The Abdus Salam
International Centre for Theoretical Physics

United Nations
Educational, Scientific and
Cultural Organization

IAEA
International Atomic Energy Agency

2022-14

Workshop on Theoretical Ecology and Global Change

2 - 18 March 2009

Climate variability and epidemic cycles: from understanding the past to anticipating the future II

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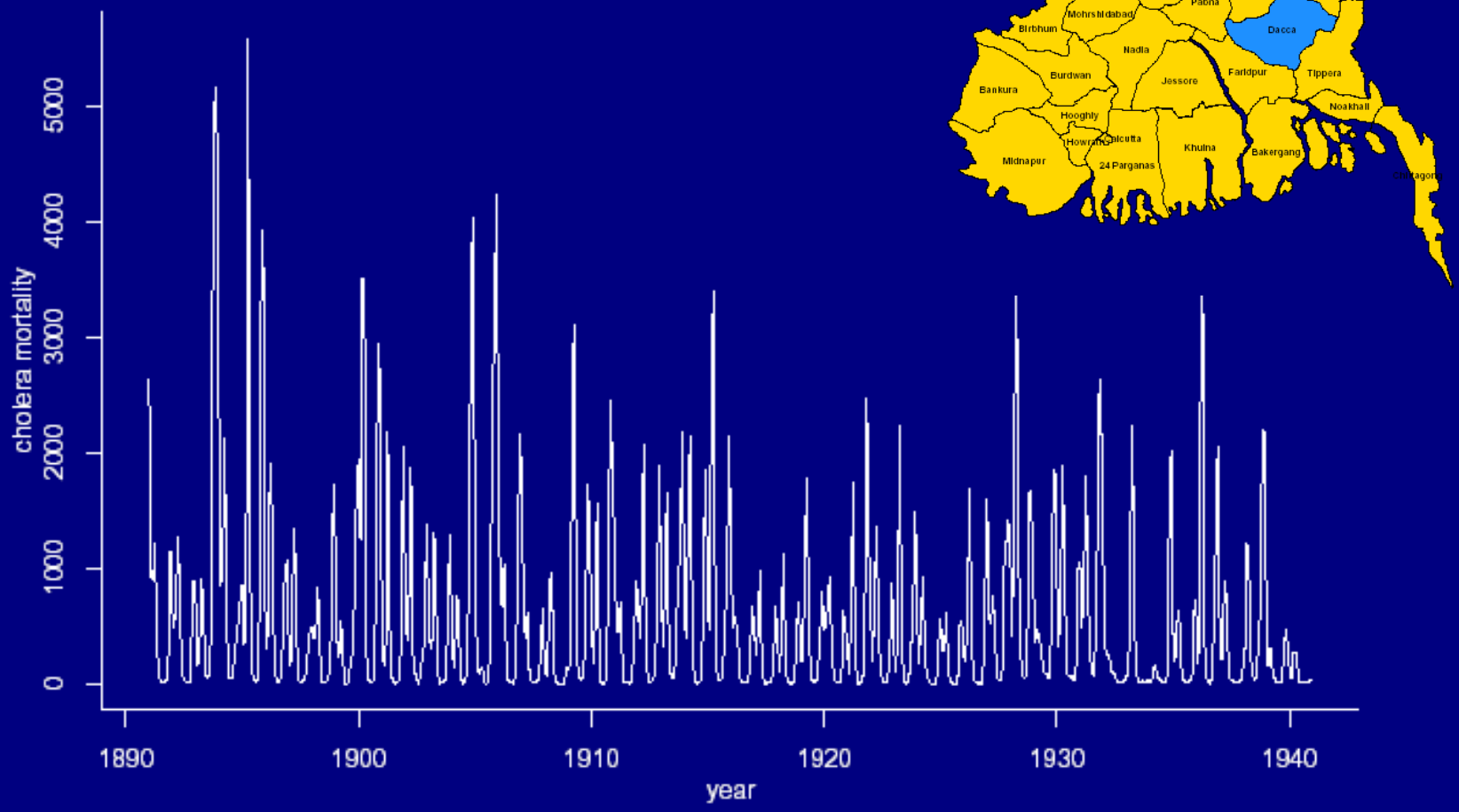
Environmental change
Evolution
Socio -economic factors
Infectious diseases
Malaria ward, Amana Hospital, in Dar es Salaam
Photograph / SAMANTHA APPLETON
Courtesy: ICDDR, Bangladesh

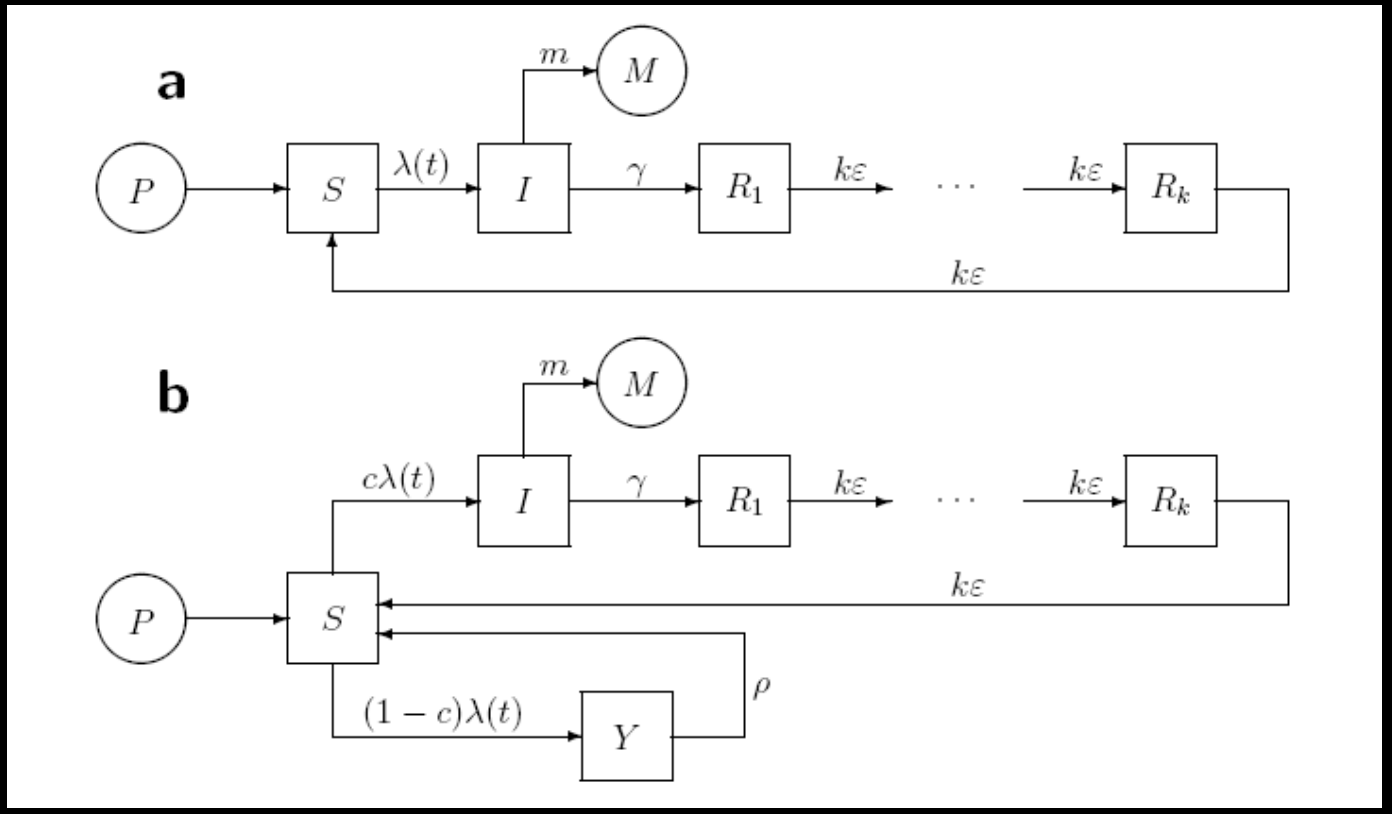
Outline

- Back to cholera and climate variability: estimating parameters in an ODE model that incorporates noise (a method based on numerical simulations and a selection process …)
- Back to epidemic malaria, but now address the role of climate change
- Climate change and pathogen evolution: the evolution of drug resistance
- Use this example to introduce the basics of Adaptive Dynamics

Historical cholera mortality

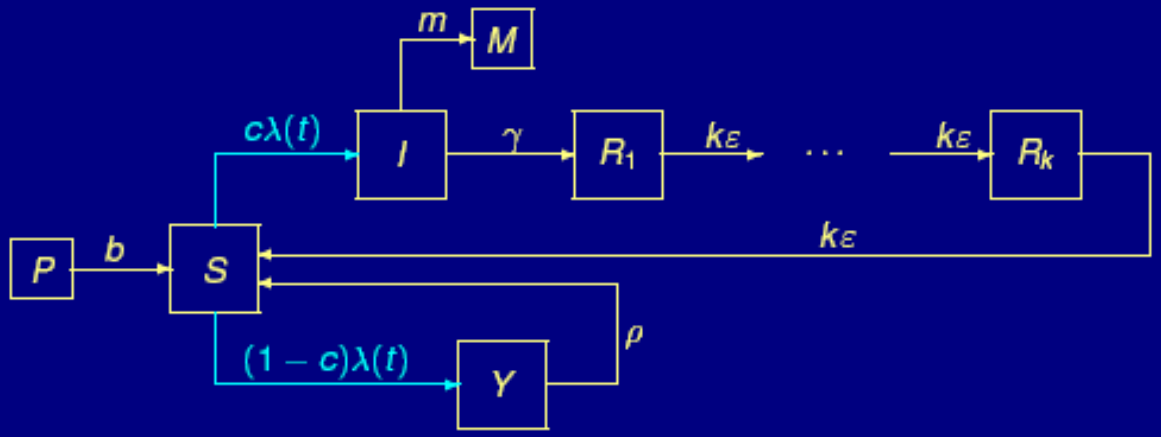


King, Ionides, Pascual, Bouma (Nature, *2008*)



King, Ionides, Pascual, Bouma
(Nature, *2008*)

Two-path model



$$\lambda(t) = \left(e^{\beta_{trend}\, t}\, \beta_{seas}(t) + \xi(t) \right) \frac{I(t)}{P(t)} + \omega$$

ω = environmental reservoir

King *et al.*, *(2008)*

New method (MIF)

Ionides, Bretó, and King (PNAS 2006)

likelihood maximization by iterated filtering

- can accommodate:
  - flexible model formulations
    - continuous time
    - unobserved variables (e.g. susceptibles)
    - stochasticity, nonstationarity
    - measurement error
- based on well-studied sequential Monte Carlo methods (particle filters)

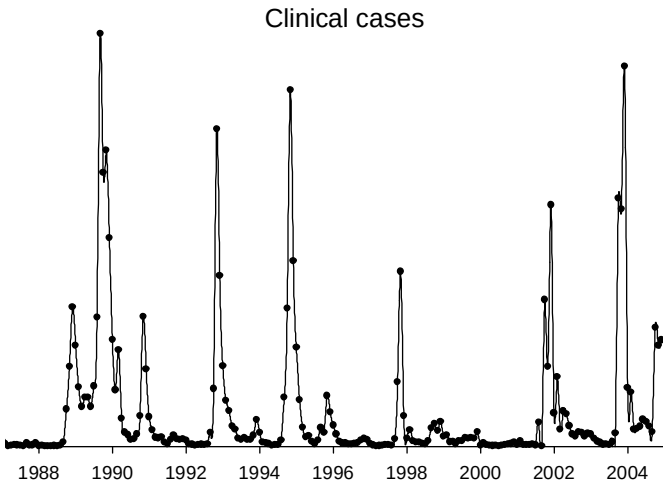
Maximum likelihood estimation

Model
A specific parameter set

Probability of the observed outcome / given the data

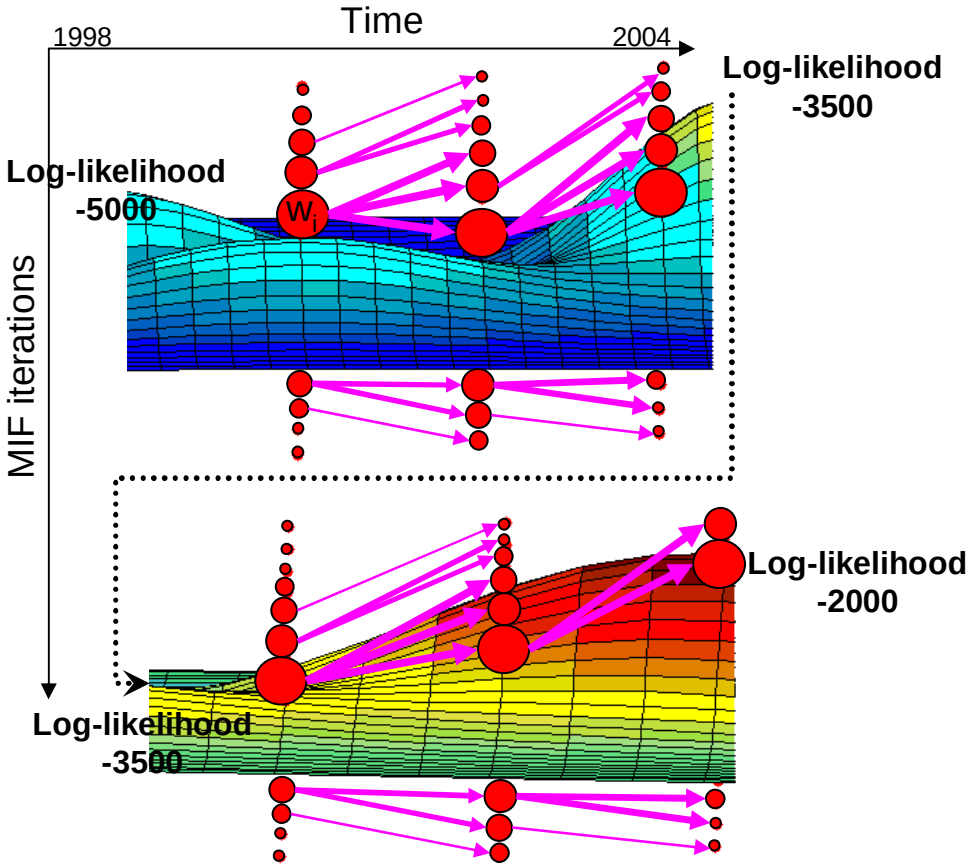
Choose parameter set that gives you the maximum probability (or likelihood)

(i.e. that makes the observed data most likely to have occurred)



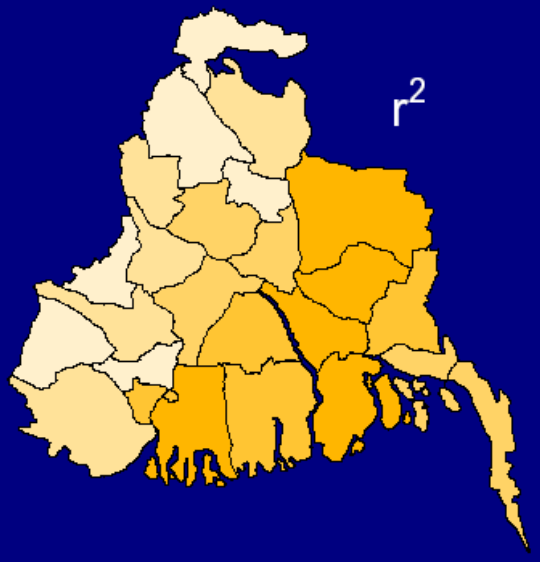
data y1,…..yn
X1,….,Xn unobserved variables
θ vector of constant parameters

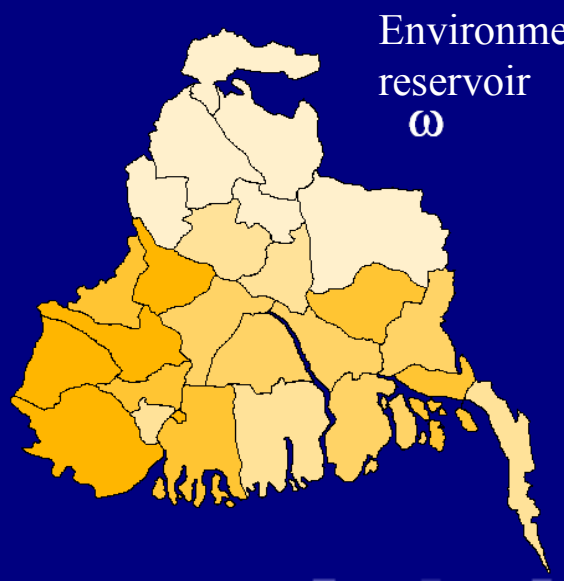
measurement model (observation process) $X_t \rightarrow y_t$
process noise (unobserved process)

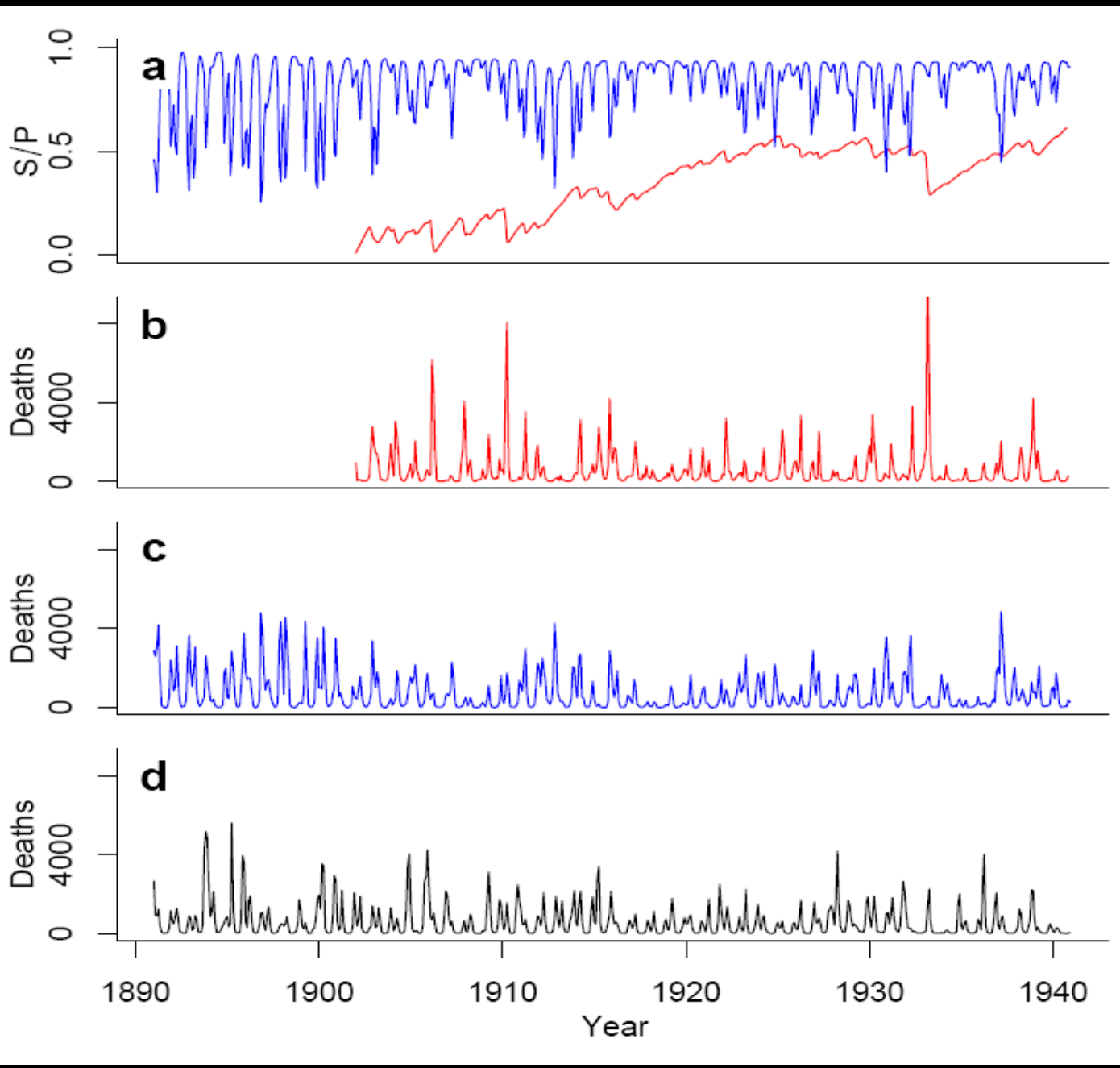


Model comparison

model	log likelihood	AIC	r^2
two-path	-3775.8	7591.6	0.848
SIRS	-3794.3	7622.6	0.849
SARMA((2,2)×(1,1))	-3804.5	7625.0	0.846
Koelle & Pascual (2004)	-3840.1	—	0.82
seasonal mean	-3989.1	8026.1	0.64





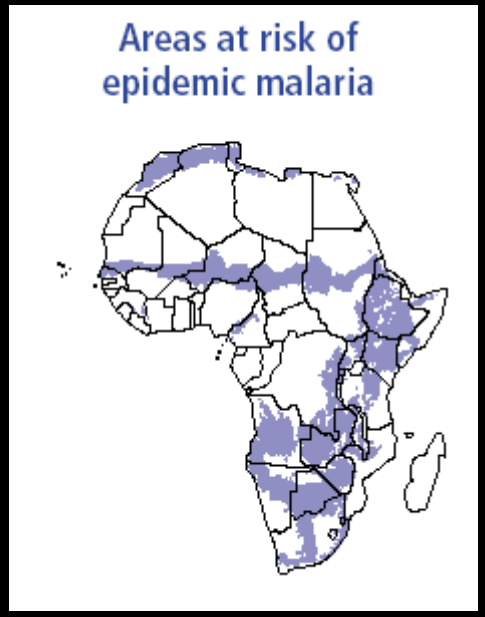


TSIRS

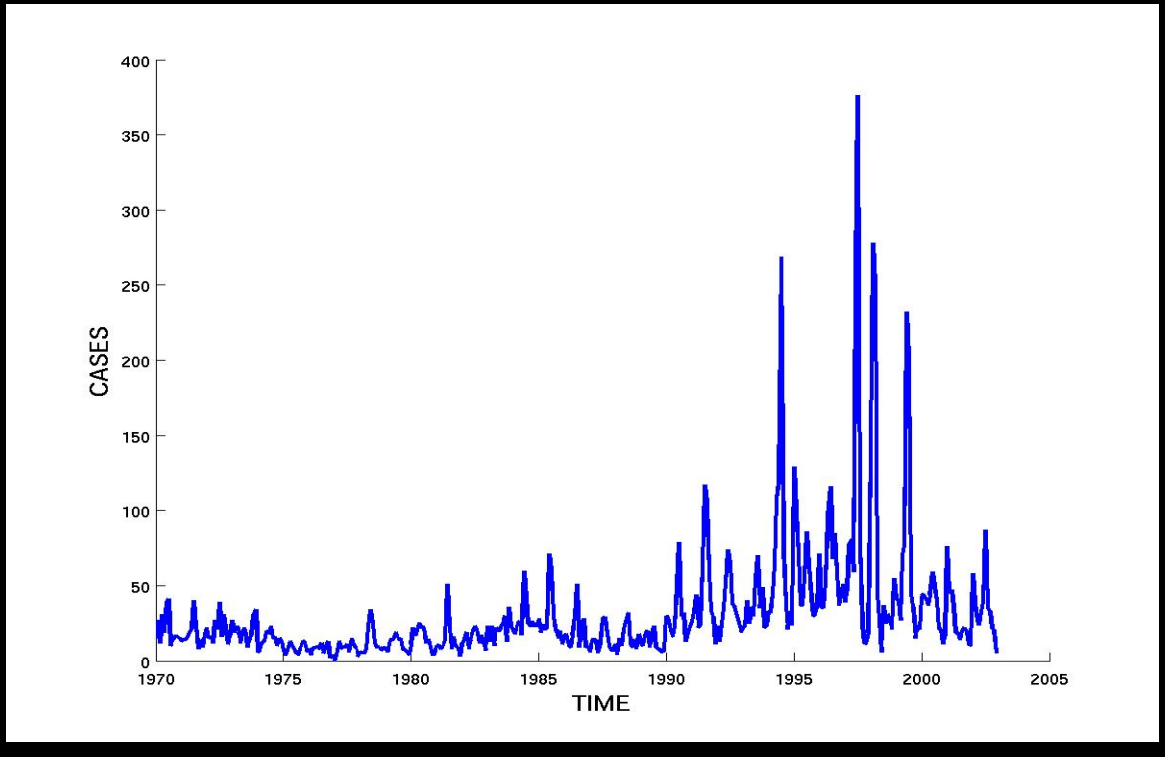
Short immunity

Data

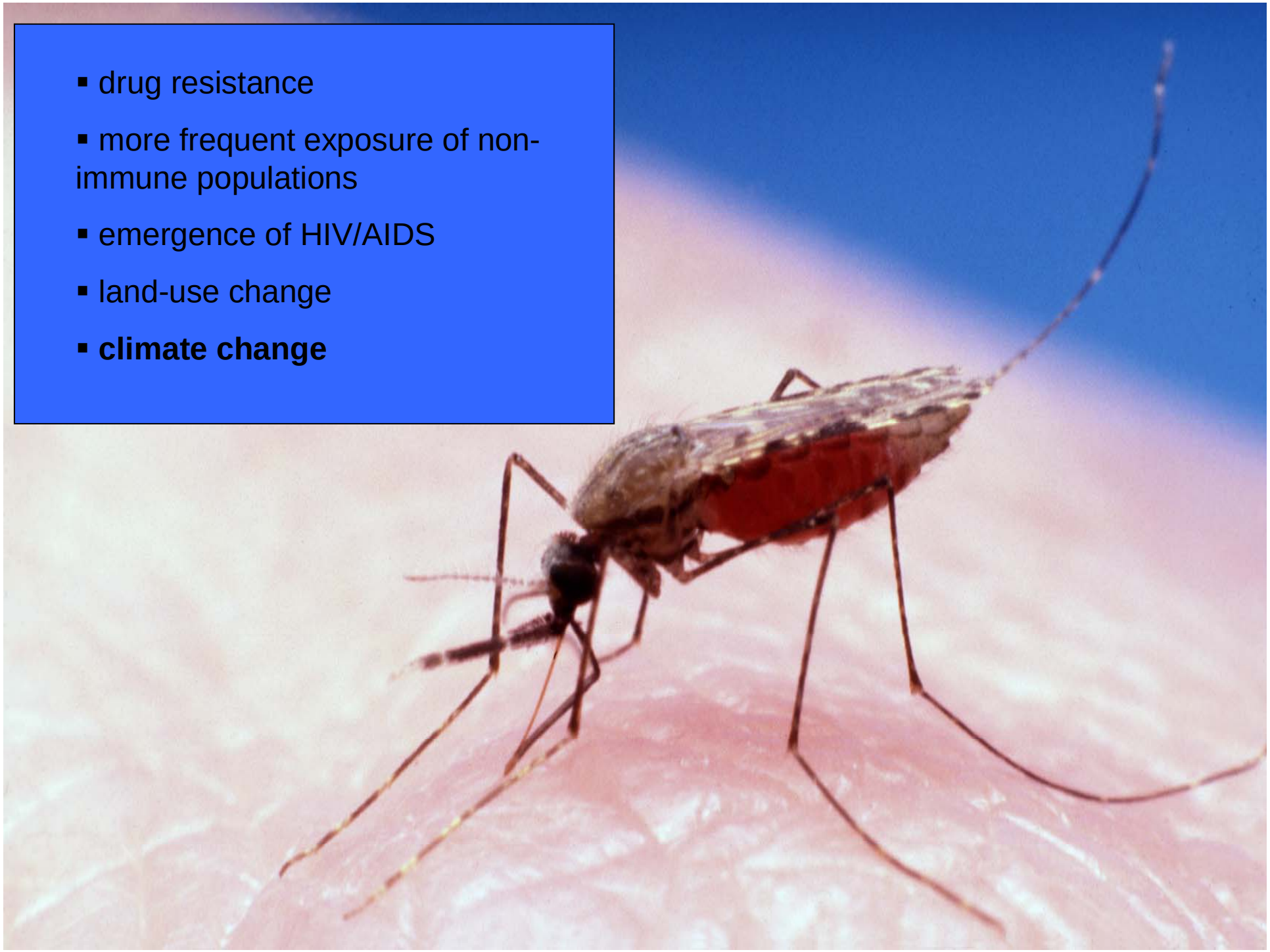
King *et al*. (Nature, *2008)*



Malaria in Rift Valley highlands (Western Kenya)

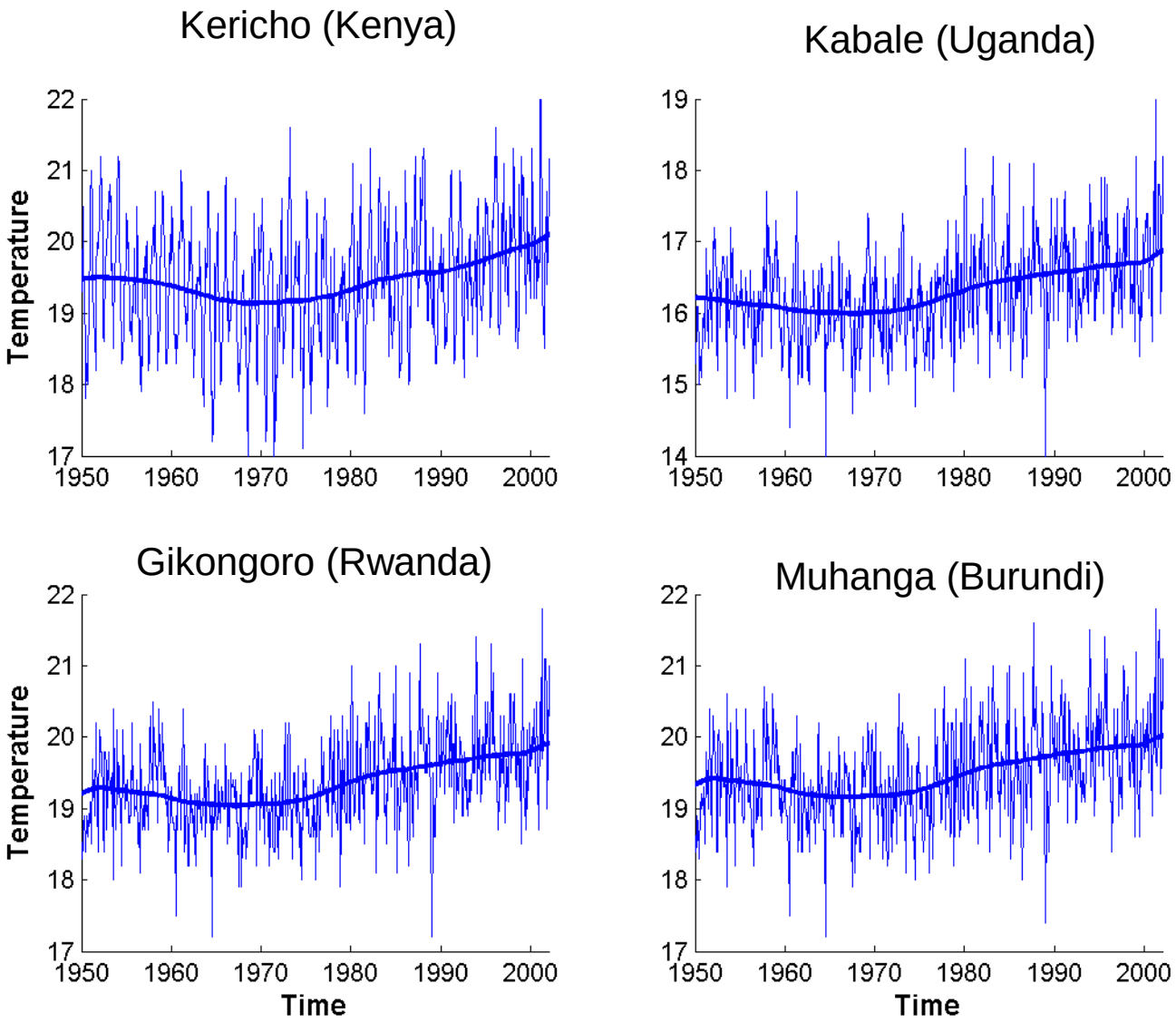


Data: courtesy of
S. Hay and G.D. Shanks


▪ drug resistance
▪ more frequent exposure of non-immune populations
▪ emergence of HIV/AIDS
▪ land-use change
▪ **climate change**

Points of contention:

- Evidence for significant trends in climate data?
- Do such trends result in a significant change in the disease itself?
- Is drug resistance a more important factor than climate change?
- (Is climate variability --- e.g. ENSO, rainfall interannual variation--- a major driver of disease dynamics?)



Pascual, Ahumada, Chaves, Rodo, Bouma (PNAS, 2006)

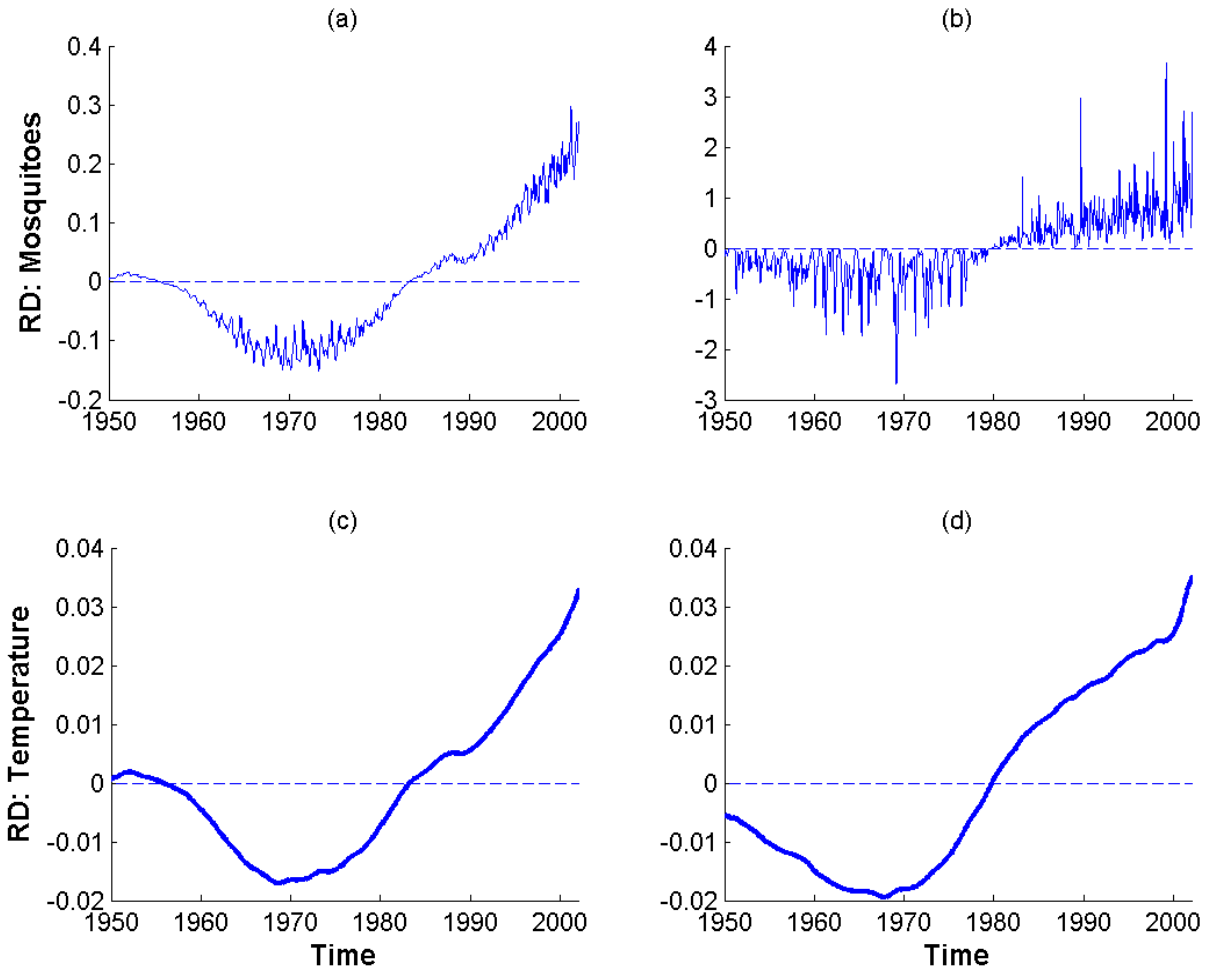
Data: CRU TS2.0 Tyndall Centre for Climate Change Research

Temperature

Temperature (without trend)

Rainfall (daily)

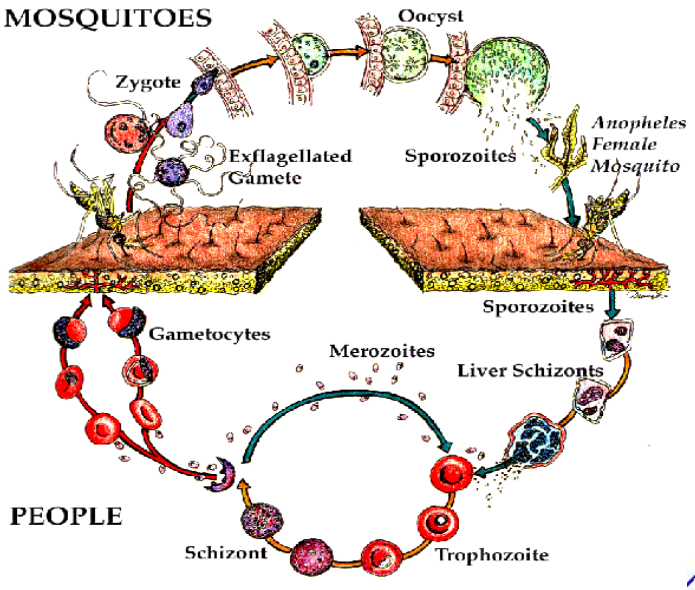
Population model for the vector abundance (larvae and adults)



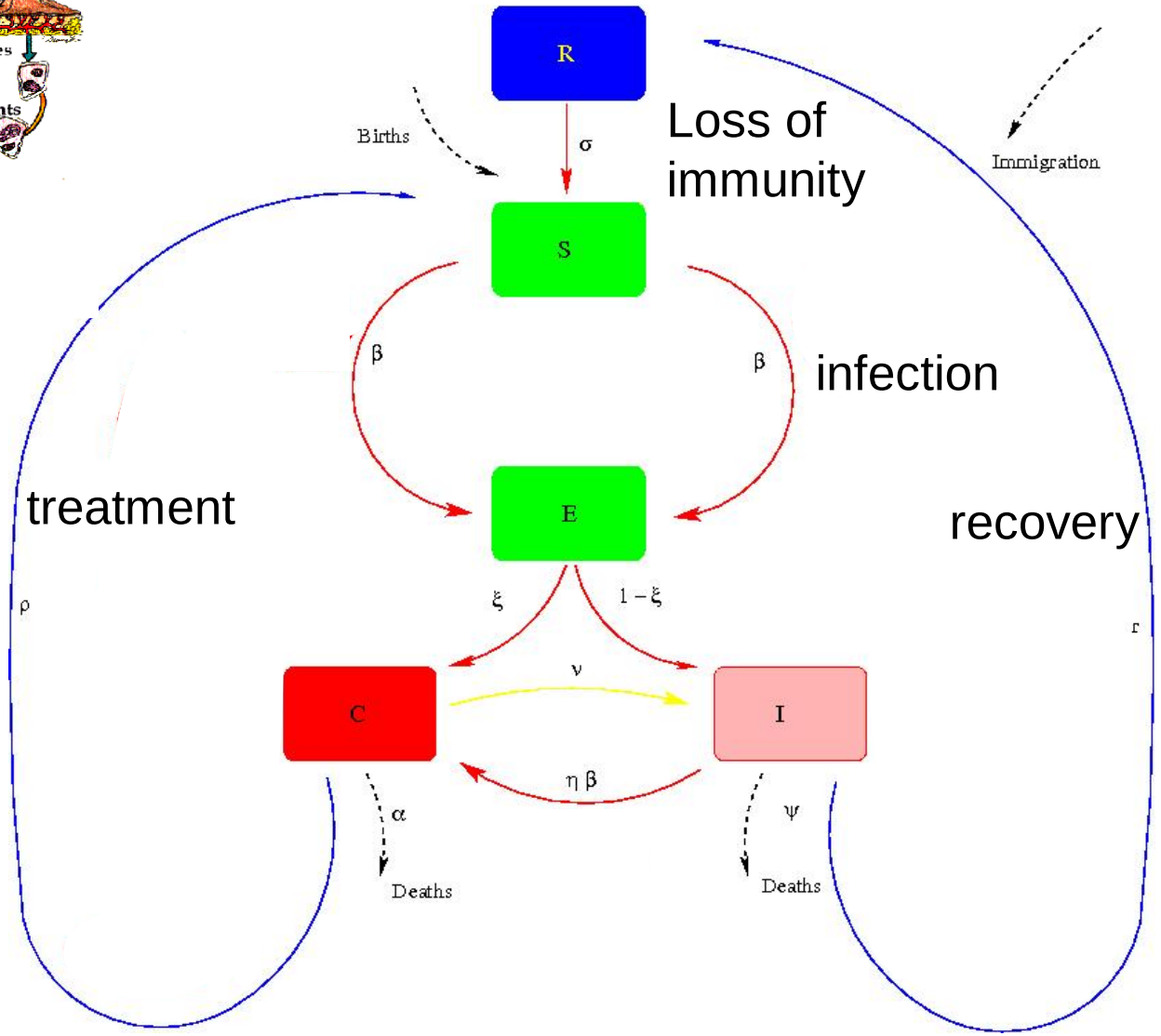
$RD = (M_T – M_{DT}) / M_{DT}$

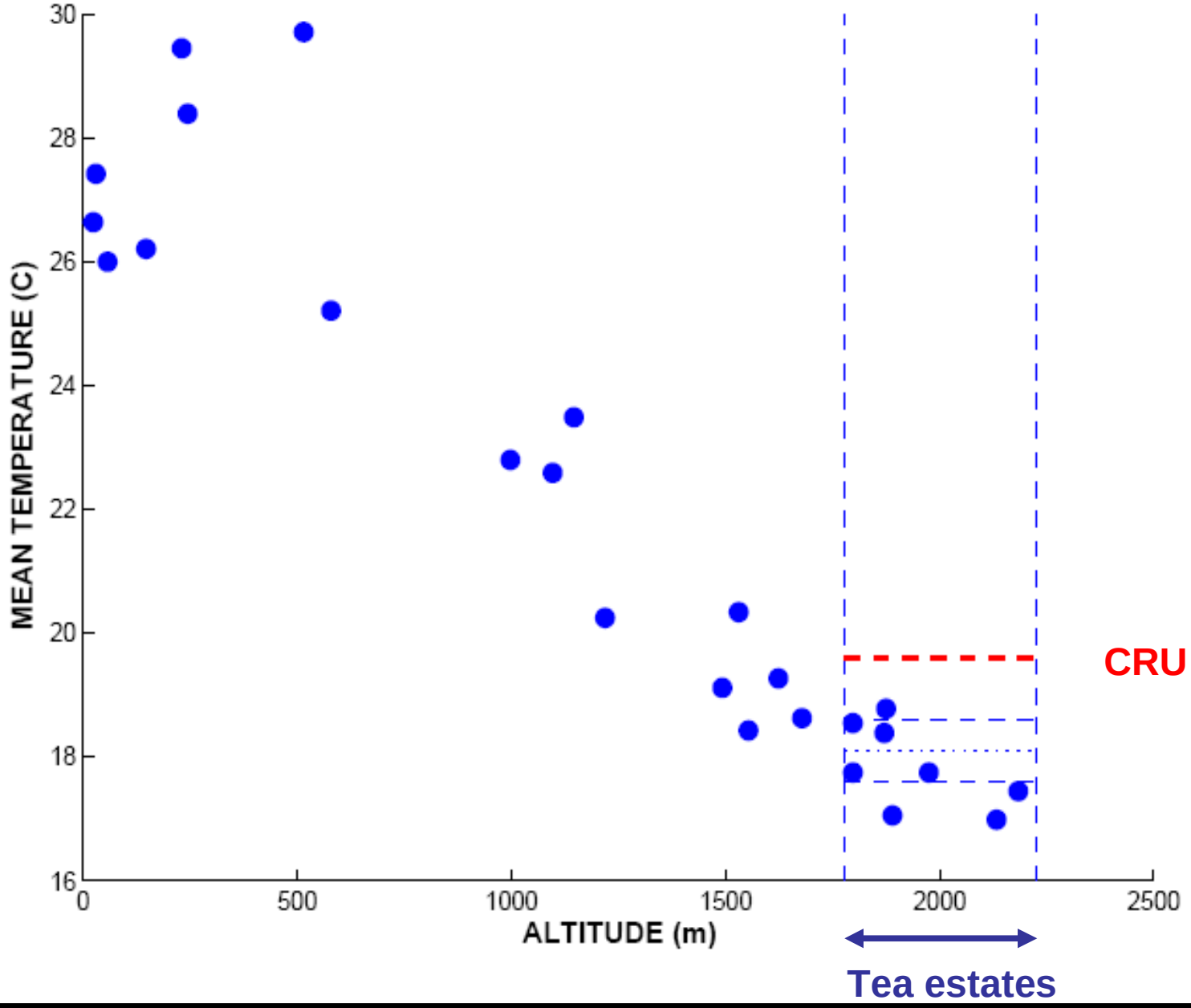
$RD = (T - T_{DT}) / T_{DT}$

Malaria transmission model



- Larvae
- Adults in three classes:
  - uninfected
  - exposed
  - infectious




MEAN TEMPERATURE (C)
30
28
26
24
22
20
18
16
0
500
1000
1500
2000
2500
ALTITUDE (m)
CRU
Tea estates

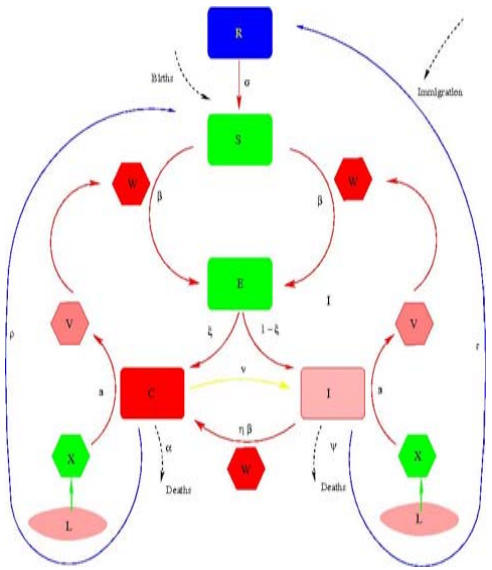
Temperature

(CRU; mean adjusted for altitude)

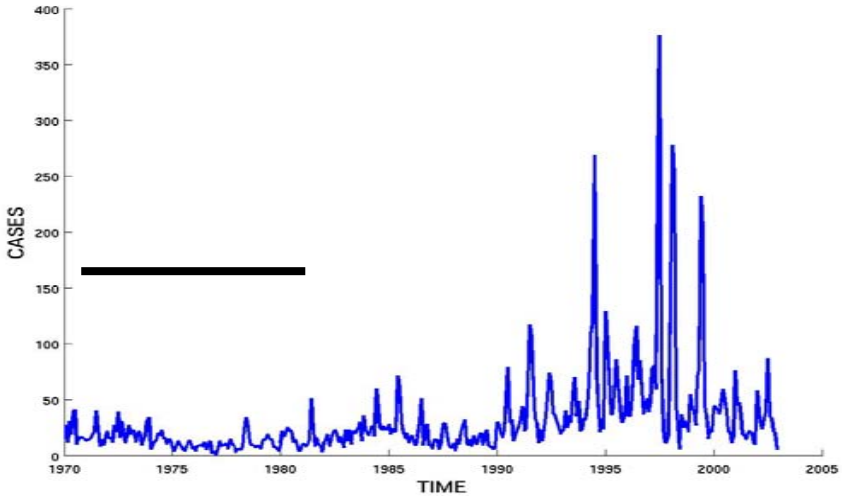
Rainfall

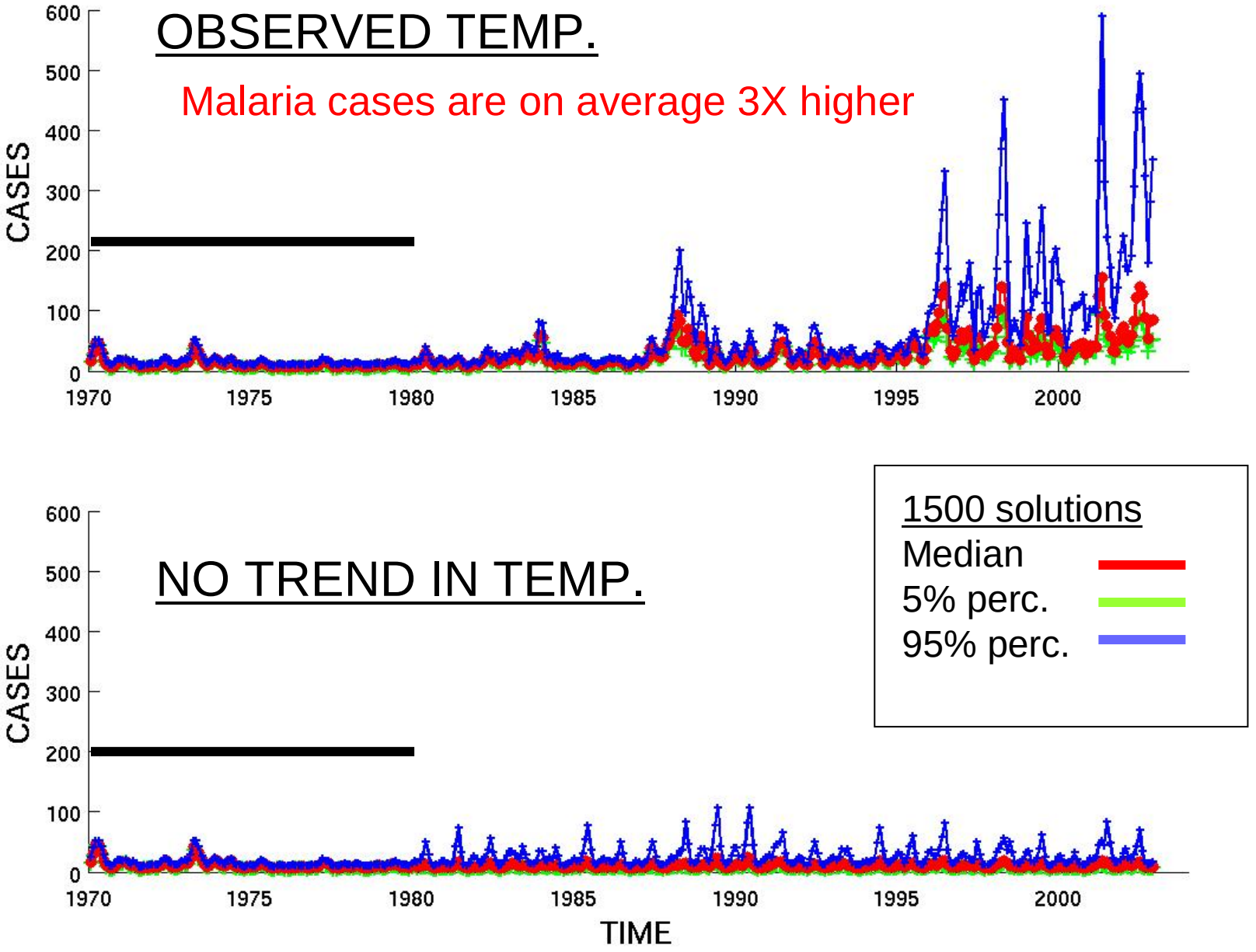
(Monthly and daily data)

- larva development (T)
- Plasmodium development (T)
- Adult and larval survival (T, R)
- Gonotrophic Cycle (biting rate , T)
- Carrying capacity (R)

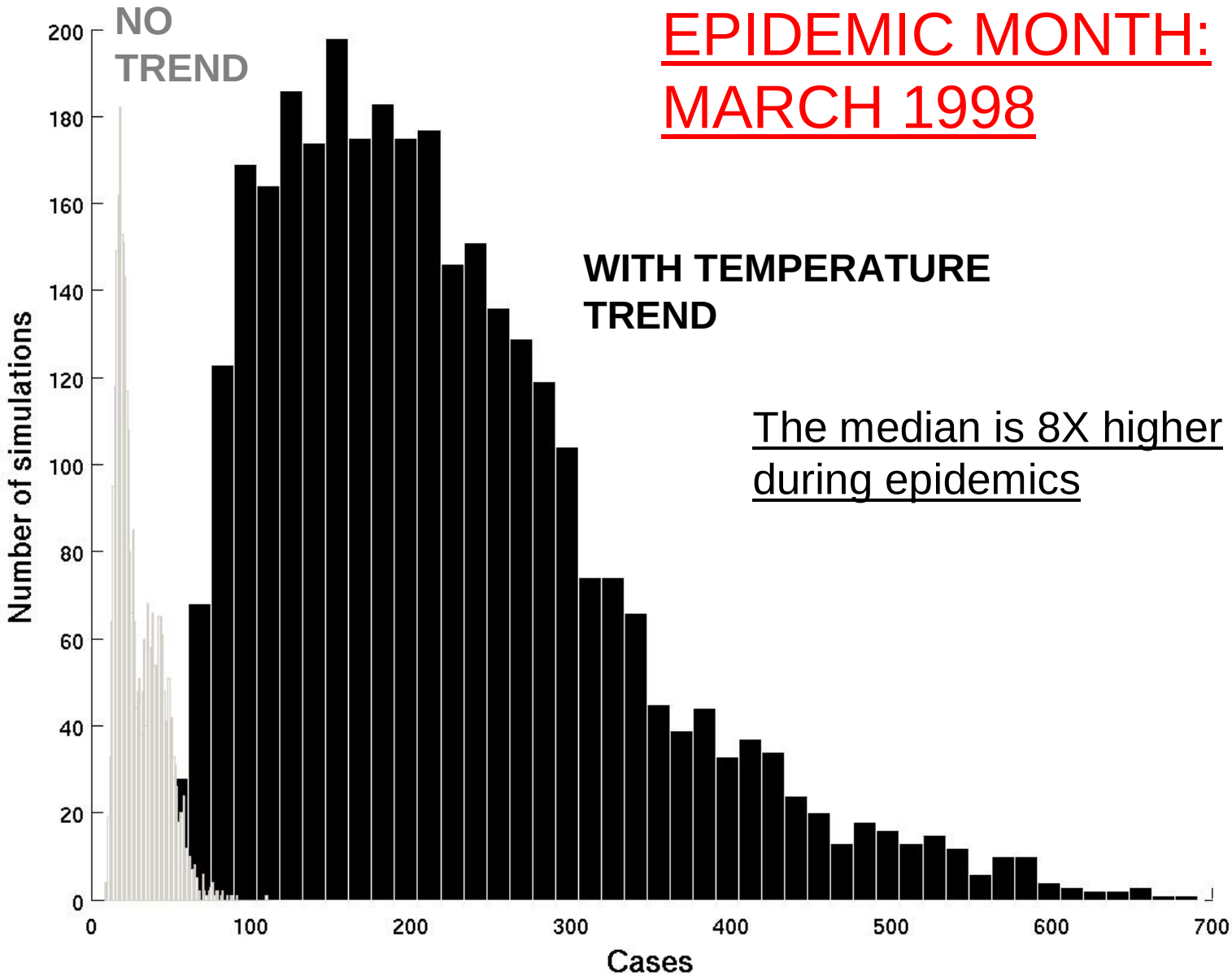


Model fitted with a Genetic Algorithm to the observed cases in the 1970s'

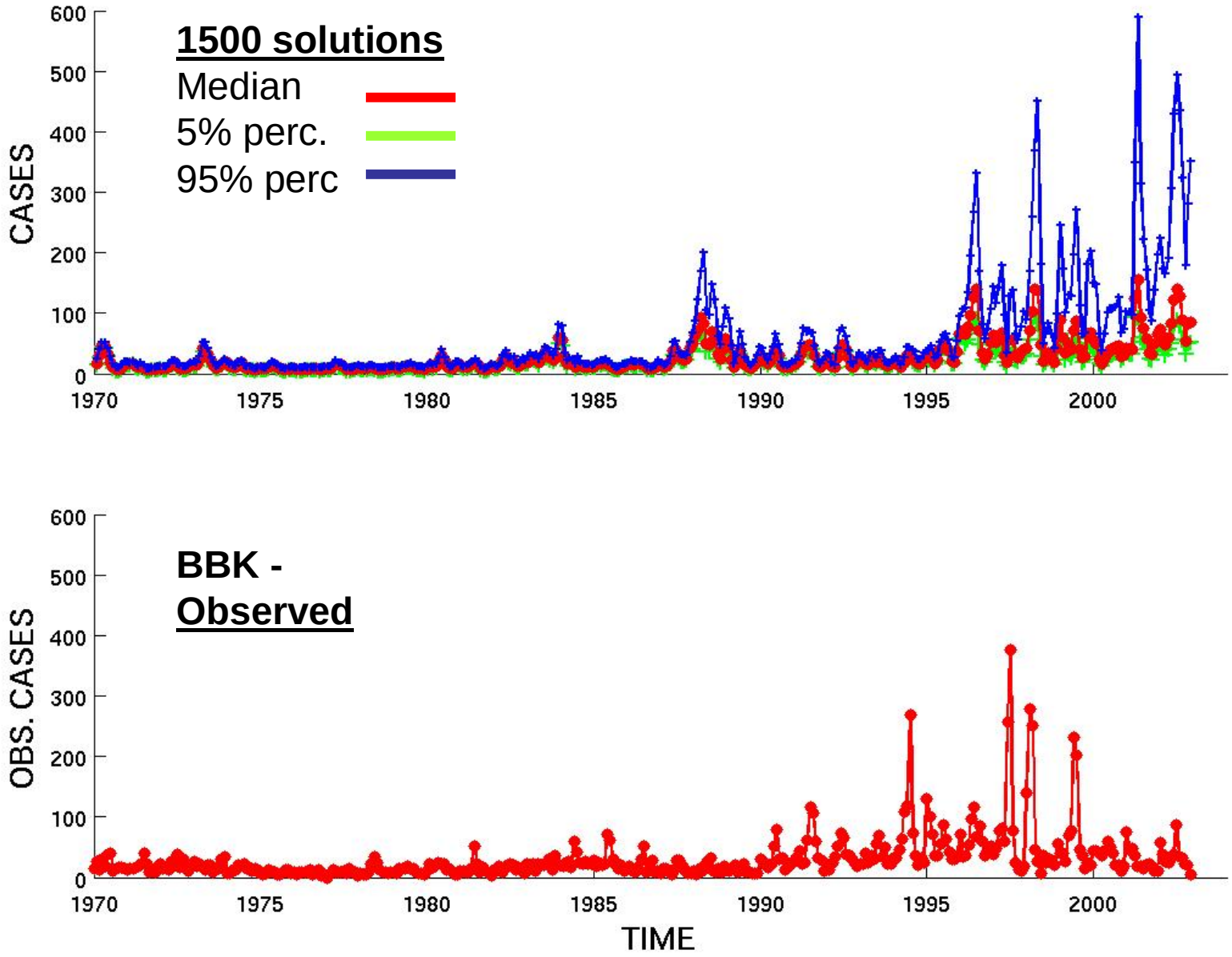



OBSERVED TEMP.
Malaria cases are on average 3X higher
NO TREND IN TEMP.
CASES
TIME
600
500
400
300
200
100
0
1970
1975
1980
1985
1990
1995
2000
1500 solutions
Median
5% perc.
95% perc.

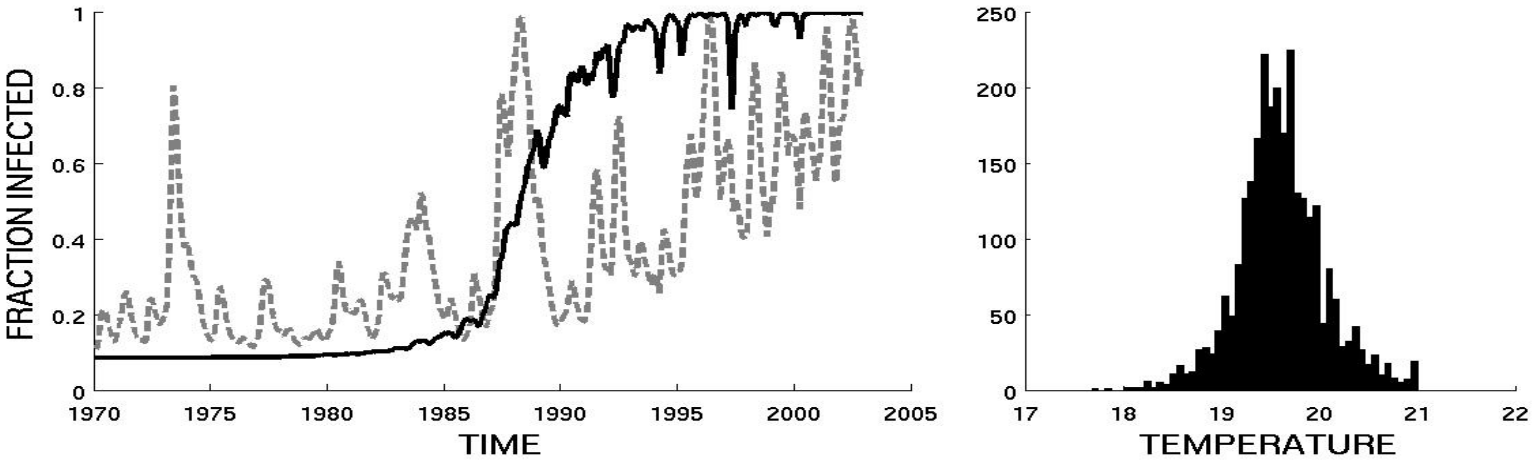
EPIDEMIC MONTH: MARCH 1998



The median is 8X higher during epidemics


1500 solutions
Median
5% perc.
95% perc
CASES
OBS. CASES
BBK -
Observed
TIME
0
100
200
300
400
500
600
1970
1975
1980
1985
1990
1995
2000

Threshold behavior



SOME CONCLUSIONS

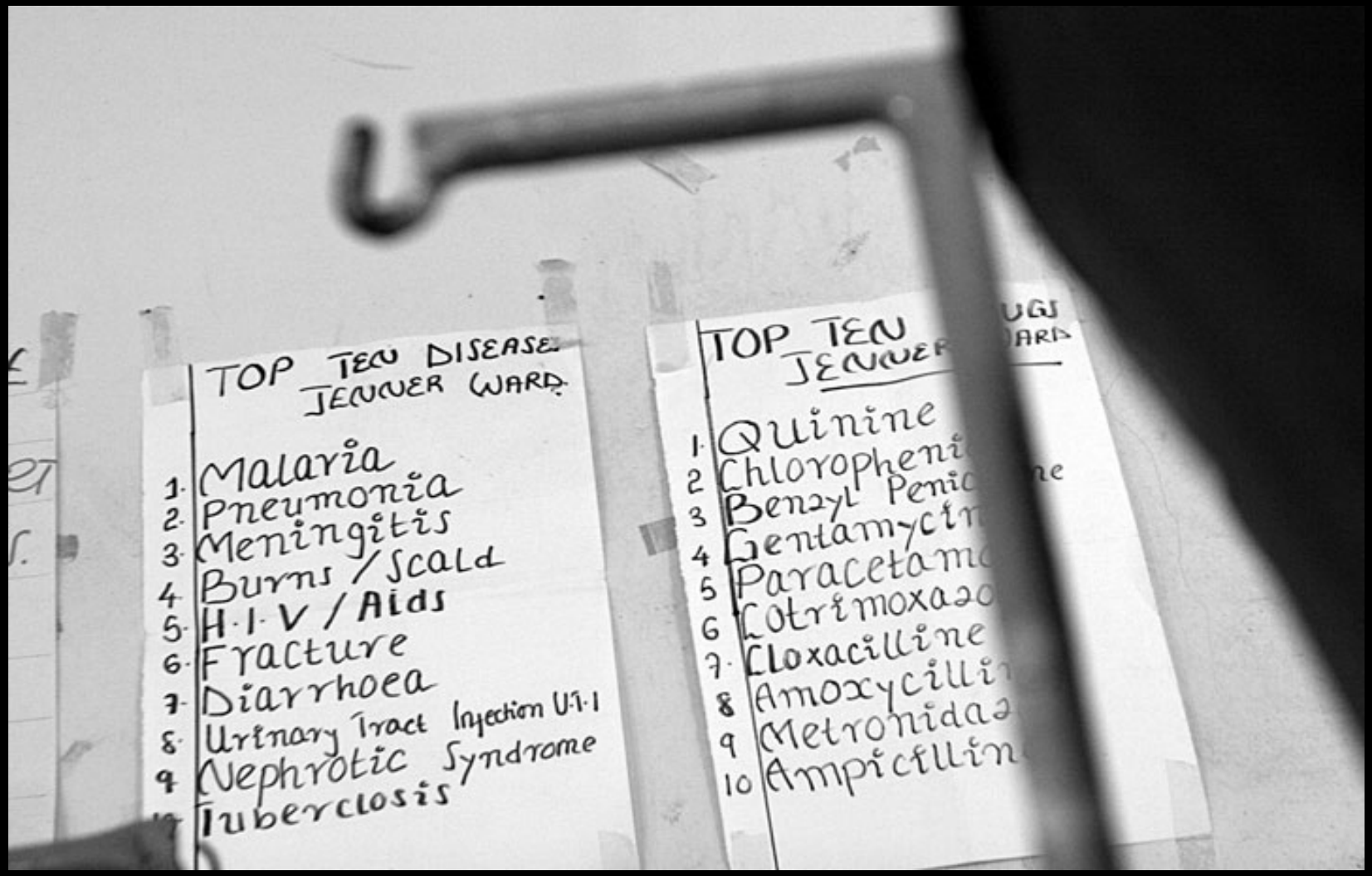
- Temperature warming can explain a significant fraction of the increase in the incidence of malaria in African highlands from the 1970s to the 1990s.

- A small temperature increase can lead to a large increase in the disease:
  - → doubling to quadrupling annual malaria cases on average (all years)
  - → with eight-fold increases in monthly cases during epidemic months

- However, the predicted cases based on the temperature trend are still below the observed values → other drivers at play

synergy of climate change and the evolution of drug resistance?

Synergy between increase transmission due to **climate change** and the evolution of **drug resistance**?



Photograph / SAMANTHA APPLETON

A detour into adaptive dynamics

- "…strain B outcompetes strain A in the environment that results from the prevalence of A, while strain C wins against B in the environment set by B, and A beats C in the C environment.

- The salient feature of such a scenario is frequency-dependent selection: selective pressures and the resulting invasion success depend on the composition of the established, or resident, pathogen population against which a variant strain is competing. Since frequency-dependent selection is ubiquitous in nature, … , the absence of an optimization principle is the rule, rather than the exception, in realistic pathogen-host interactions."

FROM ADAPTIVE DYNAMICS OF PATHOGEN-HOST INTERACTIONS
ULF DIECKMANN

Adaptive Dynamics

- Adaptive dynamics is a set of techniques developed during the 1990s for understanding the long-term consequences of small mutations in the traits expressing the phenotype. They link population dynamics to evolutionary dynamics and incorporates and generalizes the fundamental idea of frequency-dependent selection from game theory

- Two fundamental assumptions are: (1) the resident population can be assumed to be in a dynamical equilibrium when new mutants appear, and (2) the eventual fate of such mutants can be inferred from their initial growth rate when rare in the environment consisting of the resident

FROM "THE HITCHHIKER'S GUIDE TO ADAPTIVE DYNAMICS by A. Braanstrom and N.V. Festenberg

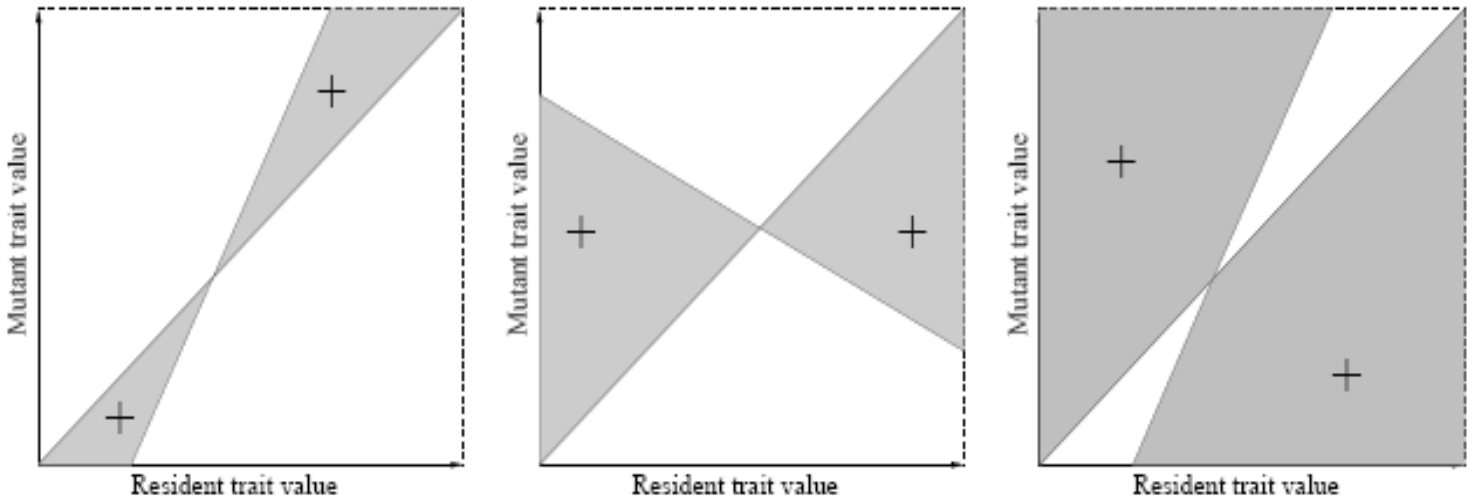


Figure 2: Examples of pairwise invasibility plots. Gray shading denotes positive invader growth rate $S_r(m)$, white shading negative $S_r(m)$, the black diagonal lines $S_r(m) = 0$. a) Evolutionarily stable strategy but not convergence stable. Such strategies should be rare in nature: if the strategy is once established it cannot be invaded locally, but it cannot be approached gradually in small steps, either. b) Evolutionarily stable strategy and convergence stable. A possible endpoint of evolution: the strategy can be attained gradually and then it will resist any invaders successfully. c) Convergence stable strategy but not evolutionarily stable. A scenario where a population can become dimorphic: the singular strategy can be established gradually, but then it can be invaded by mutants both above and below the resident strategy at the same time.

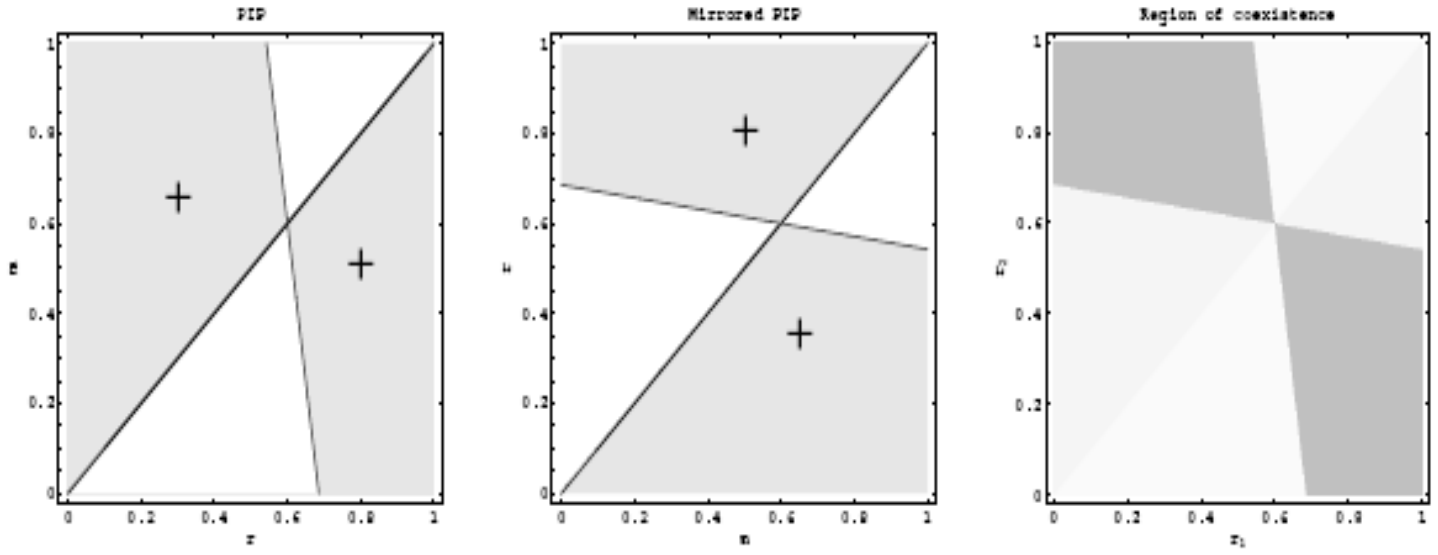


Figure 4: Illustration of the graphical method for obtaining the region of coexistence. a) A pairwise invasibility plot from the Snowdrift game (Hauert & Doebeli, 2004). b) The same pairwise invasibility plot mirrored over the main diagonal. c) The first two panels overlaid in which the region of coexistence is visible as the dark grey area. Note that protected dimorphisms are possible even though the singular strategy is evolutionarily stable and selection thus stabilising.

A continuous character?

- "Drug resistance in malaria does not usually arise through a single mutational step, but more commonly arises as the end of a longer process during which parasites accumulate mutations and become ever more tolerant of the drug" (Acta Tropica, I. Hastings and Watkins 2005)
- WHO classification:

  ✓S (sensitive): Asexual parasitaemia disappears from peripheral blood within 7 days of treatment

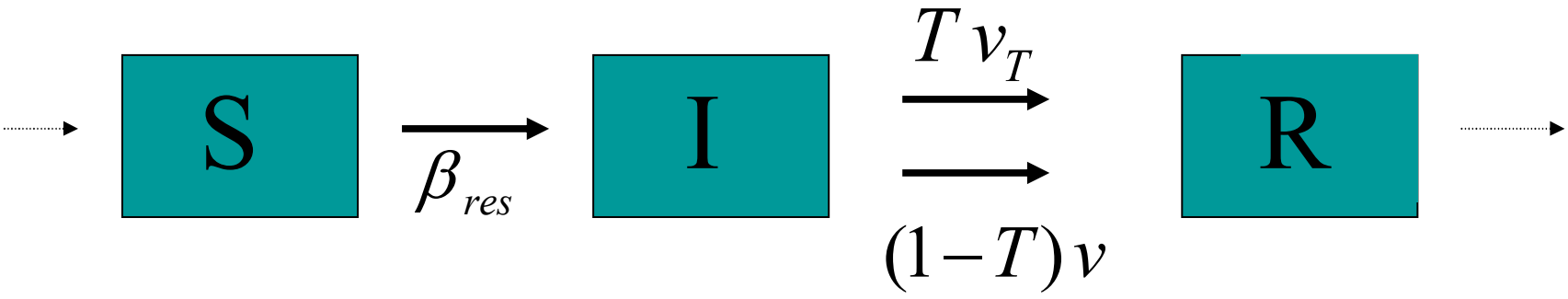
  ✓ R1 (low grade resistance): Par. disappears but reappears within 7-14 days

  ✓ R11 (medium grade): decrease par but not complete clearance from peripheral blood

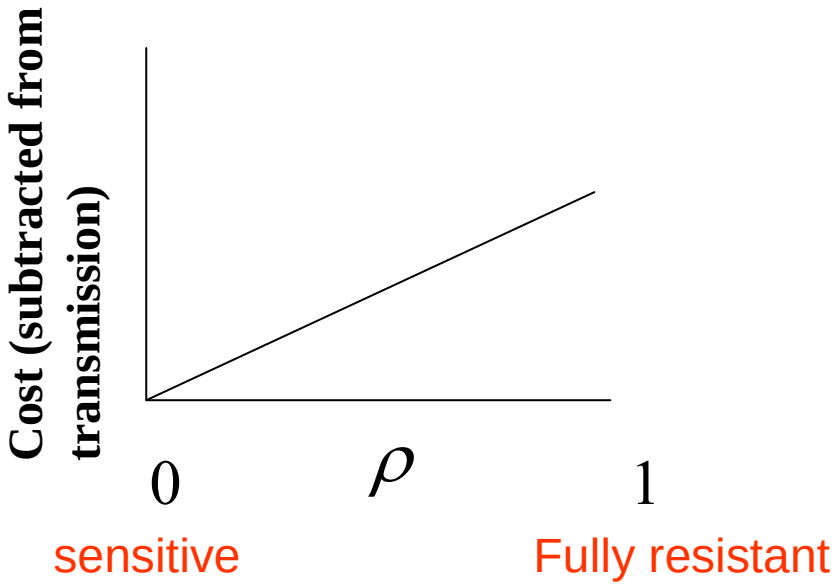
  ✓ R111 (resistant): no marked reduction of asexual parasitaemia.

A simple model:

- Recovery takes longer for untreated cases (Hastings and Watkins, 2005)
- There is a cost to resistance (e.g. study in Sudan on seasonal patterns! Babiker et al. 2005)



Resistance level $\rho = \frac{v}{v_T}$



Some equations:

The transmission equation for the resident strain (note that it assumes that the mutant strain has a negligible abundance):

$$\frac{dI}{dt} = \beta_r I \frac{S}{N} - \mu_r I - [(1-T)\nu + T\nu_{Tr}]I$$

Gives us the "environment" for the invasion by the mutant strain:

$$\Rightarrow \frac{S^*}{N} = \frac{\mu_r + [(1-T)\nu + T\nu_{Tr}]}{\beta_r}$$

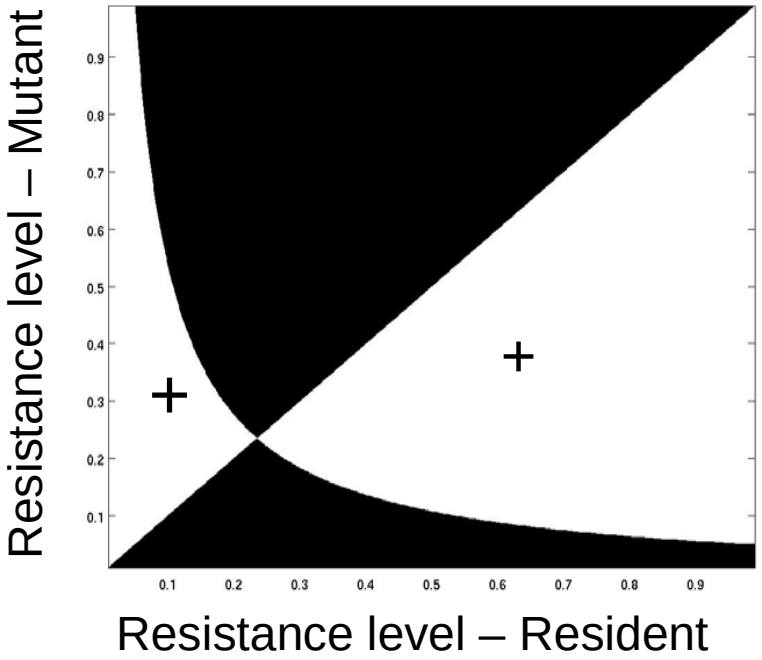
From which we can write:

$$\frac{dI_m}{dt} = \beta_m I_m \frac{S^*}{N} - \mu_m I_m - [(1-T)\nu + T\nu_{Tm}]I_m$$

Pairwise invasibility plots: is a mutant strain with a higher resistance level able to invade a resident strain at the equilibrium of the epidemiological model?

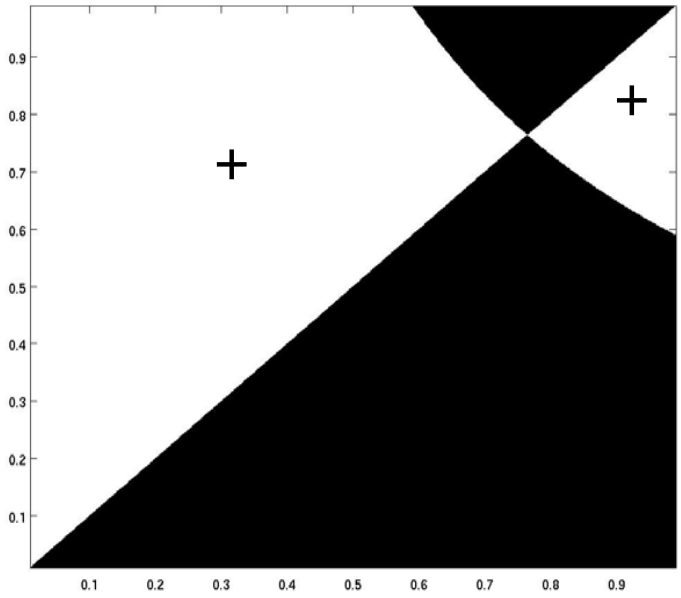
$T = 0.01$

$\beta = 0.006$



$T = 0.01$

$\beta = 0.06$



Higher transmission rate

Conclusions

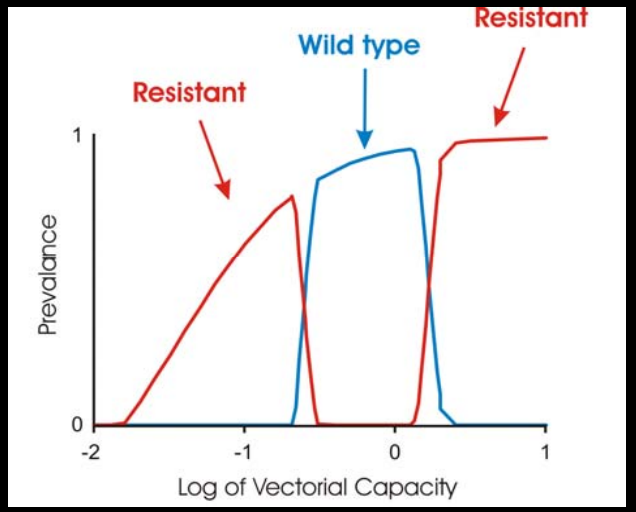
- Drug resistance and climate change can interact, resulting in the faster evolution of resistance as temperature increases
- But we have ignored the seasonal and interannual dynamics …
- Also, we have considered a very simple model of population dynamics (SIR or SIRS)
- A more complex story if we consider different levels of immunity … we do not yet fully understand the interplay of transmission intensity, including climate change, and the evolution of drug resistance!

Talisuna et al., Am. J. Trop. Med. Hyg, **77** (2007)

Table 4. Relative risk for malaria parasite resistance (clinical treatment failure) to chloroquine (CQ) or to sulfadoxine–pyrimethamine (SP) for three scenarios observed in Uganda

Scenario	CQ resistance	Relative risk (95% CI)	SP resistance	Relative risk (95% CI)
Low parasite prevalence[a]	28·0%	3·1 (1·2–7·7)	2·4%	0·5 (0·1–4·2)
Medium parasite prevalence[b]	9·6%	1·0 (reference)	5·1%	1·0 (reference)
High parasite prevalence[c]	28·0%	3·2 (1·6–6·4)	11·8%	2·3 (0·9–5·9)

[a]Estimate derived from data for one site.
[b]Estimate derived from meta-analysis of data for 2 sites.
[c]Estimate derived from meta-analysis of data for 4 sites.
95% CI, 95% confidence interval.



Back to points of contention:

- Is there evidence for significant trends in climate data?
  YES

- If so, can such a trend result in a significant change in the disease itself? YES

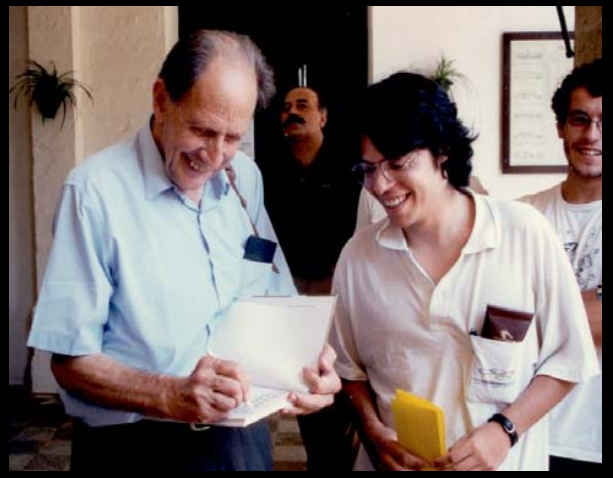
- An alternative explanation for the observed exacerbation of epidemic malaria is drug resistance.
  NOT INDEPENDENT FROM CHANGES IN TRANSMISSION AND THEREFORE, IN CLIMATE

- (Does climate variability --- e.g. ENSO, rainfall interannual variation--- drive disease dynamics?) .
  YES: LAST LECTURE

Gracias

Yael Artzy (UM)

David Alonso (UM >> Groningen)

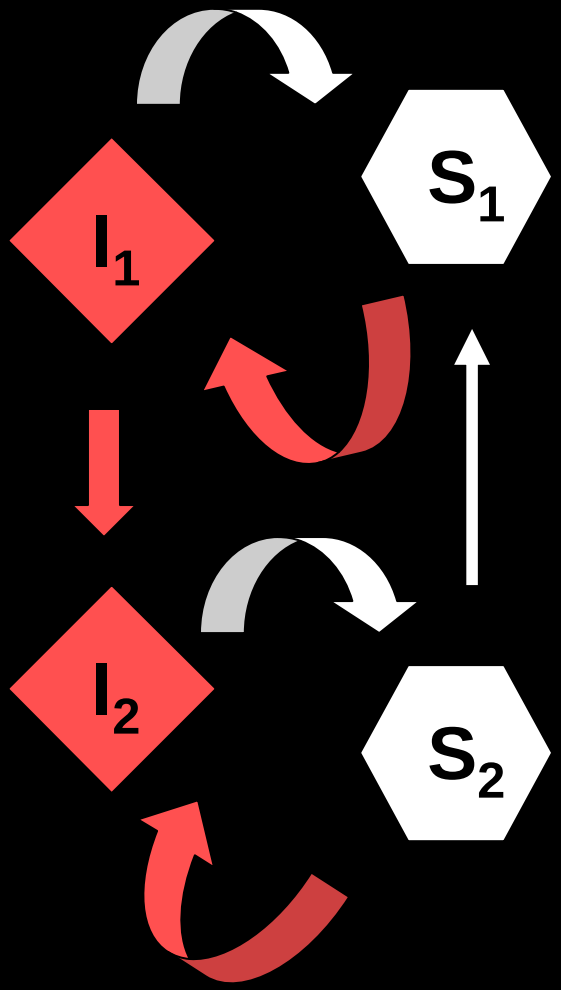


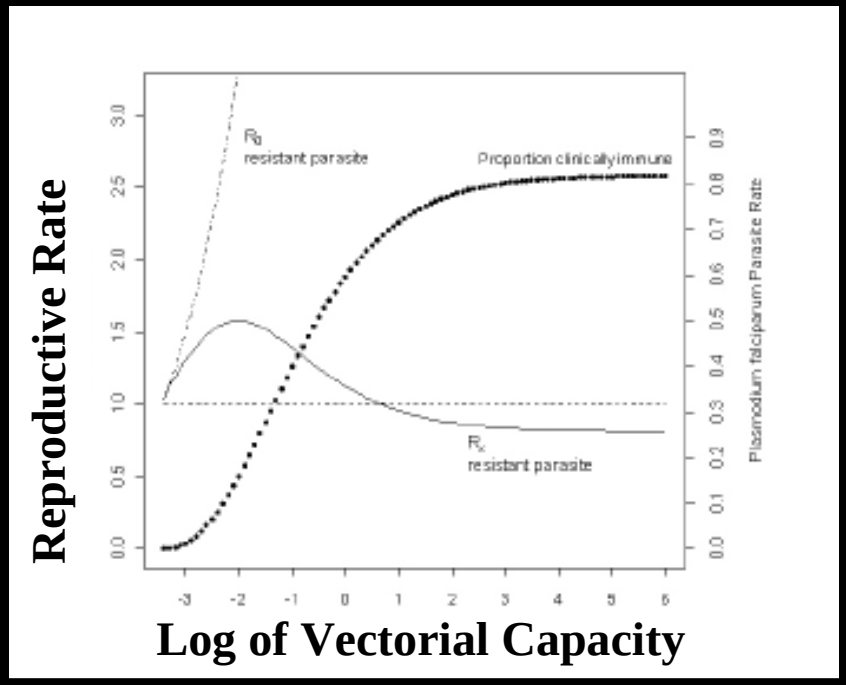
Menno Bouma (LSHTM)

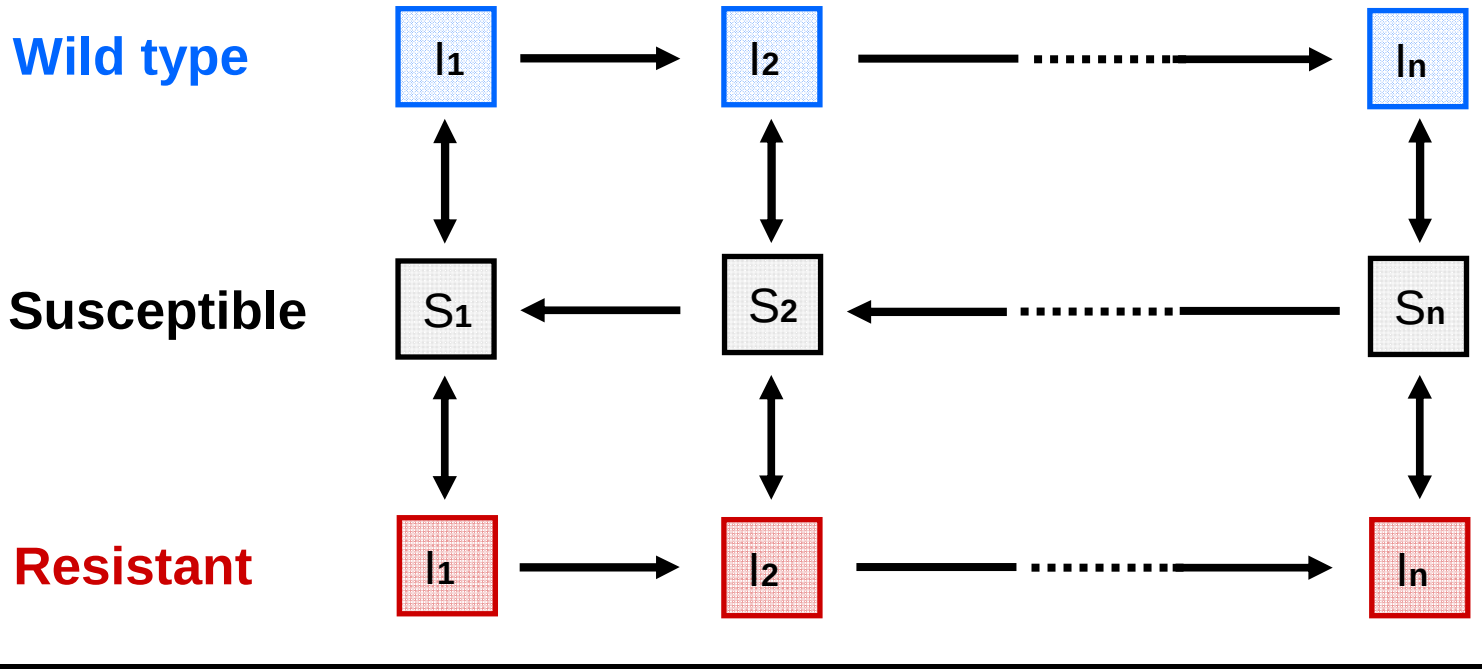
Funding:
Howard Hughes Medical Institute
J.S. McDonnell Foundation
Graham Environmental Sustainability Institute (UM)

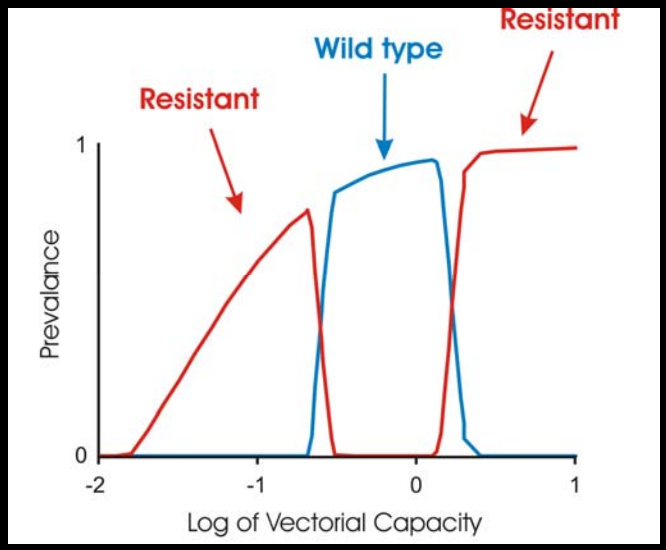
Clinically-immune hosts as a **refuge** for drug-sensitive malaria parasites

Klein, Smith, Boni and Laxminarayan, Malaria Journal 2008



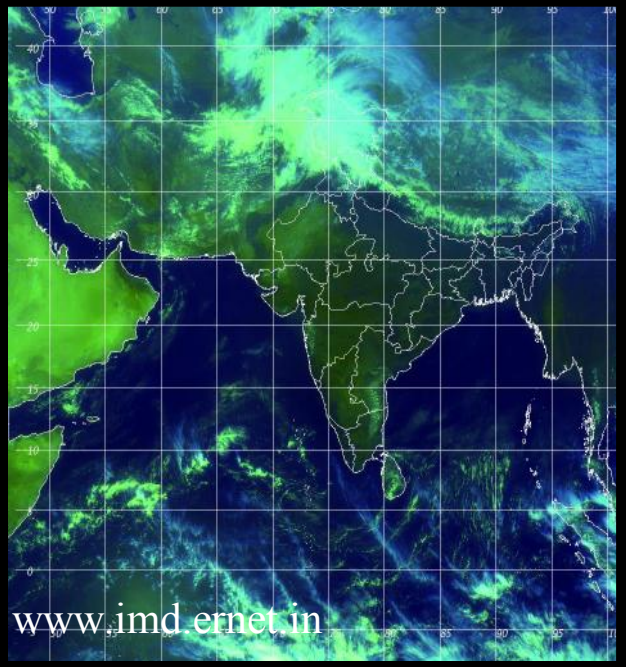






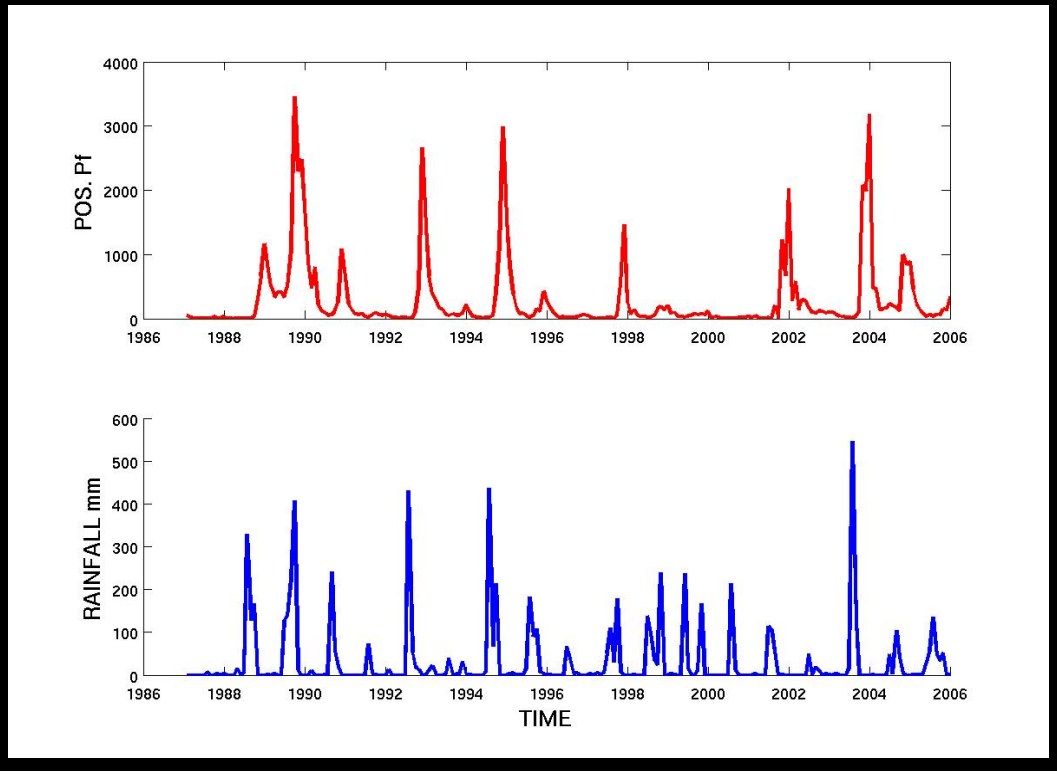
Artzy and Pascual (in prep.)

Epidemic malaria in India



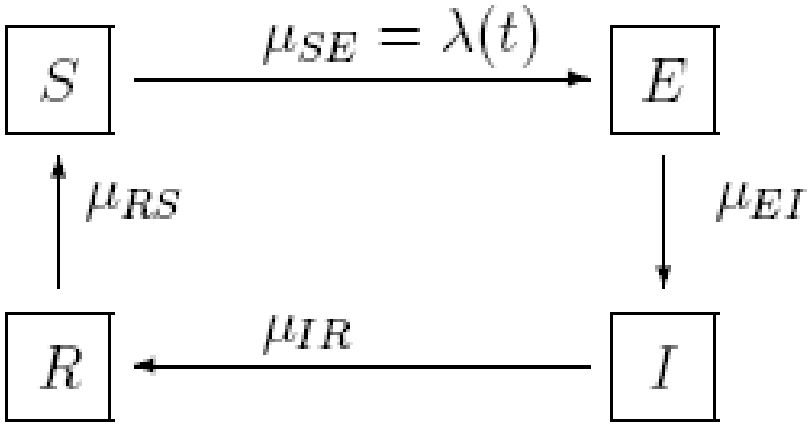
Gujarat and Rajasthan: semi-arid regions vulnerable to malaria epidemics

Malaria monthly records at the district level since 1976

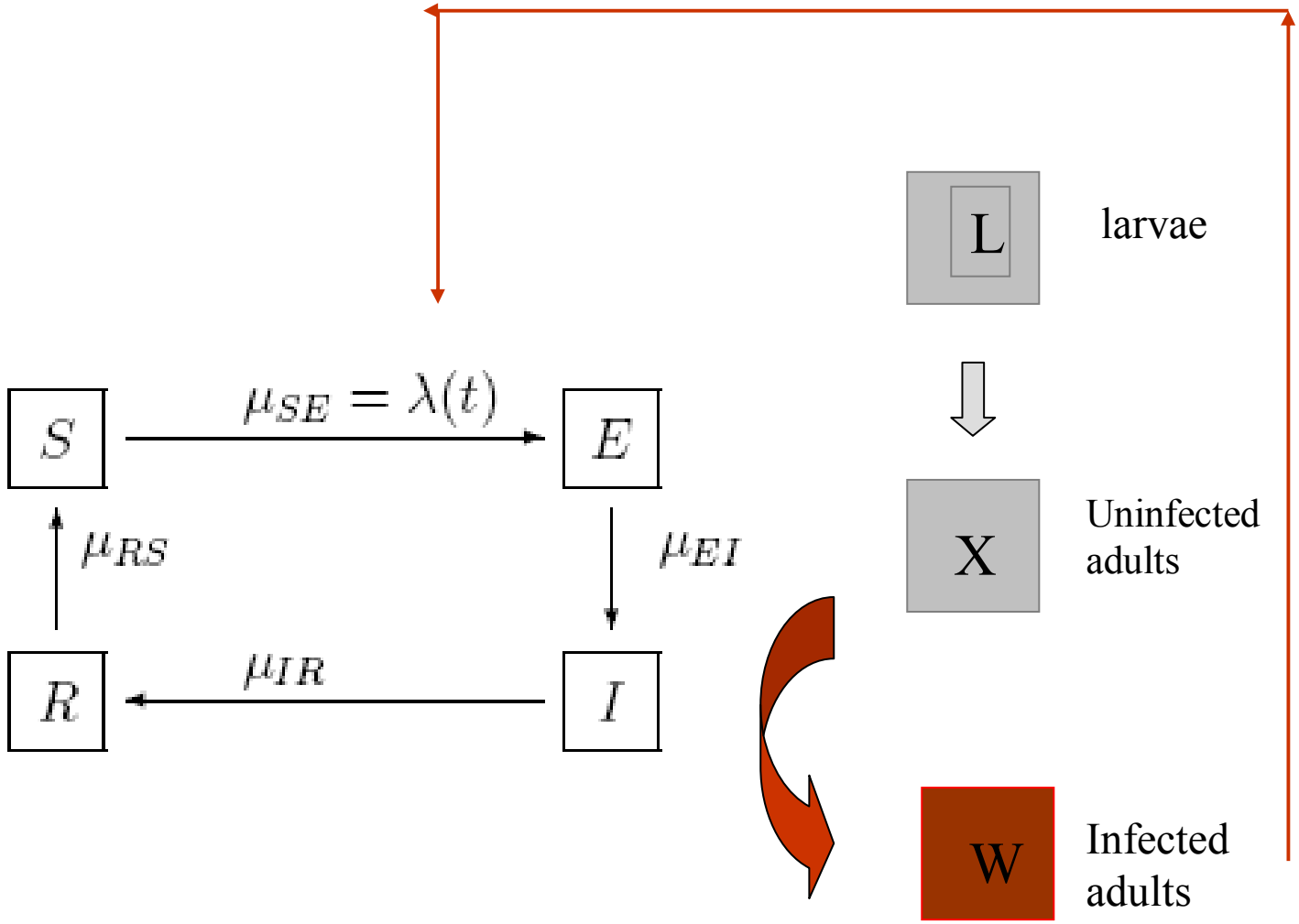


Control and treatment efforts at the moment are retroactive

The simpler model: SEIRS



This model includes vector “dynamics” in the force of infection λ(t) as follows:


L
larvae
X
Uninfected adults
W
Infected adults
S
E
I
R
$\mu_{SE} = \lambda(t)$
μ_{RS}
μ_{EI}
μ_{IR}

The force of infection through the vector introduces a distributed delay in the system

$$\lambda(t) = \int_0^t ba^2 cX(t_0) \frac{I(t_0)}{N(t_0)} p(t - t_0) dt_0$$

Biting rate

Uninfected mosquitos

Fraction of infected humans

Probability that a mosquito that acquired a parasite at time t_0 is sill alive and carries a fully developed infectious parasite at time t

We allow X(t) to vary in time: we replace it by a parameter that varies seasonally and at other temporal scales. It is the "environmental or process noise" obtained when fitting the model to the data

$$\lambda(t) = \int_0^t \beta_{seas}\beta_{t_0} \frac{I(t_0)}{N(t_0)} p(t-t_0)dt_0$$

Seasonal variation

"Process error" or

"Process noise"

NOTE: In practice, we do not use a 'sum' or integral but a chain of compartments that implements the distributed delay