. Stock-flow model of the mosquito host component of the Yang's malaria transmission model (2000)

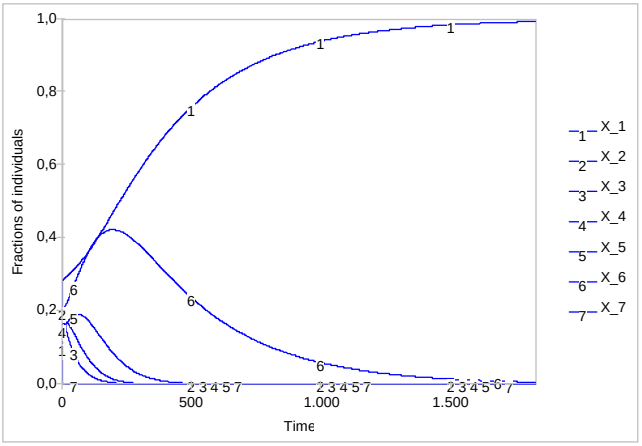


Figure 1.11. Time series of YANG model results for the case of a disease-free community but potentially under low risk. SEC=0 good social and economic conditions prevailing in the community; Area of low temperature (20°C); RISK=0 community in a low risk area of malaria (low contact); Assumed initial values: $X_1(0)=0.10$, $X_2(0)=0.20$, $X_3(0)=0.20$, $X_4(0)=0.15$, $X_5(0)=0.15$, $X_6(0)=0.10$, $X_7(0)=0.10$, $y_1(0)=60\%$, $y_2(0)=20\%$, and $y_3(0)=20\%$. Exogenous variables: $\mu=1/M\_H=1/(50*365$ days), $\alpha=1/DM\_H=1/(2{,}450*365$ days), $\theta=1/Teta\_Inv=1/(1$ day), $(1/\gamma_1)=15$ days, $(1/\gamma)=50$ days, $\pi_1=1/P\_IM=1/(40$ days), $\pi_2=1/PA\_IM=1/(0.2*365$ days), $\pi_3=1/IM\_ME=1/(1.0*365$ days), $h=0.07$, $\mu'=1/NR\_M=1/(10$ days), $\alpha'=1/IM\_M=1/(98$ days), $\phi=25$ eggs/day, $\mu_e=1/NV\_M=1/(0.052)$, $\sigma_1=1/Tao\_1=1/(26$ days), $\sigma_2=1/Tao\_2=1/(22$ days), and $f=0.13$. Under these conditions, the Basic Reproduction Rate reaches $R_o=0.075$. Time results for a simulation period of 1,825 days (5 years).

Temperature data in the GNM model is transformed into discrete values following the rule:

$$
\begin{aligned}
&\textit{If} \quad T = 0 \quad \textit{then} \quad T^z = 0 \quad \textit{and} \quad T^2 = 0 \\
&\textit{If} \quad 0 < T < 1 \quad \textit{then} \quad T^z = 1 \quad \textit{and} \quad T^2 = 1 \\
&\textit{If} \quad 1 \leq T < 2 \quad \textit{then} \quad T^z = 2 \quad \textit{and} \quad T^2 = 4 \\
&\textit{If} \quad 2 \leq T < 3 \quad \textit{then} \quad T^z = 3 \quad \textit{and} \quad T^2 = 9 \\
&\textit{If} \quad 3 \leq T < 4 \quad \textit{then} \quad T^z = 4 \quad \textit{and} \quad T^2 = 16 \\
&\textit{If} \quad 4 \leq T < 5 \quad \textit{then} \quad T^z = 5 \quad \textit{and} \quad T^2 = 25
\end{aligned}
$$

Variable T represents the maximum temperature anomaly (mean maximum temperature of the month of interest subtracted from the 'long-term' mean value), T^z the transformed data (discrete values), and T^2 the 'exponential' temperature (transformed temperature values are squared to create an exponential effect). Rainfall data is transformed into discrete values following the rule:

$$
\begin{aligned}
&\textit{If} \quad R < 150 \quad \textit{then} \quad R^z = 0 \\
&\textit{If} \quad 150 \leq R < 175 \quad \textit{then} \quad R^z = 1 \\
&\textit{If} \quad 175 \leq R < 200 \quad \textit{then} \quad R^z = 2 \\
&\textit{If} \quad 200 \leq R < 225 \quad \textit{then} \quad R^z = 3 \\
&\textit{If} \quad 225 \leq R < 250 \quad \textit{then} \quad R^z = 4 \\
&\textit{If} \quad 250 \leq R < 275 \quad \textit{then} \quad R^z = 5 \\
&\textit{If} \quad 275 \leq R < 300 \quad \textit{then} \quad R^z = 6 \\
&\textit{If} \quad R < 300 \quad \textit{then} \quad R^z = -6
\end{aligned}
$$

Negative index values are assigned to rainfall above 300 mm/month, as such rainfall causes flashing of larvae and consequent reduction in the rate of transmission. Githeko and Ndegwa (2001) proposed the maximum risk values for maximum temperature anomaly and rainfall of about 5.5°C and 320 mm/month, respectively. Finally, the authors defined an epidemic as an incidence of inpatient malaria cases of about 15% above the annual mean value.

1.7. THE DYNAMICAL MODEL PROPOSED BY RUIZ AND OTHERS (SIMULMAL)

The schematic diagram of the overall malaria model suggested by Ruiz *et al*. (2002a, 2002b, 2003, 2006) is depicted in Figure 1.12. The comprehensive tool has three linking components that can be simulated separately, if desired, except in the case of vector-host interactions. These components are the human host population, the mosquito population (vector ecology), and the weather patterns. Climate

strongly affects the corresponding interaction between populations during a blood meal, as well as the vector ecology and the availability of breeding sites.

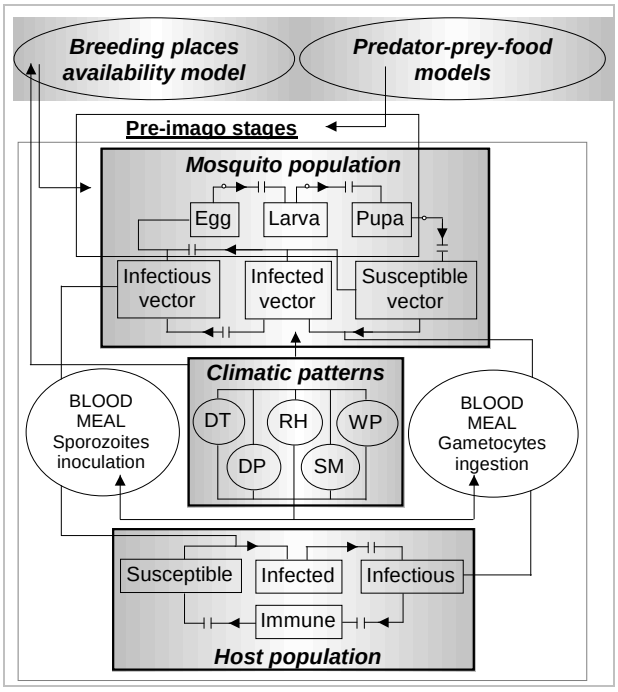


Figure 1.12. Schematic diagram of the malaria transmission model proposed by Ruiz *et al*. (2006). The main blocks represent linking components mosquito population (vector ecology), vertebrate host (human) population, and weather patterns. Level variables are represented by small rectangles: egg, larva and pupa (virtual compartments), susceptible vector, infected vector and infectious vector (top), and susceptible, infected, infectious, and immune host (bottom). Mosquito and human host populations are linked by the transmission of parasites through mosquito blood meals (vertical). The non-continuous arrows represent time delays. The ovals on top represent: (left) table functions affecting the main module and denoting the availability of adequate breeding sites, and (right) predator-prey interactions during pre-imago stages. On non-continuous arrows, the circles represent hatching, larva development and emergence success. Variables DT, RH, DP, WP, and SM represent mean daily temperatures, mean daily relative humidity values, total daily rainfall records, wind patterns, and soil moistures, respectively. DT and RH affect the vector ecology and the blood meal. DP and SM affect the availability of adequate larval habitats. At first approximation, wind patterns, which may affect mosquito densities, are not considered. The 'virtual' compartments representing pre-imago stages are only used when vector densities obtained by simulation are required for estimating the Vectorial Capacity.

The proposed tool follows Martens' equations for the human host population, although considering the infective stage of the human hosts. Accordingly, the system of differential equations for

the human population component and hence, the dynamics of malaria transmission in human hosts is the following:

$$\frac{d(HUS)}{dt} = R_{na} \cdot P_{hu} + \gamma \cdot HUM - R_{mo} \cdot HUS - VC \cdot \frac{HUF}{P_{hu}} \cdot HUS \ ,$$

$$\frac{d(HUI)}{dt} = VC \cdot \frac{HUF}{P_{hu}} \cdot HUS - [HUI]_{t-(k_{in}+k_{er})} - R_{mo} \cdot HUI \ ,$$

$$\frac{d(HUF)}{dt} = [HUI]_{t-(k_{in}+k_{er})} - V \cdot HUF - R_{mo} \cdot HUF \ , \text{ and}$$

$$\frac{d(HUM)}{dt} = V \cdot HUF - \gamma \cdot HUM - R_{mo} \cdot HUM \ .$$

The variables *HUS*, *HUI*, *HUF*, and *HUM* denote the total number of susceptible, malaria-infected, infectious, and immune human hosts at a given time t, respectively. Parameters R_{na} and R_{mo} represent, respectively, the natural per-capita human birth rate and the natural per-capita human death rate, both functions of the social and economic conditions (SEC) prevailing in the community at risk. Variable P_{hu} denotes the total population at risk. Parameters k_{in} y k_{er} represent, respectively, the average duration of the *exo-erythrocytic schizogony* in the *parenchymal* cells of the liver, and the average duration of the *erythrocytic schizogony* in the red corpuscles of the blood.

The SIMULMAL mathematical tool uses two infectious disease models (the Vectorial Capacity and the Entomological Inoculation Rate-EIR) for five assumptions on vector density: the Human Biting Rate observed during field campaigns for both indoor and outdoor landing captures; vector densities obtained through simulation by considering the dynamics of mosquito ecology; critical density thresholds necessary to maintain parasite transmission; assumed constant densities; and variable vector densities considering seasonal fluctuations. If the EIR is proposed, the model requires an observed sporozoite rate, SR, or proportion of naturally sporozoite-infected mosquitoes.

For the vector ecology component, the model uses the following system of coupled non-linear differential equations to describe the dynamics of the pre-imago stages of the vector population (virtual compartments):

$$\frac{d(E)}{dt} = T_1(f_L) \cdot f_L \cdot f_{L\_S} \cdot \left\langle (VS + VI + VF) \cdot R_{po} \right\rangle_{FI} - \frac{E}{k_E} - E \cdot \mu_E \cdot T_2(E),$$

$$\frac{d(L)}{dt} = \frac{E}{k_E} - \frac{L}{k_L} - L \cdot \mu_L \cdot T_3(L) - a_S \cdot L \cdot PD \text{, and}$$

$$\frac{d(PU)}{dt} = \frac{L}{k_L} - PU \cdot \mu_{PU} \cdot T_4(PU) - \frac{PU}{k_{em}} \ .$$

The dynamic variables *E*, *L*, and *PU* denote the total number of eggs, larvae, and pupae at a given time t, respectively. The egg laying of vector population into main module is affected by the variables f_L and f_{L_S} of the breeding places availability model. These functions represent, respectively, the water availability and the level of desiccation of breeding sites of several capacities. The function $\langle (VS + VI + VF) \cdot R_{po} \rangle_{FI}$ represents the net oviposition that occur every 'Feeding Interval' pulse. That is, it is assumed that the interval between blood meals (i.e. the length of the gonotrophic cycle) is equivalent to the time interval between successive ovipositions. Variables k_E, k_L and k_{em} represent, respectively, the cycle durations from egg to larva-1st instar, from larva-1st instar to pupa, and from pupa to imago stage. Variables μ_E, μ_L and μ_{PU} represent, respectively, the rate of eggs becoming non-viable, larvae becoming non-viable, and pupae becoming non-viable. Finally, table functions T_1, T_2, T_3, and T_4 represent the multiplier factors affecting oviposition (competition during egg-laying), and eggs, larvae and pupae mortalities, respectively.

To represent the dynamics of natural predators (and only for the representation of biological control campaigns), the predator-prey equation proposed by Lotka-Volterra (Lotka, 1925; Volterra, 1926; Sharov, 1996) is considered in the overall malaria model (i.e. $\frac{d(PD)}{dt} = b_p \cdot L \cdot PD - m_p \cdot PD$), where *PD* represents the predator population, a_S the predation rate coefficient, b_p the reproduction rate of predators per 1 prey eaten, and m_p the predator mortality rate.

To describe the dynamics of the imago stages of the vector population and hence, the dynamics of malaria transmission in adult female mosquitoes, the model uses a second set of differential equations:

$$\frac{d(VS)}{dt} = \frac{PU}{k_{em}} - (\mu_m + \alpha_m) \cdot VS - VS \cdot f \cdot \frac{HUF}{P_{hu}} \cdot S\_V ,$$

$$\frac{d(VI)}{dt} = VS \cdot f \cdot \frac{HUF}{P_{hu}} \cdot S\_V - (\mu_m + \alpha_m) \cdot VI - \frac{VI}{n} , \text{ and}$$

$$\frac{d(VF)}{dt} = \frac{VI}{n} - (\mu_m + \alpha_m) \cdot VF ,$$

where the dynamic variables *VS*, *VI*, and *VF* represent the susceptible or non-infectious, malaria-infected, and malaria infectious mosquito (adult females) population sizes at a given time t, respectively. Variables μ_m and α_m represent the natural and induced mortality of mosquitoes, respectively. Finally, variables *f* and *n* represent the transmission rate and the duration of the sporogonic cycle, as discussed previously.

The stock-flow model (created on Powersim Constructor® Version 2.51) of the human host and vector ecology components are depicted in Figures 1.13 and 1.14.

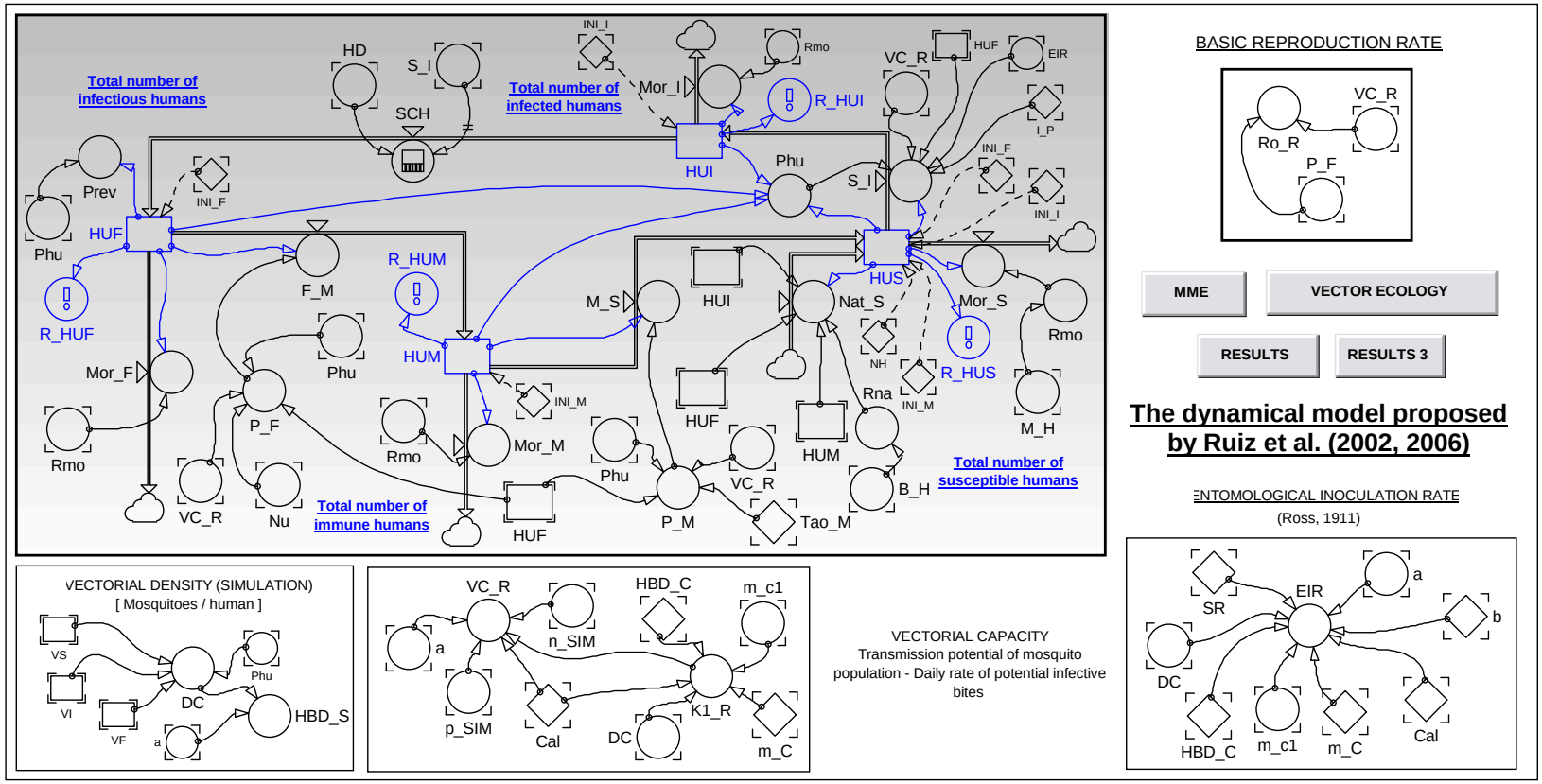


Figure 1.13. Stock-flow model of the human host component of the mathematical tool proposed by Ruiz *et al.* (2006)

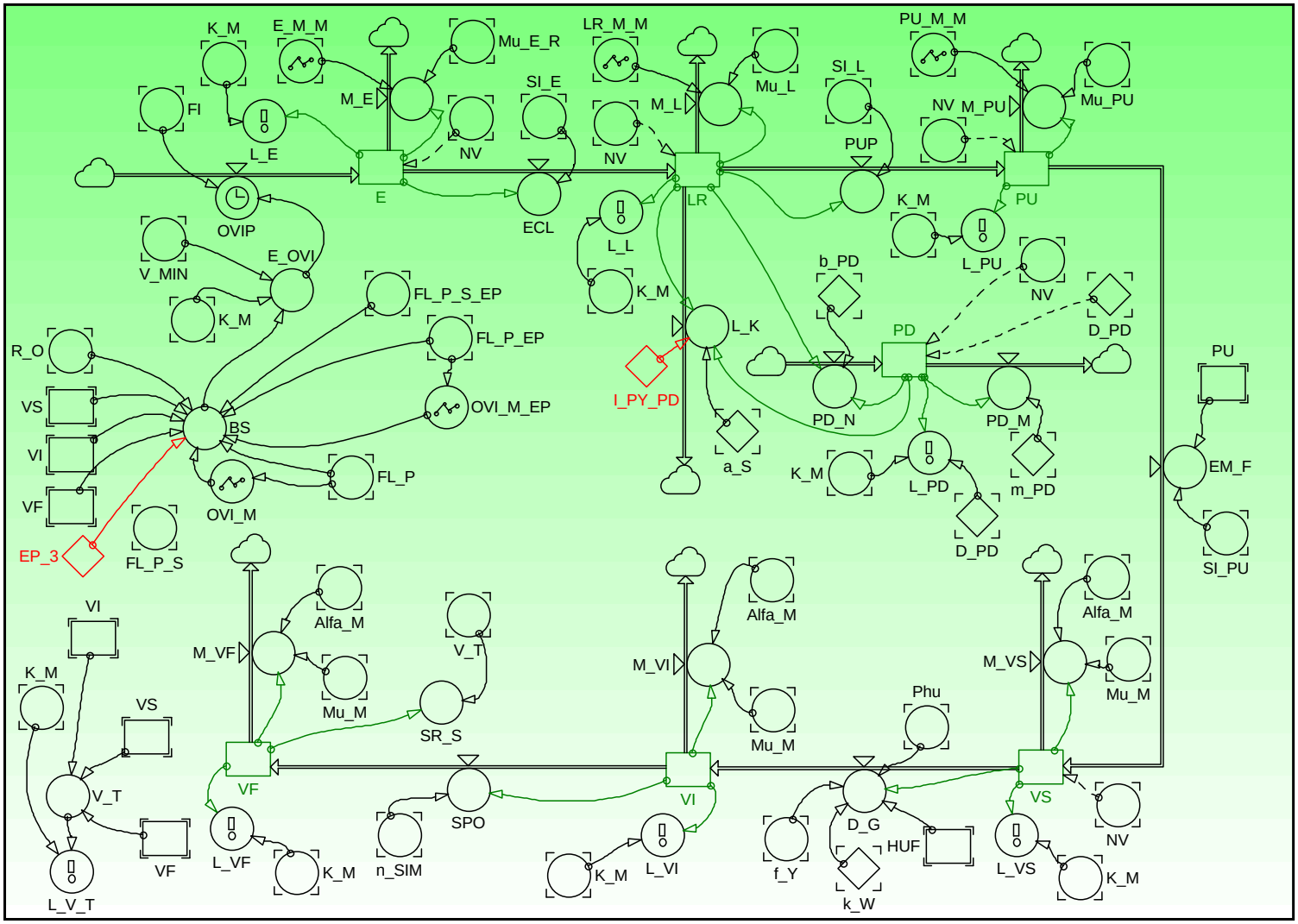


Figure 1.14. Stock-flow model of the vector ecology component of the mathematical tool proposed by Ruiz *et al.* (2006)

1.8. THE NON-SPATIAL MALARIA EPIDEMIOLOGY MODEL (CDE-III)

The non-spatial malaria epidemiology model was proposed as a modified form of the differential-equation version of the McKenzie *et al*. (1998) discrete-event model. Time delays for parasite development in human and mosquito hosts are taken into account, since malaria transmission dynamics are very sensitive to the time delay of parasite development inside mosquito vectors. The model was proposed to represent malaria transmission in highland areas, in which humans have low exposure rates to *Plasmodium* species and thus have low immunity to malaria parasites.

Four major revisions were proposed: (i) Human population dynamics were included. (ii) Malaria-induced death was considered. (iii) For simplicity the stage variable for the immune human host was not considered, because it is not tested whether or not individual humans are immune to re-infection. And (iv), the stage variable for the infected mosquito density was ignored, because in the field it is normally tested whether or not a mosquito is infectious (for instance, by *sporozoite* assay) rather than whether or not it is infected with *ookinetes* or *oocysts*. The non-spatial malaria epidemiology model makes the following assumptions:

- The human population growth is density-independent. The human population is divided into three categories: proportions of susceptible (*S* or *SSS*), malaria-infected (*I*) and infectious (*G* or *GGG*) human hosts.
- The population size of malaria-infected human hosts (*I*) is proportional to the mosquito-biting rate (*b* or *h_YR*), the density of infectious mosquitoes (*F* or *FFF*) and susceptible human hosts (*SSS*).
- An infected/infectious human becomes susceptible with probability q_R (malaria clearance rate in humans) usually with the help of antimalarial drugs.
- The mosquito population is divided into two categories: noninfectious (*U* or *UUU*) and infectious (*F* or *FFF*). The overall mosquito population exhibits a logistic growth with a carrying capacity K_t, which is a function of several environmental variables, including rainfall, temperature and availability of suitable aquatic habitats.
- Malaria parasites take *c* days to develop from *zygotes* into *sporozoites* in the mosquito vector, and take ν days to develop from *sporozoites* into gametocytes in the human host.

Thus, the model is based on the following system of five differential equations:

$$\frac{dS}{dt} = \alpha\left(S+I+G\right)+q_R\left(I+G\right)-b\,F\,S-\beta_1\,S\,,$$

$$\frac{dI}{dt} = b\,F\,S-\left[b\,F\,S\right]_{t-v}-\left(\beta_1+\beta_2+q_R\right)\,I\,,$$

$$\frac{dG}{dt} = \left[b\,F\,S\right]_{t-v}-\left(\beta_1+\beta_2+q_R\right)\,G\,,$$

$$\frac{dU}{dt} = r\left(U+F\right)\left[1-\frac{\left(U+F\right)}{K_t}\right]-\left[1-e^{-c\,\mu_m}\right]\left[b\,G\,U\right]_{t-c}-\mu_m\,U\,,\text{ and}$$

$$\frac{dF}{dt} = \left[1-e^{-c\,\mu_m}\right]\left[b\,G\,U\right]_{t-c}-\mu_m\,F\,,$$

where α and β_1 denote the natural per-capita human birth and death rate, respectively, both functions of the social and economic conditions prevailing in the community. Parameters β_2 and r denote the differential (disease-induced) mortality for the human host and the mosquito per-capita intrinsic growth rate, respectively.

The stock-flow model (created on Powersim Constructor® Version 2.51) and some modeling results are shown in Figures 1.15, 1.16 and 1.17, respectively.

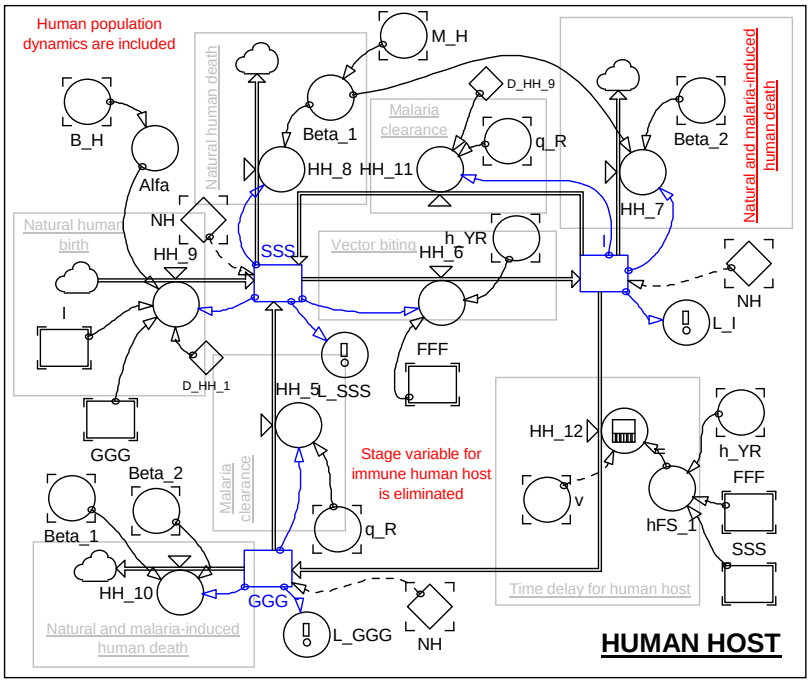


Figure 1.15. Stock-flow model of the human host component of the non-spatial malaria epidemiology model suggested by Ruiz and Yan (2003)

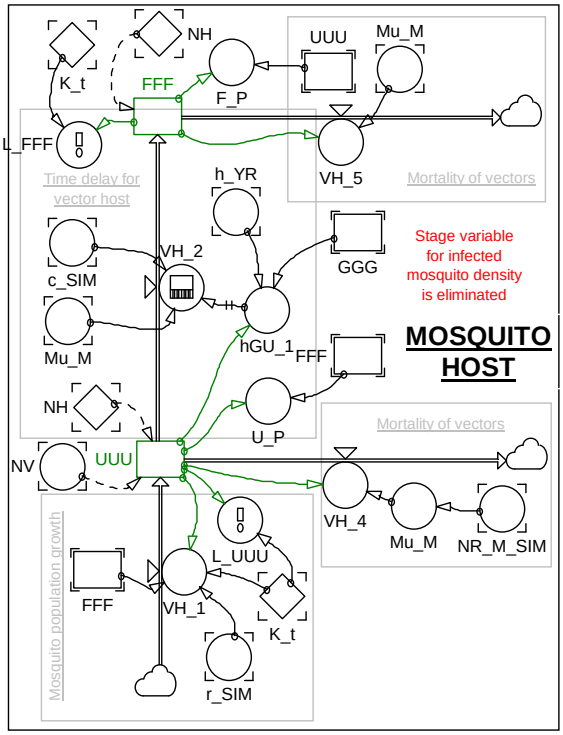
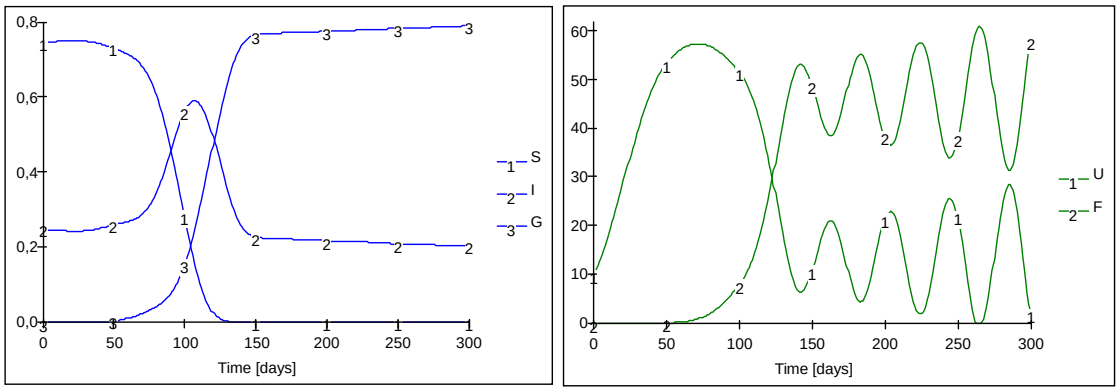


Figure 1.16. Stock-flow model of the mosquito host component of the non-spatial malaria epidemiology model suggested by Ruiz and Yan (2003)



(a) (b)

Figure 1.17. Time series of CDE-III model results for the human host (a) and mosquito host (b) components. Level variables: SSS(0)=375/NH, I(0)=125/NH, GGG(0)=0/NH, UUU(0)=NV/NH, and FFF(0)=0/NH. Exogenous variables: NH=500, α=1/B_H=1/(50*365 days) (SEC=0; good social and economic conditions prevailing in the community at risk), ν=20 days, q_R=LN(2)/CR (where CR=3*365 days), β_1=1/M_H=1/(50*365 days) (for SEC=0), β_2=1/DM_H=1/(2450*365 days) (for SEC=0), r=0.125, c=12 days, μ_m=1-0.95, b=0.50, and K_t=100 mosquitoes.

1.9. THE WEATHER-DRIVEN MODEL OF MALARIA TRANSMISSION PROPOSED BY HOSHEN AND MORSE (HMOR)

The weather-driven model proposed by Hoshen and Morse (2004) simulates both the infection and infectiousness status of human and mosquito carrier populations. For the latter, both immature (eggs, larvae and pupae stages) and mature mosquito dynamics are represented. The immature population is simulated as a set of v virtual boxes with populations $I(n)$ ($n = 1, \ldots, v$; each box representing the inverse of v, the length of the immature phase in days). The *per diem* fractional maturation rate, m, defined as the fraction of the total immature stage covered in a single day, is estimated as the inverse of the sum of the duration of the immature stages, as follows:

$$m = \frac{1}{L_e + L_l + L_p},$$

where L_e, L_l and L_p represent the length of the eggs, larvae and pupae stages, respectively. A fixed *per diem* survival rate, σ, is assumed to represent larval and pupal predation in well-established pools. Thus, at each simulated day the whole population of each box is multiplied by the *per diem* survival rate σ and moved on by mv boxes. New eggs (box number 1) are laid as a fraction of the number of ovipositing adult females (the oviposition rate is roughly assumed to be proportionate to both the ovipositing mosquito number and the dekadal (ten-daily) rainfall R_d filling pools; each ovipositing female lays γR_d viable eggs, where γ is a constant). Then, at each time step t, the immature population at stage s, $I(s,t)$, has the dynamics $I(s+mn, t+1) = \sigma I(s,t)$.

Maturing pupae (reaching age n and above) are removed and enter the mature mosquito dynamics according to $\sigma \cdot \sum_{s=v(1-m)}^{v} I(s,t)$. That is, all immature mosquitoes within one day of maturation (at stages above $v(1-m)$) will become mature mosquitoes the next day, if they survive (σ).

In the mature mosquito dynamics, a small constant trickle of young uninfected mosquitoes is added to the population of maturing mosquitoes. The time for biting is estimated through the duration of the gonotrophic cycle, which can be calculated by $G_c = 1 + \frac{D_d}{T - T_c}$, where D_d represents the number of degree-days required for the development of each cohort of eggs, T_c the threshold beneath which development halts, and T the daily average temperature. The daily progress rate (part of gonotrophic cycle covered in one day) is calculated as $P_R = 1/G_c$. The completion of a cycle is established when the sum of

daily P_R values reaches 1. The survival of the adult mosquito per gonotrophic cycle, α, is assumed to be constant and independent of the duration of the cycle. The *per diem* survival is calculated by $P = \alpha^{1/G_c}$. A total of 37 boxes (corresponding to D_b=*37 degree-days*) are used, between which the mosquitoes progress in steps of P_R reduced by multiplication by the survival rate. At the end of a gonotrophic cycle (upon arrival at box 37), each mosquito oviposits and then begins a new cycle.

The daily change ($\delta\varphi$) in the total number of mosquitoes (N_m) is calculated as the difference between the new mosquitoes maturing (and not dying in the period) and the fraction of mature mosquitoes dying (the daily cycle completion rate $1/G_C$ multiplied by the death rate $1-\alpha$):

$$\delta\varphi = \sigma \cdot \sum_{s=v(1-m)}^{v} I(s,t) - N_m\left(\frac{1-\alpha}{G_c}\right).$$

The proportion of infectious humans (H_i) rather than non-infectious (H_n) bitten is the human infectious ratio, $r = \frac{H_i}{H_i + H_n}$. The mosquito infection per bite probability is estimated as $M_{IP} = \chi B r$, where B denotes the Human Blood Index and χ the fraction of mosquitoes that bite infective humans and become themselves infected.

The daily sporogonic progress (in degree days) is estimated as $S_R = 111/S_C$, where S_C represents the length of the sporogonic cycle. To combine the gonotrophic and sporogonic processes, each of the 37 box-stages of the gonotrophic cycle are sub-divided in the model into 112 sub-sections, numbered 0 to 111, representing progress in degree-days. Subsection 0 reflects an uninfected mosquito.

An infected mosquito sub-population, $M(s,S_s,t)$, at stage s of the gonotrophic cycle and at stage S_s of the sporogonic cycle at time t progresses each day by gonotrophic rate P_R and by the sporogonic rate S_R: $M(s+P_R, S_s+S_R, t+1) = p\, M(s,S_s,t)$.

A finite fraction ($1-p$) of the mosquito population dies and does not make the transition. Upon completion of the gonotrophic cycle, the process restarts. Upon the completion of the sporogonic cycle the mosquito remains at the infectious stage. If the mosquito is not infected at biting, it remains uninfected throughout the gonotrophic cycle (cycle without infection): $M(s+P_R,0,t+1) = p\, M(s,0,t)$, but upon biting an infectious human, an uninfected mosquito has a finite probability of either becoming infected (new infection): $M(P_R, S_R, t+1) = p\, M(0,0,t) M_{IP}$, or not: $M(P_R,0,t+1) = p\, M(0,0,t)(1 - M_{IP})$.

Mosquitoes may arrive at the uninfected biting stage **M(0,0,t+1)** by two processes, either just after maturation or else by completing an uninfected gonotrophic cycle:

$$M(0,0,t+1) = \sigma \cdot \sum_{s=v(1-m)}^{v} I(s,t) + p \cdot \sum_{s=N-P_R}^{N} M(s,0,t).$$

New eggs are laid by mosquitoes completing a gonotrophic cycle:

$$I(0,t+1) = \gamma \cdot R_d \cdot p \cdot \sum_{S_s=0}^{111} \left(\sum_{s=N-P_R}^{N} M(s,S_s,t) \right).$$

This means that all mosquitoes located less than P_R from the end of the gonotrophic cycle will oviposit. Their number must be summed over all infection states 0...111.

In the dynamics of the infected host population, newly infected patients are not infectious for two weeks (intra-hepatic phase and early *erythrocytic* stage), before *gametocytaemia* rises sufficiently for significant transmission: $H(h+l,t+l) = \delta H(s,t)$, for **13>h>l.** δ denotes the daily rate at which patients may become uninfected (malaria clearance). New infections are introduced at a constant low rate.

There are three components of the human infectious population at time *t+1*, **H(14,t+1)**: (i) individuals remaining so from time t, (ii) those who complete the hepatic latent period, and (iii) new imports: $H(14,t+1) = (H(14,t) + H(13,t))\delta + Trickle$.

A host may be uninfected at time *t+1*, by either remaining uninfected with probability (*1-*H_{IR}), where H_{IR} denotes the probability of a human being bitten by an infectious mosquito each day, or else being an infected host (*S(H(s,t))*) and clearing his/her infection with probability (*1-*δ): $H(0,t+1) = (1-H_{IR})H(0,t) + (1-\delta)S(H(s,t))$. A newly infected host begins the latent phase: $H(1,t+1) = H_{IR}\,H(0,t)$.

The stock-flow model of the immature stages (created on Powersim Constructor® Version 2.51) is depicted in Figure 1.18.

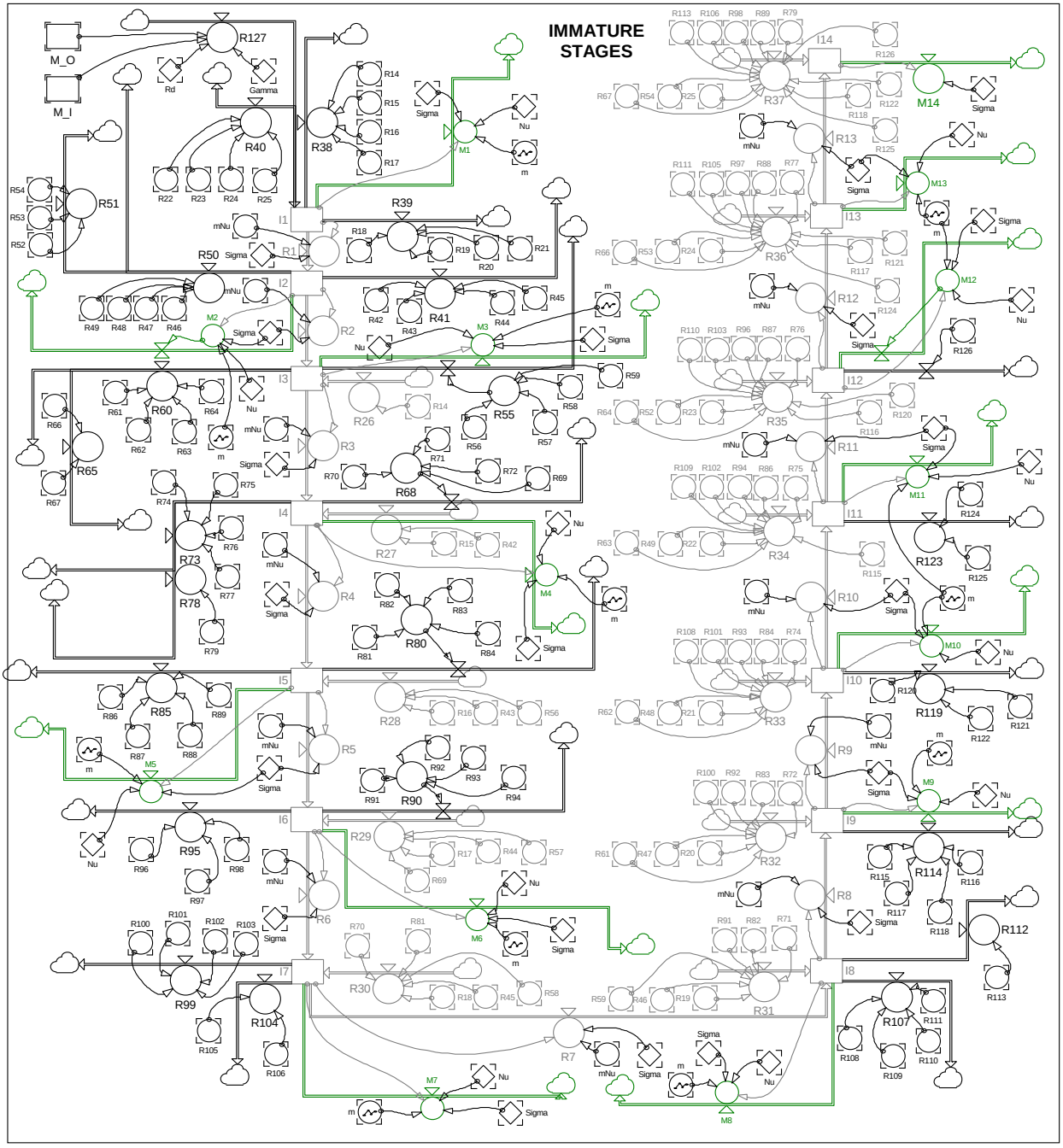


Figure 1.18. Stock-flow model representing the immature stages of the weather-driven model of malaria transmission proposed by Hoshen and Morse (2004)

1.10. THE MATHEMATICAL MODEL PROPOSED BY WORRALL, CONNOR AND THOMSON (WCT)

Worral, Connor and Thomson (2007) developed a temperature- and rainfall-driven dynamic model of malaria transmission to predict epidemics in areas where brief seasonal transmission and occasional epidemics do not enable acquired immunity, and to examine the relationship between the intervention timing and transmission intensity on the effectiveness of indoor residual spraying (IRS). The mathematical tool is composed by six sub-models that allow estimating: (Sub-model 1, SM1) the number of adult female mosquitoes as a function of rainfall; (SM2) the length of the gonotrophic or feeding cycle as a function of temperature; (SM3) the duration of the sporogonic cycle as a function of temperature; (SM4) the vector survivorship in terms of survival probability per gonotrophic cycle and per day; (SM5) the sporozoite rate; and (SM6) the number of new infections, super-infections and recoveries. The combination of SM3 and SM4 allows calculating 'the probability of the vector surviving long enough for sporogonic development to be completed'. SM4 is also used 'to simulate the effects of a residual spray program, which is considered in terms of its impact upon the probability of vector survival per gonotrophic cycle'.

In SM1, the number of mosquitoes emerging each month (q) is estimated through the linear regression $q = \mu R$, where μ represents the linear scaling factor (or rainfall to mosquito constant) and R the monthly rainfall total. In SM2, the total gonotrophic cycle length (U) is estimated as:

$$U = \upsilon + \left(\frac{f_u}{(T + l) - g_u} \right),$$

where $\frac{f_u}{(T + l) - g_u}$ (or u) represents the period of time required by a female *Anopheles* to digest the blood meal (maturation of the ovaries), and υ denotes the length of the period required by the adult mosquito to search for a suitable water body, lay the cohort of eggs, find a new host and bite again. f_u represents the total number of degree-days needed to complete development, g_u the threshold temperature below which development ceases, and $(T+l)$ the indoor temperatures, which are function of the outdoor ambient temperatures (T) and an adjustment factor (l). In SM3, the length of the sporogonic cycle is expressed as:

$$N = \frac{f_N}{(T_N - g_N)},$$

where f_N represents the number of degree-days needed to complete development, and g_N denotes the temperature threshold below which development ceases. Temperature T_N is 'adjusted to account for differences between indoor and outdoor resting temperatures, using a weighting system, based on the period of time the vector spends indoors as a proportion of gonotrophic cycle length' ($T_N = T + \frac{l\,u}{U}$).

SM4 defines two populations of mosquitoes: covered (C) and not covered (1-C) by the spray program, where C represents the percentage coverage achieved by the spraying campaign. The daily survival probability of the mosquito vector is expressed as $\alpha^{1/U}$, where α (or α_W) denotes the probability of the vector surviving each gonotrophic cycle (assumed to be constant) in the population not covered by the campaign. α is reduced by β in the population covered by the spray program immediately after spraying, gradually increasing back towards α at a rate of $\beta/6$ per month over the effective residual life of the insecticide (assumed to be 6 months). Thus, the mean probability of the daily survival (P) for the whole mosquito population is given by:

$$(\alpha(1-C)+\alpha\beta C)^{1/U}.$$

In SM5, the sporozoite rate (S) is estimated through the equation: $S = \frac{xhkvP^N}{(1-\alpha+xhkv\alpha)}$, where x denotes the proportion of humans that are infectious, h the proportion of human blood fed mosquitoes, k the probability of the vector becoming infected per infectious meal, and v the probability of the vector becoming infectious with the malaria parasite. The formula uses the probability of surviving the gonotrophic cycle for an unsprayed population (α); in a sprayed situation this parameter is substituted for $(\alpha(1-C)+\alpha\beta C)$.

Finally, in SM6 the frequency at which mosquitoes feed on humans (a) is estimated as h/U, and the number of infectious mosquitoes biting humans is calculated as the product of the sporozoite rate (S), the number of mosquitoes (q), and the person biting habit (a). The probability of a human receiving an infectious bite (R) is given by $1-\left(1-\frac{1}{d}\right)^{Sqa}$, where d denotes the total human population at risk. The number of people recovering at time t (c_t) is given by $c = (I-Z)r$, where I represents the number of infected humans, r the probability of recovery of new infected humans after time t, and Z the number of super-infections (or $Z = R\,I$). Thus, the number of infected humans at time t (I_t) is given by:

$$I_t = I_{t-1} - c_t + F_t,$$

where F_t denotes the number of people newly infected at time t or *R(d-I)*. The total number of reported infected humans at time t is given by: $\lambda * I_t$, where λ denotes the proportion of positive cases in the community reported to health facilities. The schematic diagram of the WCT model and the stock-flow diagrams of its SM3 (estimation of the length of the sporogonic cycle) and SM6 (dynamics of new infections, super-infections and recoveries) sub-models are depicted in Figure 1.19.

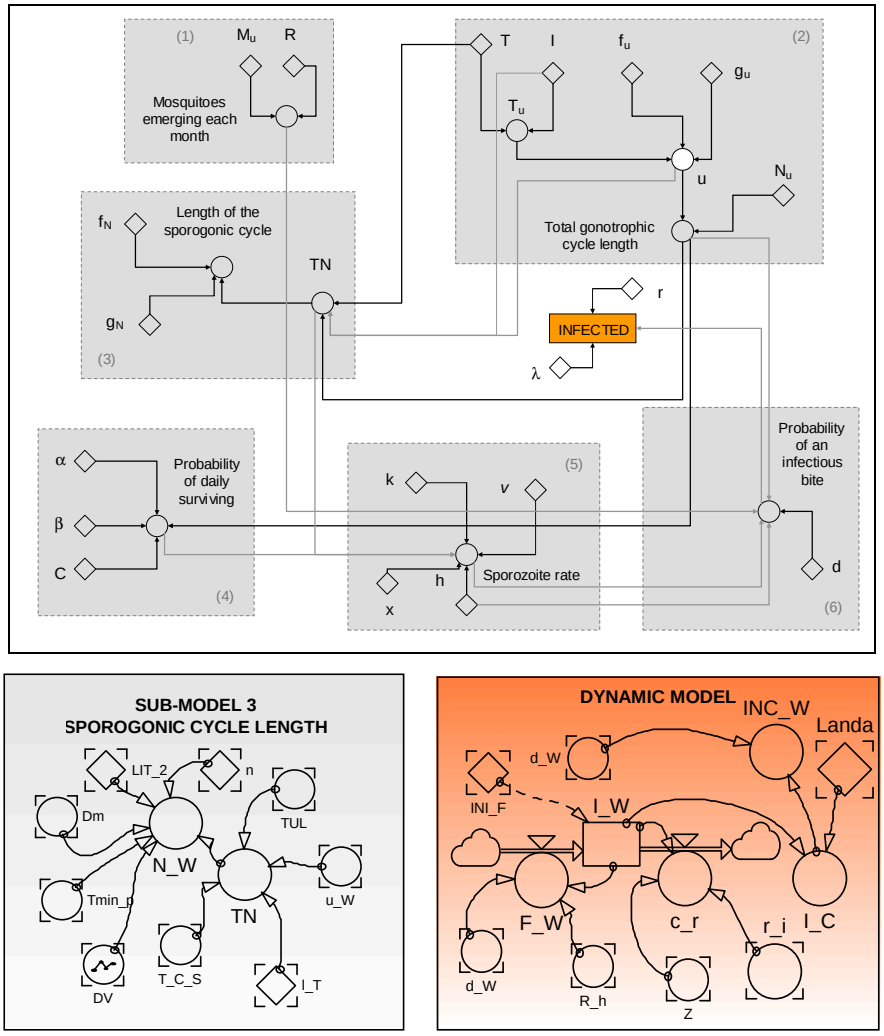


Figure 1.19. Schematic diagram (top) and stock-flow diagrams of the SM3 and the SM6 sub-models (bottom) of the mathematical tool proposed by Worrall, Connor, and Thomson (2007)

1.11. THE TRANSMISSION MODEL PROPOSED BY CHIYAKA, GARIRA AND DUBE (CHGD)

Chiyaka, Garira and Dube (2006) proposed a malaria transmission model with three discrete delays (latent period in the host population, latent period in the vector population, and duration of partial immunity) for representing human malaria in a *partially* immune population. The human host component (see Figure 1.20(A)) of the malaria transmission model is based upon the following system of ordinary differential equations:

$$\frac{d}{dt}S_h(t) = \Lambda_h + r_h\, I_h(t) - \beta_h\, c\, I_m(t)\,\frac{S_h(t)}{N_h(t)} - \mu_h\, S_h(t) + q_h\, I_h(t-\omega)\, e^{-\mu_h \omega},$$

$$\frac{d}{dt}E_h(t) = \beta_h\, c\, I_m(t)\,\frac{S_h(t)}{N_h(t)} - \beta_h\, c\, I_m(t-\tau_h)\,\frac{S_h(t-\tau_h)}{N_h(t-\tau_h)}\, e^{-\mu_h \tau_h} - \mu_h\, E_h(t),$$

$$\frac{d}{dt}I_h(t) = \beta_h\, c\, I_m(t-\tau_h)\,\frac{S_h(t-\tau_h)}{N_h(t-\tau_h)}\, e^{-\mu_h \tau_h} - \left(r_h + \mu_h + q_h + \alpha_h\right) I_h(t), \text{ and}$$

$$\frac{d}{dt}R_h(t) = q_h\, I_h(t) - q_h\, I_h(t-\omega)\, e^{-\mu_h \omega} - \mu_h\, R_h(t).$$

Level variables S_h, E_h, I_h, and R_h represent the total population of humans at a given time t who are susceptible, exposed, infectious, and partially immune, respectively. Exposed humans are those without infectious gametocytes but with asexual stages of the parasite. Infectious human hosts are those with infectious gametocytes in the blood stream (at this stage a host may die from the disease, recover into the susceptible class or may recover with acquired partial immunity). Partially immune hosts still have protective antibodies and other immune effectors at low levels. If inoculated with sporozoites, an effective immune response will be elicited before asexual parasitaemia develops.

In the system of equations Λ_h represents the human input (birth) rate, expressed in 1/day; μ_h and α_h the natural and disease-induced death rates, respectively, expressed in 1/day; r_h the rate of recovery into the susceptible class from being infectious, expressed in 1/day; τ_h the period of time from being infected until the appearance of gametocytes in the blood, expressed in days; β_h the probability that a bite by an infectious mosquito results in transmission of the disease to the susceptible human; c the contact rate between an infectious mosquito and a susceptible human ($\beta_h c$ thus represents the inoculation rate); ω the duration of partial immunity, expressed in days; and ($1/q_h$) the average time to build up an effective immune response, expressed in 1/day.

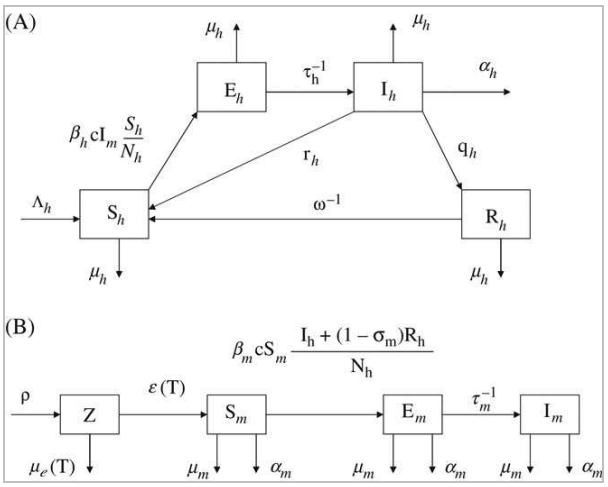


Figure 1.20. Schematic diagram of the transmission model of endemic human malaria proposed by Chiyaka, Garira and Dube (2007): (A) human host and (B) mosquito vector. Source: Chiyaka, Garira and Dube (2006). The level variable Z, in the vector population component, represents the egg class, but is not considered in the model.

The mosquito vector component (see Figure 1.20(B)) is based upon the following system of ordinary differential equations:

$$\frac{d}{dt}S_m(t) = \rho\frac{\in(T)}{\in(T)+\mu_e(T)} - \beta_m\, c\, S_m(t)\,\frac{I_h(t)+(1-\sigma_m)R_h(t)}{N_h(t)} - (\mu_m+\alpha_m)S_m(t),$$

$$\frac{d}{dt}E_m(t) = \beta_m\, c\, S_m(t)\,\frac{I_h(t)+(1-\sigma_m)R_h(t)}{N_h(t)} - \beta_m\, c\, S_m(t-\tau_m)\,\frac{I_h(t-\tau_m)+(1-\sigma_m)R_h(t-\tau_m)}{N_h(t-\tau_m)}e^{-(\mu_m+\alpha_m)\tau_m} - (\mu_m+\alpha_m)E_m(t),$$

$$\frac{d}{dt}I_m(t) = \beta_m\, c\, S_m(t-\tau_m)\,\frac{I_h(t-\tau_m)+(1-\sigma_m)R_h(t-\tau_m)}{N_h(t-\tau_m)}e^{-(\mu_m+\alpha_m)\tau_m} - (\mu_m+\alpha_m)I_m(t).$$

Level variables S_m, E_m, and I_m represent the total number of susceptible, exposed and infectious mosquitoes at a given time t, respectively (exposed mosquitoes are those that have ingested gametocytes but do not have infectious sporozoites in their salivary glands yet). In the system of equations ρ represents the rate of oviposition, expressed in 1/day; T the temperature; $\in^{-1}(T)$ the cycle duration from the egg to the mature adult; and $\mu_e(T)$ the rate at which eggs become non-viable (thus, the probability of egg transformation during the time period of $\in^{-1}(T)$ into an adult mosquito is the ratio $\in(T)/(\in(T)+\mu_e(T))$); and β_m represents the probability that a bite results in transmission of the parasite to a susceptible mosquito (hence, $\beta_m c$ represents the rate of transmission). The transmission of the parasite to a mosquito

from a partially immune human is reduced by a factor $(1-\sigma_m)$, where σ_m is the effectiveness of the immune system in reducing infectiousness from a partially immune individual to a susceptible mosquito. If $\sigma_m=0$, then rate of infection is the same for infectious and partially immune humans. If $\sigma_m=1$, then there is no transmission of parasites from a partially immune human to a susceptible mosquito. μ_m and α_m are the natural and induced (for example, by insecticides) mortality rates of mosquitoes, respectively, expressed in 1/day. And τ_m denotes the duration of sporogony (development from the gametocytes to the appearance of infectious sporozoites in the salivary glands) in the mosquito, expressed in days.

The CHGD transmission model makes the following assumptions: (a) longevity of the vector is unaffected by the infection; (b) the probability of feeding on hosts is unaffected by the number of previous feeds or by differences in host type; (c) the parasite presence does not affect preference by vectors; (d) there is no super-infection; (e) the latent period for both populations and duration of partial immunity are constant; (f) the infectious period of a mosquito ends with its death; (g) mosquitoes do not die from the malaria infection; and (h) the infectiousness of partially immune and infectious humans are different.

Using the fact that: $E_h(t)=N_h(t)-S_h(t)-I_h(t)-R_h(t)$ and $E_m(t)=N_m(t)-S_m(t)-I_m(t)$, and by assuming $\rho\frac{\in(T)}{\in(T)+\mu_e(T)}=\Lambda_m$, $\beta_h\, c=\zeta_h$, $\beta_m\, c=\zeta_m$, and $(1-\sigma_m)=\eta_m$, the authors propose the following equivalent system of differential equations:

$$\frac{d}{dt}S_h(t)=\Lambda_h+r_h\,I_h(t)-\zeta_h\,I_m(t)\frac{S_h(t)}{N_h(t)}-\mu_h\,S_h(t)+q_h\,I_h(t-\omega)\,e^{-\mu_h\omega},$$

$$\frac{d}{dt}I_h(t)=\zeta_h\,I_m(t-\tau_h)\frac{S_h(t-\tau_h)}{N_h(t-\tau_h)}e^{-\mu_h\tau_h}-(r_h+\mu_h+q_h+\alpha_h)I_h(t),$$

$$\frac{d}{dt}R_h(t)=q_h\,I_h(t)-q_h\,I_h(t-\omega)\,e^{-\mu_h\omega}-\mu_h\,R_h(t),$$

$$\frac{d}{dt}N_h(t)=\Lambda_h-\mu_h\,N_h(t)-\alpha_h\,I_h(t),$$

$$\frac{d}{dt}S_m(t)=\Lambda_m-\zeta_m\,S_m(t)\frac{I_h(t)+\eta_m\,R_h(t)}{N_h(t)}-(\mu_m+\alpha_m)S_m(t),$$

$$\frac{d}{dt}I_m(t)=\zeta_m\,S_m(t-\tau_m)\frac{I_h(t-\tau_m)+\eta_m\,R_h(t-\tau_m)}{N_h(t-\tau_m)}e^{-(\mu_m+\alpha_m)\tau_m}-(\mu_m+\alpha_m)I_m(t),\text{ and}$$

$$\frac{d}{dt}N_m(t)=\Lambda_m-(\mu_m+\alpha_m)N_m(t).$$

The basic reproductive number, R_o, proposed by Chiyaka, Garira and Dube (2006) is given by $R_o=R_{mh}*R_{hm}$, where R_{mh} denotes the total number of humans who become infectious during the entire

infectious period of a single newly infectious mosquito entering the disease-free population at equilibrium, and R_{hm} the total number of mosquitoes infected from infectious and partially immune humans. R_{mh} and R_{hm} are estimated using the equations:

$$R_{mh} = \frac{\zeta_h \, e^{-\mu_h \tau_h}}{\mu_m + \alpha_m}, \text{ and } R_{hm} = \frac{\zeta_m \Lambda_m e^{-(\mu_m + \alpha_m)\tau_m}}{\Lambda_h (\mu_m + \alpha_m)(r_h + \mu_h + q_h + \alpha_h)} \left[\left(1 - e^{-\mu_h \omega} \right) q_h \, \eta_m + \mu_h \right].$$

The stock-flow models of the human host and mosquito vector components of the CHGD model (created on Powersim Constructor® Version 2.51) are depicted in figures 1.21 and 1.22, respectively. Time series of CHGD model results for the base scenario discussed by Chiyaka, Garira and Dube (2006) are presented in Figure 1.23.

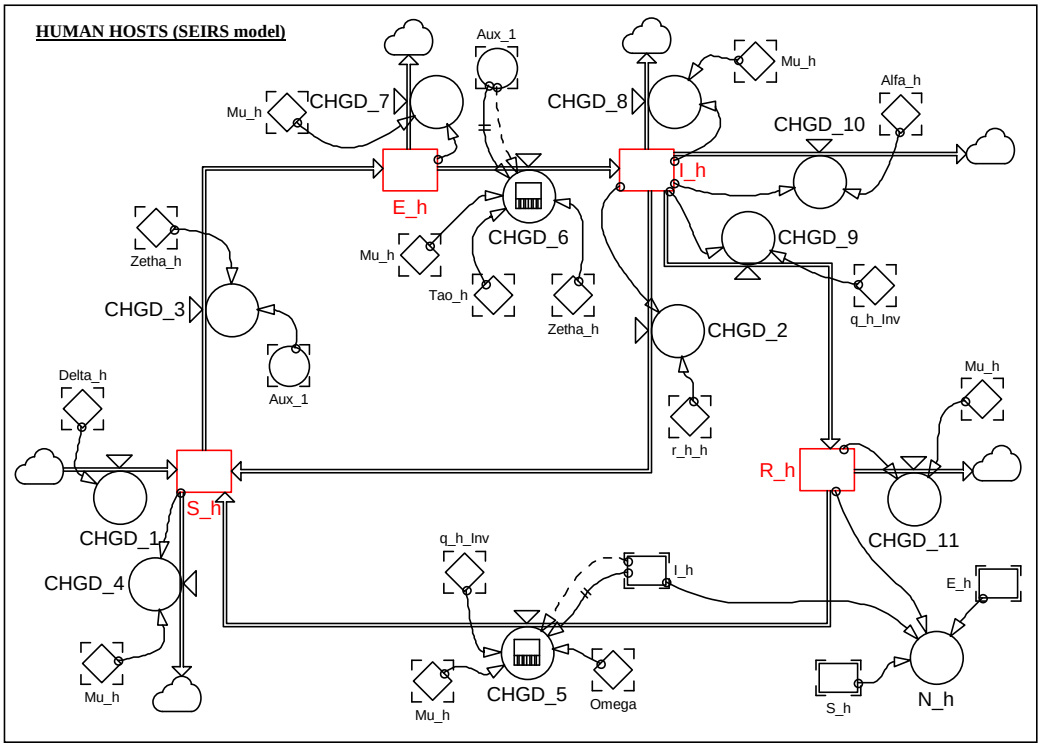


Figure 1.21. Stock-flow model of the human host component of the malaria transmission model proposed by Chiyaka, Garira and Dube (2006)

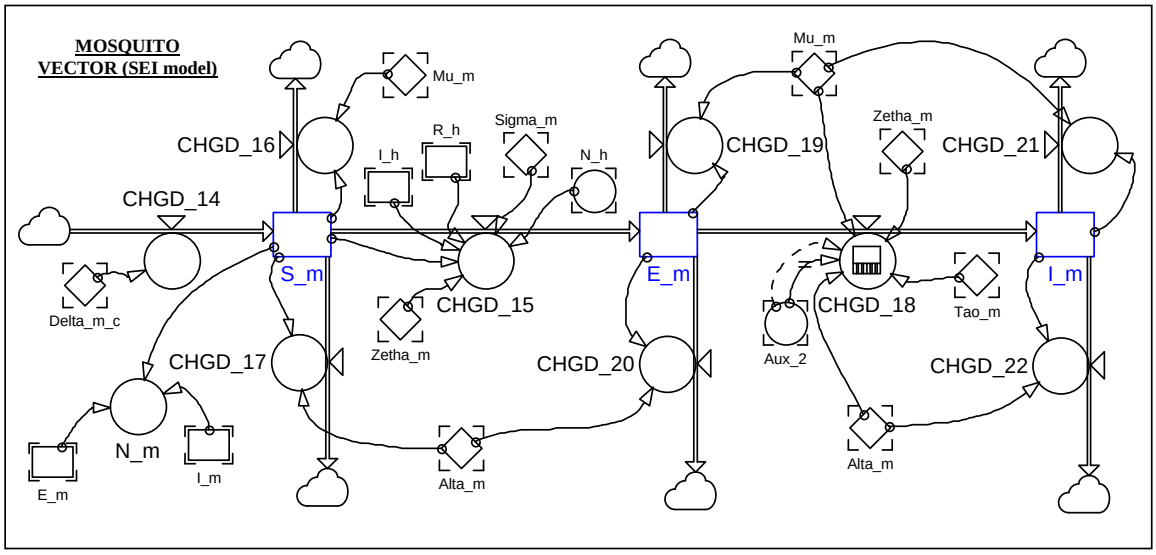


Figure 1.22. Stock-flow model of the mosquito population component of the malaria transmission model proposed by Chiyaka, Garira and Dube (2006)

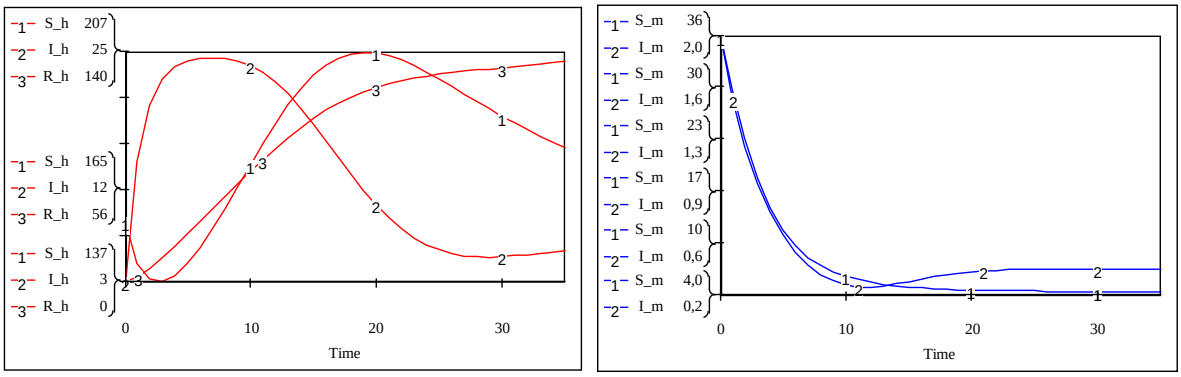


Figure 1.23. Time series of CHGD model results for the base scenario. Level variables: $S_h(0)=155$ individuals, $I_h(0)=3$ individuals, and $R_h(0)=0$ individuals (for the human host population); $S_m(0)=36$ mosquitoes and $I_m(0)=2$ mosquitoes (for the mosquito population). Exogenous variables for the human host population: $\Lambda_h=0.5$ day^{-1}, $\mu_h=0.0031$ day^{-1}, $\alpha_h=0.03$ day^{-1}, $r_h=0.38$ day^{-1}, $\tau_h=14$ days, $\zeta_h=\beta_h c=10.0$, $\omega=100$ days, and $q_h=0.35$. Exogenous variables for the mosquito vector population: $\Lambda_m=3.2$ day^{-1}, $\zeta_m=\beta_m c=0.7$, $\eta_m=(1-\sigma_m)=0.7$, $\mu_m=0.055$ day^{-1}, $\alpha_m=0.2$ day^{-1}, $\tau_m=12$ days, $R_o\approx 2.8$.

1.12. THE MALARIA-SICKLE-CELL MODEL PROPOSED BY GOMERO (GOM)

The malaria-sickle-cell model proposed by Gomero (2008) explores the role of the sickle-cell trait (AS) in the spread of malaria, by incorporating genetic variations within the human host population caused by the presence of the AS. The sickle-cell trait is an adaptive evolutionary response to reduce attacks to red blood cells, and describes the way a person can inherit one of the genes of sickle cell disease, but not develop recurrent symptoms. Individuals who have the AS 'have significant resistance to lethal forms of malaria caused by *P. falciparum*'. Thus, this model is an attempt to include the proposed 'positive correlation between resistance to severe forms of malaria and the prevalence of the sickle-cell trait in places where malaria is highly endemic'.

The relationship between resistance to *P. falciparum* infection and the frequency and distribution of the sickle-cell gene in populations exposed to endemic malaria is quantified through the Hardy-Weinberg law:

$$p^2 + 2pq + q^2 = 1,$$

where p^2 is the frequency of the homozygous dominants, $2pq$ is the frequency of the heterozygotes, and q^2 is the frequency of the homozygous recessives.

In the malaria-sickle-cell model, the homozygous sickle cell trait or the SS population is ignored. The Hardy-Weinberg variables p and q denote, respectively, the probability that a gene will be of type A ($p = 1 - \frac{q_0}{2}$), and the probability that a gene will be of type S ($q = \frac{q_0}{2}$). p_0 and q_0 represent, respectively, the proportion of individuals whose gene pairs are AA ($p_0=1-q_0$), and the proportion of individuals whose gene pairs are AS.

The malaria-sickle-cell-model makes the following assumptions:

- The total human population is variable.
- The extra death rate in the AS population due to the trait is not included.
- The disease-induced death rate of the infectious class of the AA population is 15% greater than that of the AS population.
- The rate of progression from the exposed (E_i) to the infected (I_i) class is the same for both the AA and AS populations.
- The infection rate of mosquitoes depends on both infected and recovered AA and AS populations.

Figures 1.24 and 1.25 depict the schematic diagram and the stock-flow model of the GOM-malaria-sickle-cell model. For the human host population, the model incorporates the sickle-cell trait into a traditional SEIRS-like deterministic model:

$$\frac{dS_i}{dt} = F_i\ \theta\ N_h + \omega_i\ R_i - \eta_i\ b_v\ \frac{I_v}{N_v}\ S_i - d\ S_i\ ,$$

$$\frac{dE_i}{dt} = \eta_i\ b_v\ \frac{I_v}{N_v}\ S_i - \lambda_i\ E_i - d\ E_i\ ,$$

$$\frac{dI_i}{dt} = \lambda_i\ E_i - \rho_i\ I_i - \delta_i\ I_i - d\ I_i\ ,\ \text{and}$$

$$\frac{dR_i}{dt} = \rho_i\ I_i - \omega_i\ R_i - d\ R_i\ ,$$

where S_i, E_i, I_i, and R_i represent the total number of susceptible, exposed (to the infection), infected (infectious), and recovered (immune, asymptomatic) humans of *i* genotype, respectively; *i=1* for those individuals who are homozygous for the sickle-cell gene (the so-called AA subgroup), and *i=2* for individuals who are heterozygous for the sickle-cell gene (AS subgroup). Variables N_i and N_h represent, respectively, the total human population with genotype *i* ($N_i = S_i + E_i + I_i + R_i$), and the total human host population ($N_h = \sum_{i=1}^{2}(S_i + E_i + I_i + R_i)$). Parameters F_1 and F_2 represent, respectively, the probability that a person will be AA in the next generation ($p^2 = 1 - q_0 + \frac{q_0^2}{4}$), and the probability that a person will be AS in the next generation ($2pq = q_0\left(1 - \frac{q_0}{2}\right)$). The parameter θ denotes the human birth rate, expressed in 1/day; ω_i the rate of R_i to S_i progression, expressed in 1/day; η_i the infection rate of mosquitoes, or probability that a human gets the disease when bitten by an infected mosquito; b_v the '(SIC) number of human bites per mosquito per day'; *d* the human natural death rate, expressed in 1/day; λ_i the rate of E_i to I_i progression, expressed in 1/day; ρ_i the rate of I_i to R_i progression, expressed in 1/day; and δ_i the human disease-induced death rate, expressed in 1/day.

For the mosquito vector population, the model follows the SEI transmission pattern:

$$\frac{dS_v}{dt} = \theta_v\ N_v - \sum_{i=1}^{2} \frac{\gamma_i\ b_h\ I_i + \beta_i\ b_h\ R_i}{N_i} S_v - d_v\ S_v\ ,$$

$$\frac{dE_v}{dt} = \sum_{i=1}^{2} \frac{\gamma_i\ b_h\ I_i + \beta_i\ b_h\ R_i}{N_i} S_v - \lambda_v\ E_v - d_v\ E_v\ ,\ \text{and}$$

$$\frac{dI_v}{dt} = \lambda_v\ E_v - d_v\ I_v\ ,$$

where S_v, E_v, and I_v represent the total number of susceptible, exposed (to the infection), and infected (infectious) mosquitoes, respectively. Variable N_v represents the total mosquito population given by $N_V = S_V + E_V + I_V$. The parameter θ_v denotes the mosquito birth rate, expressed in 1/day; γ_i the infection rate of I_i individuals, or the probability that biting an infected human leads to infection in mosquitoes; β_i the infection rate of R_i individuals, or the probability that biting a recovered human leads to infection in mosquitoes; b_h the number of mosquito bites per human per day; d_v the mosquito natural death rate, expressed in 1/day; and λ_v the rate of E_v to I_v progression, expressed in 1/day.

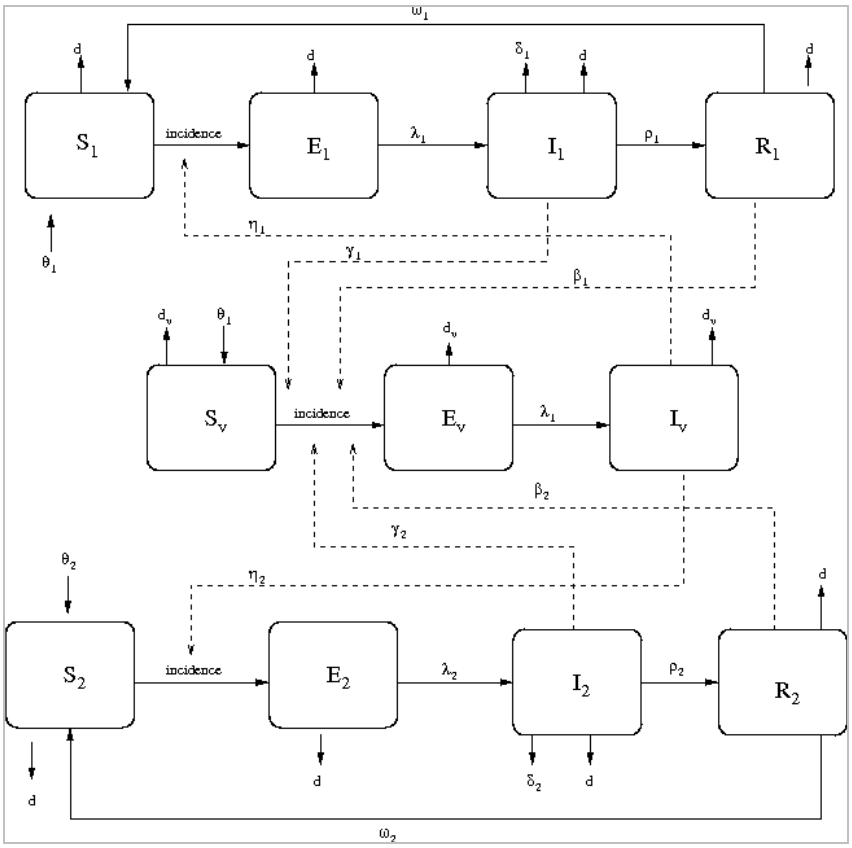


Figure 1.24. Schematic diagram of the GOM-malaria-sickle-cell model (source: Gomero, 2008). The human population is divided into AA (top, *i=1*, individuals who are homozygous for the sickle-cell gene) and AS (bottom; *i=2*; individuals who are heterozygous for the sickle-cell gene) subgroups. Variables on top of the continuous arrows represent the rate of movement from class to class.

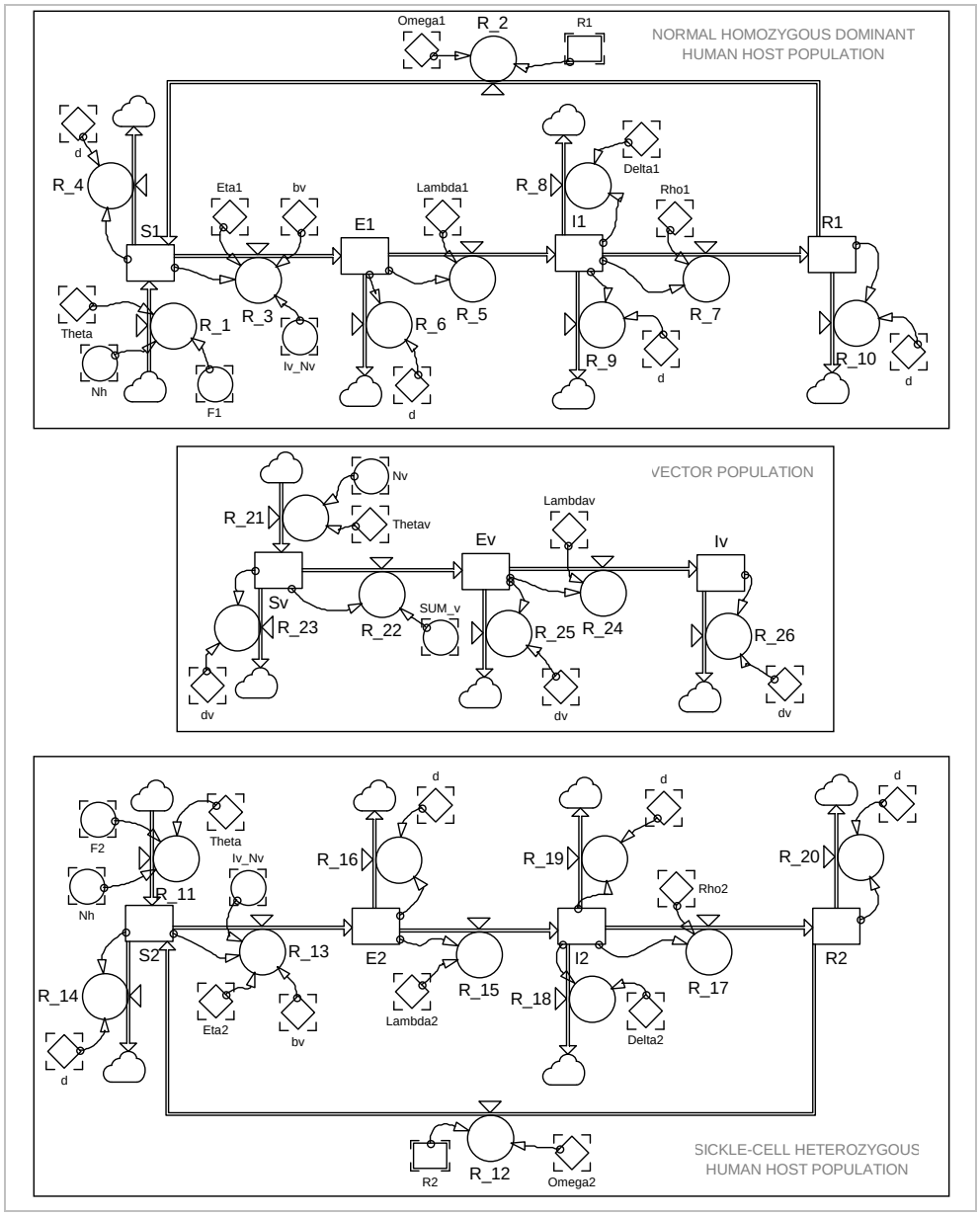


Figure 1.25. Stock-flow model of the malaria-sickle-cell model proposed by Gomero (2008)

Figure 1.26 depicts the results of the 'baseline parameter values' or first scenario proposed by Gomero (2008). Figure 1.27 depicts the simulation outputs for various initial susceptible mosquito population (S_v) values, and for a range of η_2 values.

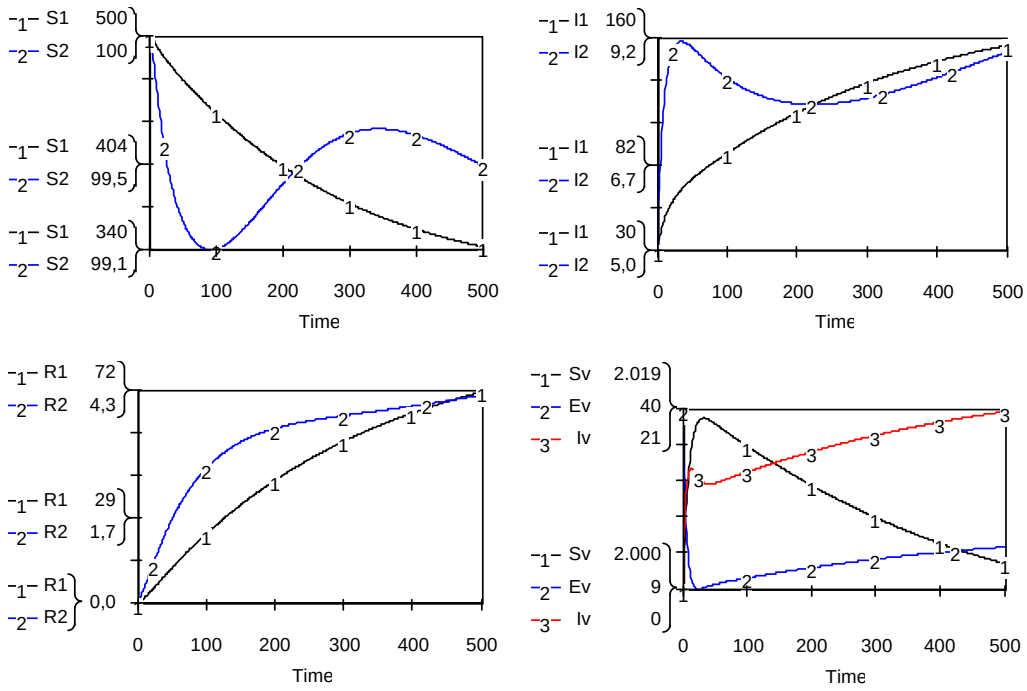


Figure 1.26. Time series of GOM-malaria-sickle-cell model results for the 'baseline parameter values'. Level variables: $S_1(0)$=500 individuals, $E_1(0)$=30 individuals, $I_1(0)$=30 individuals, $R_1(0)$=0 individuals, $S_2(0)$=100 individuals, $E_2(0)$=5 individuals, $I_2(0)$=5 individuals, $R_2(0)$=0 individuals, $S_v(0)$=2,000 mosquitoes, $E_v(0)$=40 mosquitoes, and $I_v(0)$=0 mosquitoes. Exogenous variables for the human host population: θ=0.041/365 day^{-1}; ω_1=1/100 day^{-1}; ω_2=1/100 day^{-1}; η_1=0.5; η_2=0.1; b_v=0.5 human bites/mosquito/day; d= 0.017/365 day^{-1}; λ_1=1/10 day^{-1}; λ_2=1/10 day^{-1}; ρ_1=1/200 day^{-1}; ρ_2=1/200 day^{-1}; δ_1=58/(31685*365) day^{-1}; and δ_2=(58/(31685*365))*0.85day^{-1}. Exogenous variables for the mosquito vector population: θ_v= 1/14 day^{-1}; γ_1= 0.2; γ_2= 0.2; β_1=0; β_2=0; b_h=7/365 mosquito bites/human/day; d_v= 1/14 day^{-1}; and λ_v=1/11 day^{-1}.

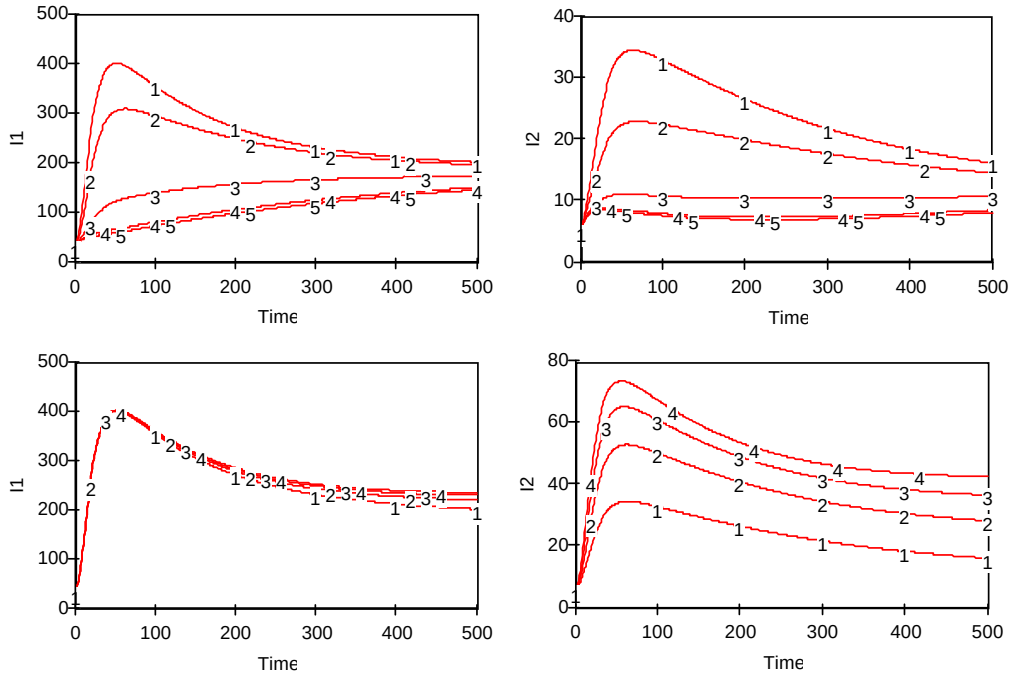


Figure 1.27. Time series of GOM-malaria-sickle-cell model results for (top) changes in initial susceptible mosquito populations and for (bottom) a range of η_2 values. Top panels: values of $S_v(0)$ ranging from 0 to 2,000 mosquitoes (i.e. 0, 1, 10, 100, and 2,000 mosquitoes; time series 1, 2, 3, 4, and 5, respectively), $E_v(0)$=1 mosquito, and $I_v(0)$=0 mosquitoes. Similar exogenous variables to the 'baseline parameter values' scenario described above. Bottom panels: $S_v(0)$=0 mosquitoes, $E_v(0)$=1 mosquito, and $I_v(0)$=0 mosquitoes. η_2 ranges from 0.1 to 0.4 (i.e. 0.1, 0.2, 0.3, and 0.4; time series 1, 2, 3, and 4, respectively).

Table 1.1. Description of level variables – Human host component

MODEL	MAC	MAR	CDE-I	CDE-II	YANG	GNM	SimulMal	CDE-III	WCT	CHGD	GOM
Total variables	**2** 1 human 1 vector	**3** 3 human 0 vector	**7** 4 human 3 vector	**7** 4 human 3 vector	**10** 7 human 3 vector	**0** 0 human 0 vector	**4** (or 7) 4 human 3 vector	**5** 3 human 2 vector	**1** 1 human 0 vector	**7** 4 human 3 vector	**7** (or 11) 4 (or 8) human 3 vector
Human susceptibility	--	X	S	SS	X_1	--	HUS	SSS	--	S_h	S_i
Human potential infectivity	--	--	M	MM	X_2	--	HUI	I	--	E_h	E_i
Human infectivity	X	Y	G	GG	X_3	--	HUF	GGG	I	I_h	I_i
Human immunity	--	Z	R	RR	X_4, X_5, X_6, and X_7	--	HUM	--	--	R_h	R_i

Table 1.1 (Cont.). Description of level variables – Vector population component

MODEL	MAC	MAR	CDE-I	CDE-II	YANG	GNM	SimulMal	CDE-III	WCT	CHGD	GOM
Total variables	**2** 1 human 1 vector	**3** 3 human 0 vector	**7** 4 human 3 vector	**7** 4 human 3 vector	**10** 7 human 3 vector	**0** 0 human 0 vector	**4** (or 7) 4 human 3 vector (3 virtual)	**5** 3 human 2 vector	**1** 1 human 0 vector	**7** 4 human 3 vector	**7** (or 11) 4 (or 8) human 3 vector
Vector susceptibility	--	--	U	UU	Y_1	--	VS (E, LR, and PU)	UUU	--	S_m	S_v
Vector potential infectivity	--	--	L	LL	Y_2	--	VI	--	--	E_m	E_v
Vector infectivity	Y	--	F	FF	Y_3	--	VF	FFF	--	I_m	I_v

Table 1.2. Description of exogenous variables – Community-based

MODEL	MAC	MAR	CDE-I	CDE-II	YANG	GNM	SimulMal	CDE-III	WCT	CHGD	GOM
Human population at risk	--	--	NH	NH	--	--	P_{hu}	NH	d	--	N_i, N_h
Human natural birth	--	--	--	--	--	--	R_{na}	α	--	Λ_h	F_i, θ
Human natural mortality	--	μ	--	--	μ=f(M_H)	--	R_{mo}	β_1	--	μ_h	d
Human induced mortality	--	--	--	--	α=f(DM_H)	--	--	β_2	--	α_h	δ_i
Spray programs	--	--	--	--	--	--	--	--	C	--	--
Surveillance	--	--	--	--	--	--	--	--	λ	--	--

Table 1.2 (Cont.). Description of exogenous variables – Malaria parasites

MODEL	MAC	MAR	CDE-I	CDE-II	YANG	GNM	SimulMal	CDE-III	WCT	CHGD	GOM
Parasite species	--	PAR	--	--	--	PAR	PAR	--	--	--	--
Sporogony	n	n=f(D_m, $T_{min,p}$)	DV	cc	$\tau_2=1/\sigma_2$	n=f(D_m, $T_{min,p}$)	n=f(D_m, $T_{min,p}$)	c	N=f(f_N, g_N)	τ_m	λ_v

Table 1.2 (Cont.). Description of exogenous variables – Human host (individuals)

MODEL	MAC	MAR	CDE-I	CDE-II	YANG	GNM	SimulMal	CDE-III	WCT	CHGD	GOM
Host delay for infectivity	HD	--	HD	kk	τ or $1/\gamma_1$	--	k_{in} and k_{er}	*v*	x	τ_h	λ_i
Host window for immunity	WN	υ	--	pp	--	--	υ	--	--	--	ρ_i
Host immunity	--	τ	ATIS	--	$1/\gamma$, $1/\pi_1$, $1/\pi_2$, and $1/\pi_3$	--	τ	q_R	--	ω, $(1/q_h)$	ω_i
Human resistance	--	--	--	--	θ	--	--	--	--	--	--
Human susceptibility	--	b	--	--	--	--	b	--	--	β_h	η_i
Human recovery	--	c_l	--	--	--	--	--	--	r	r_h	ω_i

Table 1.2 (Cont.). Description of exogenous variables – Mosquito population

MODEL	MAC	MAR	CDE-I	CDE-II	YANG	GNM	SimulMal	CDE-III	WCT	CHGD	GOM
Vector natality	--	--	b_MK	b	ϕ and $1/\mu_e$	--	R_{po}	r	μ	Λ_m	θ_v
Vector natality II	--	--	--	--	$\tau_1=1/\sigma_1$	--	k_E, k_L, and k_{em} T_1, T_2, T_3, and T_4 μ_E, μ_L and μ_{PU}	--	--	--	--
Vector survivorship	p	p=f(T)	d=f(VS)	d=f(VS)	μ'	p=f(PR, a)	p and μ_m	μ_m	α_W, β	f(μ_m)	f(d_v)
Vector induced mortality	--	--	--	--	α'	--	α_m	--	--	α_m	--
Vector feeding	a	a= HBI/FI FI=f(D_{bd}, $T_{min,bd}$)	h	h	h and f	a	a= HBI/FI FI=f(D_{bd}, $T_{min,bd}$) f	h_YR	u=f(f_u, g_u), υ and h	c	b_h
Vector infectivity	b	--	--	--	--	--	SR	--	k, v and S	--	b_v
Vector density	m	k_1	NV/NH	NV/NH	--	m	m	NV/NH	--	--	--
Environment carrying capacity	--	--	--	--	--	--	--	K_t	--	--	--
Vector susceptibility	--	k_W	--	--	--	--	k_W	--	--	β_m, σ_m	γ_i, β_i

Table 1.3. Summary of exogenous variables

Description	Level of understanding of malaria transmission dynamics		
	Poor	**Partial**	**Good**
Community-based exogenous variables	(V1) Demographic census	(V1.I) Total human population at risk	(V1.I.1) Total individuals living in rural areas
			(V1.I.2) Total individuals living in urban areas
		(V1.II) Human population growth rate	(V1.II.1) Natural per-capita human birth rate
			(V1.II.2) Natural per-capita human mortality rate
			(V1.II.3) Differential (disease-induced) mortality rate or case-fatality rate
			(V1.II.4A) Individual (economic-driven) migration patterns, expressed as total new individuals
			(V1.II.4B) Massive (displaced) migration patterns, expressed as total new individuals
	(V2) Conducted (or absent) control campaigns	(V2.I) Description of spray program	(V2.I.1) Total percentage coverage achieved by the spray program
			(V2.I.2) Percentage coverage achieved by the IRS program
			(V2.I.3) Percentage coverage achieved by space spraying of insecticides
		(V2.II) Description of activities blocking adult female-human host interactions	(V2.II.1) Total percentage coverage achieved by the blocking program
			(V2.II.2) Percentage coverage achieved by the screening program
			(V2.II.3) Percentage coverage achieved by the bed-net program
		(V2.III) Description of activities controlling immature mosquitoes	(V2.III.1) Percentage coverage achieved by the controlling program
			(V2.III.2) Percentage coverage achieved by the larvivorous fish program
			(V2.III.3) Percentage coverage achieved by biological larvicides
			(V2.III.4) Percentage coverage achieved by chemical larvicides
			(V2.III.5) Percentage coverage achieved by mechanical larvicides
		(V2.IV) Description of environmental interventions	(V2.IV.1) Percentage of modified breeding sites
			(V2.IV.2) Percentage of manipulated breeding sites
	(V3) Description of surveillance activities	(V3.I) Total malaria positive cases	(V3.I.1) Proportion of cases reporting at health facilities
			(V3.I.2) Total *Plasmodium falciparum* positive cases
			(V3.I.3) Total *Plasmodium vivax* positive cases
		(V3.II) Description of particularities	(V3.II.1) Age distribution
			(V3.II.2) Gender distribution
			(V3.II.3) Pregnancy
			(V3.II.4) Locality – source of case
		(V3.III) Description of socioeconomic conditions prevailing in the communities at risk (Good, moderate, deteriorating)	Economic variables / quantitative factors: (V3.III.1A) Poverty/Basic needs (V3.III.1B) Coverage of health services (V3.III.1C) Coverage of treatment (V3.III.1D) Living conditions (V3.III.1E) Distance to water bodies (V3.III.1F) Employment

Description	Level of understanding of malaria transmission dynamics		
	Poor	**Partial**	**Good**
			Cultural variables / quantitative factors: (V3.III.2A) Education level (V3.III.2B) Water use (V3.III.2C) Waste disposition (V3.III.2D) Self-protection (V3.III.2E) Auto-medication Cultural variables / qualitative factors: (V3.III.2F) Disease knowledge (V3.III.2G) Costumes and belief (V3.III.2H) Quality of health workshops
			Political variables / quantitative factors: (V3.III.3A) Institutional arrangements (V3.III.3B) Public interests Political variables / qualitative factors: (V3.III.3C) Social organizations or non-institutional arrangements
Parasite exogenous variables	(V4) Prevalent parasite species	(V4.I) Duration of the sporogonic cycle/extrinsic cycle/vector delay	(V4.I.1) Number of degree-days required for the development of the parasite inside mosquito host
			(V4.I.2) Minimum temperature required for parasite development inside mosquito host
		(V4.II) Drug resistance (evidences)	(V4.II.1) Drug resistance
Human host (individual) exogenous variables	(V5) Total host window	(V5.I) Host delay for infectivity	(V5.I.1) Duration of the *Exo-Erythrocytic Schizogony*
			(V5.I.2) Duration of the *Erythrocytic Schizogony*
		(V5.II) Host delay for immunity	(V5.II.1) Fixed period of time during which the infection endures (*Plasmodium vivax*)
			(V5.II.2) Fixed period of time during which the infection endures (*Plasmodium vivax*)
		(V5.III) Immunity window	(V5.III.1) Average time in the immune state or fixed period of time during which immunity endures
			(V5.III.2) Average period to build up an effective immune response
			(V5.III.3) Average period to build up a protective immunity
			(V5.III.4) Average period to build up a partial immunity
			(V5.III.5) Average period to build up an immunologic memory
	(V6) Description of individuals	(V6.I) Human inherent characteristics	(V6.I.1) Human resistance
			(V6.I.2) Human susceptibility
			(V6.I.3) HIV infections

Description	Level of understanding of malaria transmission dynamics		
	Poor	Partial	Good
			(V6.I.4) Human recovery
Mosquito population exogenous variables	(V7) Vector density	(V7.I) Vector natality	(V7.I.1) Availability of breeding sites (location, characteristics, seasonality)
			(V7.I.2) Daily rate of vector natality, or mosquito per-capita intrinsic growth rate, or rainfall to mosquito constant
			(V7.I.3) Rate of oviposition (in eggs/day or eggs/batch)
			(V7.I.4) Environmental carrying capacity
			(V7.I.5) Eggs becoming non-viable / eggs mortality multiplier
			(V7.I.6) Cycle duration from egg to larva-1st instar
			(V7.I.7) Larvae becoming non-viable / Larvae mortality multiplier
			(V7.I.8) Cycle duration from larva-1st instar to pupae
			(V7.I.9) Pupae becoming non-viable / Pupae mortality multiplier
			(V7.I.10) Cycle duration from pupae to imago stage
		(V7.II) Vector survivorship	(V7.II.1) Probability of a mosquito surviving through one whole day, or natural mortality
			(V7.II.2) Probability of a vector surviving each gonotrophic cycle
			(V7.II.3) Parity rate
			(V7.II.4) Induced (for instance, by insecticides) mortality of mosquitoes
			(V7.II.5) Percentage of vectors surviving each feeding cycle in sprayed population, if the campaign is carried out
			(V7.II.6) Resistance against insecticides
			(V7.II.7) Resting habitats (indoor/outdoor)
	(V8) Vector species	(V8.I) Vector biting or feeding frequency	(V8.I.1) Inoculation rate and transmission rate
			(V8.I.2) Number of degree-days required for the digestion of a portion of ingested blood
			(V8.I.3) Minimum temperature required for the digestion of a blood meal
			(V8.I.4) Human Blood Index
			(V8.I.5) Duration of the second and third phases of the gonotrophic cycle
			(V8.I.6) Feeding and resting habits (indoor/outdoor)
		(V8.II) Vector infectivity and susceptibility	(V8.II.1) Sporozoite rate
			(V8.II.2) Proportion of *anophelines* with *sporozoites* in salivary glands which are actually infective
			(V8.II.3) Probability of becoming infected per infectious meal
			(V8.II.4) Probability of becoming infectious after an infectious blood meal
Environmental variables	(V9) General characterization of hydroclimatic conditions	(V9.I) Mean annual temperature and annual cycle	(V9.I.1) Mean daily ambient temperatures
			(V9.I.2) Minimum daily ambient temperatures
			(V9.I.3) Maximum daily ambient temperatures
		(V9.II) Total annual rainfall and annual cycle	(V9.II.1) Total daily rainfall records

Description	Level of understanding of malaria transmission dynamics		
	Poor	Partial	Good
		(V9.III) Mean annual relative humidity and annual cycle	(V9.III.1) Mean daily relative humidity
	(V10) General characterization of other environmental variables	(V10.I) Characterization of land use	(V10.I.1) Percentage of urban/rural areas
		(V10.II) Characterization of land cover	(V10.II.1) Normalized Difference Vegetation Index

The socio-economic conditions affect the following twelve variables: (1) the natural birth for the human host population, (2) the natural mortality rate for the human host population, (3) the differential (disease-induced) mortality for the human hosts, (4) the host delay (or length of the interval between infection -sporozoite inoculation- and the onset of infectivity -gametocyte maturation- in a human host), (5) the rate of oviposition of the vector population, (6) the natural resistance rate of human individuals against malaria, (7 to 10) the average periods to build up an immunologic memory, a partial immunity, a protective immunity, and an effective immune response in the human hosts, (11) the natural mortality of mosquitoes, and (12) the induced (for instance, by insecticides) mortality of mosquitoes.