MULTI-SCALE MODELING OF MALARIA: FROM ENDEMICITY TO ELIMINATION

or the DEATH of SEIR models

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Collaborators

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MaHPIC Project: Mary Galinski, Emory Vaccine Center. Supported by NIH's NIAID cooperative agreement U19AI089702-01 (2012-2017).

Malaria Today

- Half the world population is at risk.
- Every year, 5% to 10% of the human population is infected. 216 million **symptomatic** cases reported in 2010
- Mortality was estimated around 615,000 deaths in 2010 (WHO Malaria Report, 2010).
- 5^{th} leading cause of death worldwide.

Malaria Life Cycle

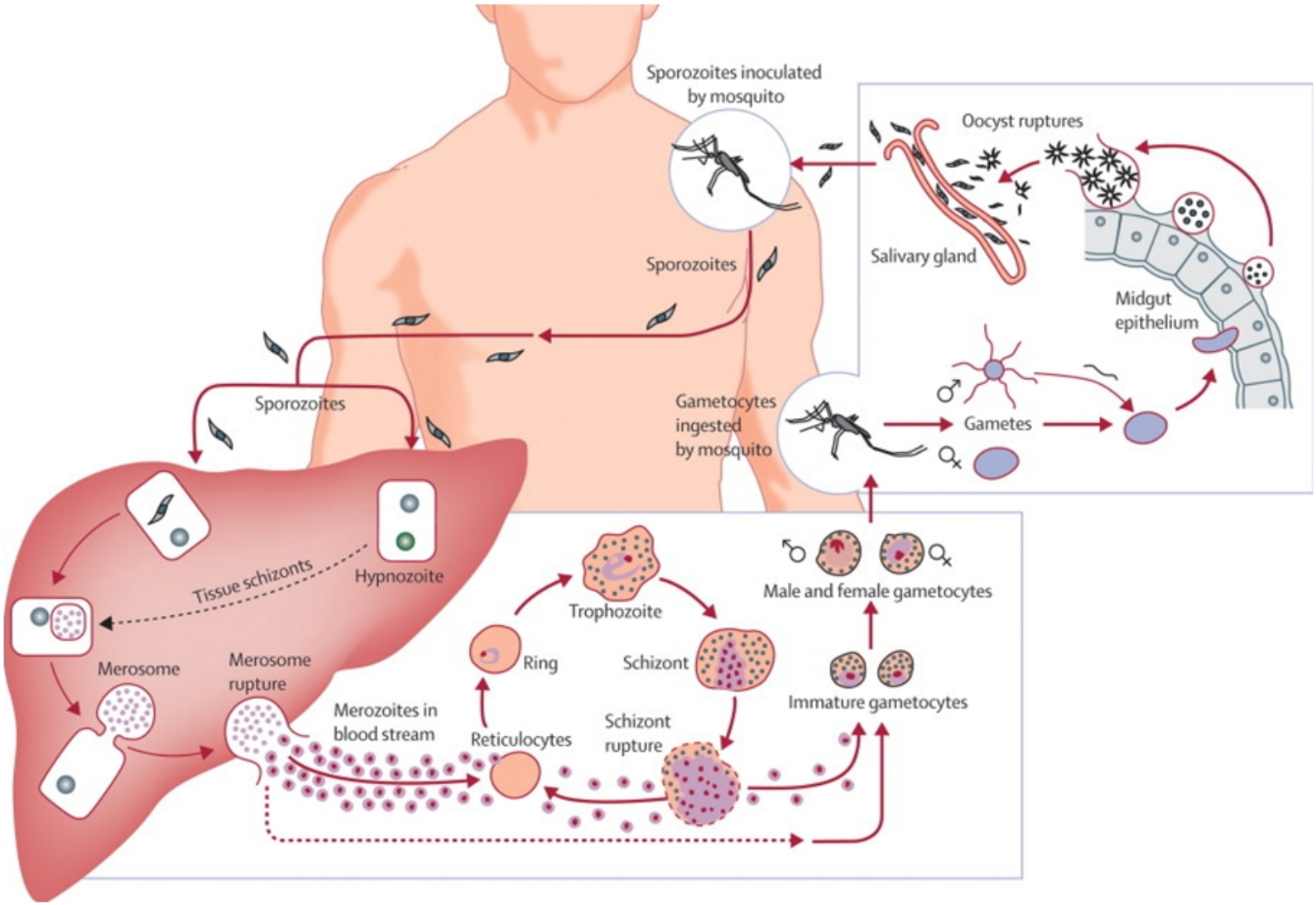


Image source: Muller et al., 2009

Field Data

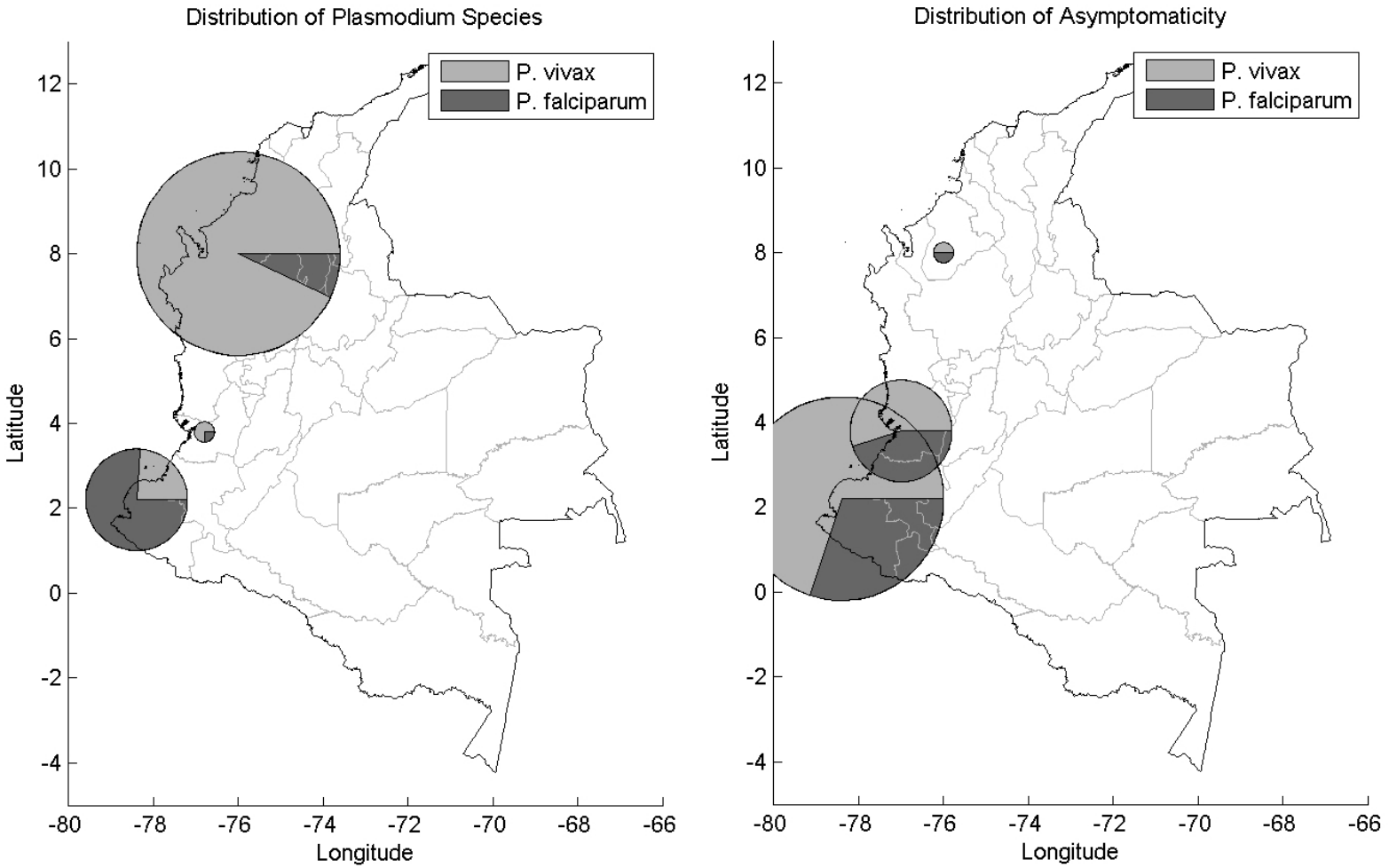


Image source (2012): `CLAIMProject(ICEMR)`

Field Data

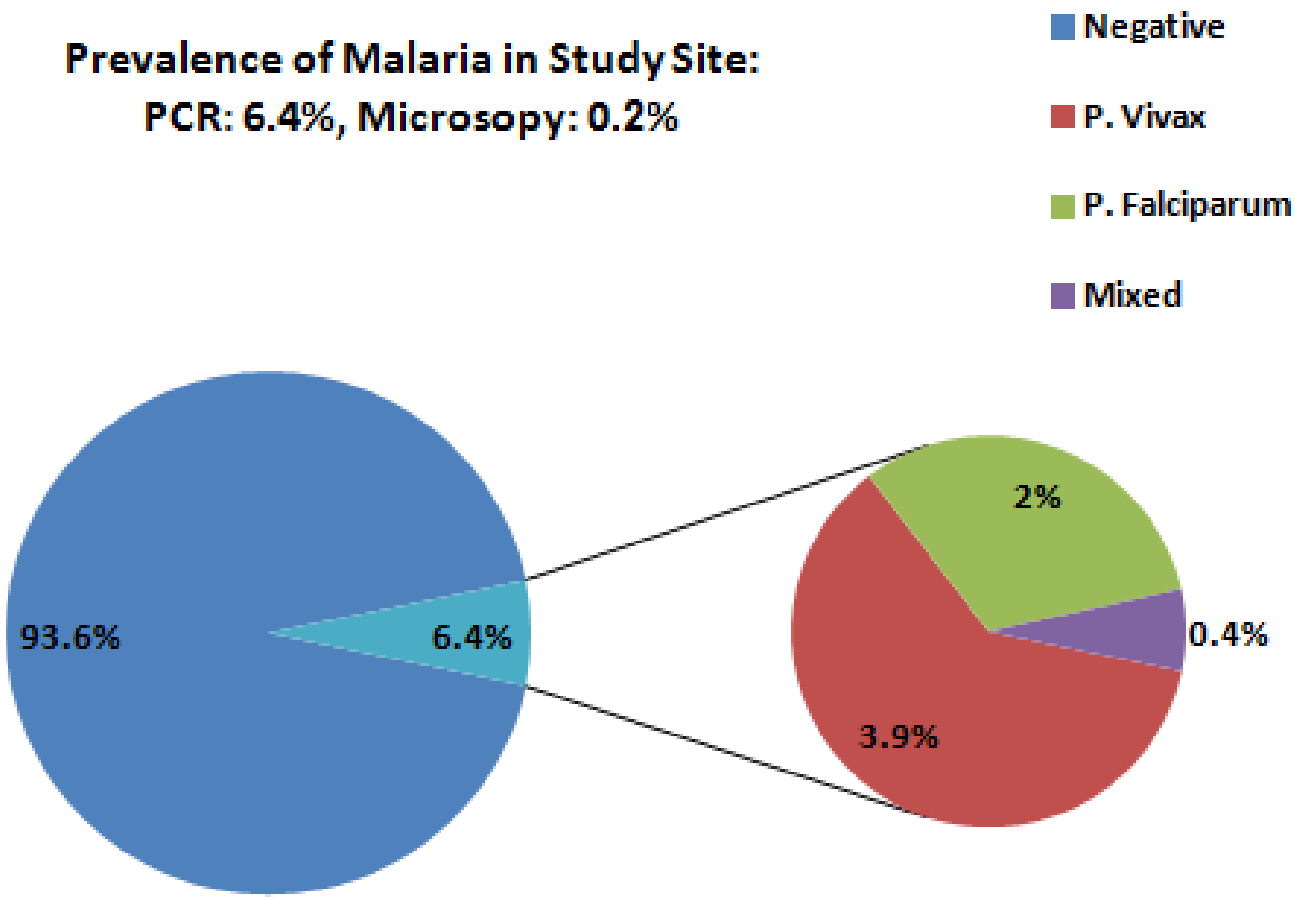


Image source (2012): `CLAIMProject(ICEMR)`

Origin of Malaria Mathematical Models

(a) **Ross model**

$$\frac{dI_h}{dt} = a\,b\,m\,I_m\,(1 - I_h) - r\,I_h$$

$$\frac{dI_m}{dt} = a\,c\,I_h\,(1 - I_m) - \mu_2\,I_m$$

$$\frac{m\,a^2\,b\,c}{r\,\mu_2}$$

a : Man biting rate [0.01-0.5 day^{-1}]
b : Proportion of bites that produce infection in human [0.2-0.5]

(b) **Macdonald model**

$$\frac{dI_h}{dt} = a\,b\,m\,I_m(1 - I_h) - r\,I_h$$

$$\frac{dE_m}{dt} = a\,c\,I_h(1 - E_m - I_m) - a\,c\,I_h(t - \tau_m)\left[1 - E_m(t - \tau_m) - I_m(t - \tau_m)\right] e^{-\mu_2 \tau_m} - \mu_2\,E_m$$

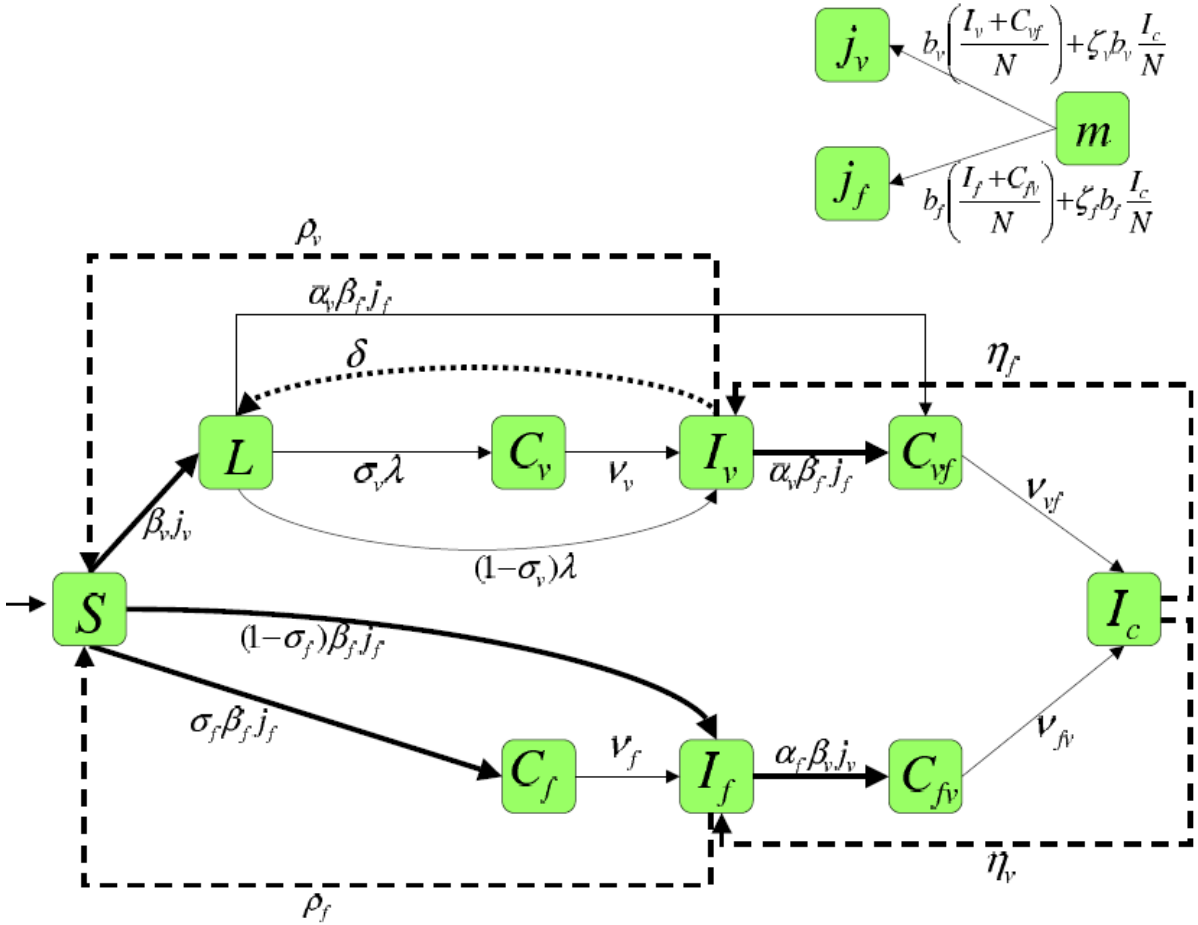
$$\frac{dI_m}{dt} = a\,c\,I_h(t - \tau_m)\left[1 - E_m(t - \tau_m) - I_m(t - \tau_m)\right] e^{-\mu_2 \tau_m} - \mu_2\,I_m$$

$$\frac{m\,a^2\,b\,c}{r\,\mu_2} e^{-\mu_2 \tau_m}$$

c : Proportion of bites by which one susceptible mosquito becomes infected [0.5]
m : Ratio of number of female mosquitoes to that of humans [0.5-40]
r : Average recovery rate of human [0.005-0.05 day^{-1}]

Source: Mandal et al. Malaria Journal 2011, 10:202

Example of a Current Mathematical Model of Malaria



Source: Prosper, 2011

Key Aspects of Malaria Cannot Be Studied with Prevalent Paradigm

1. Individuals living in malaria endemic areas can harbor chronic infections comprised of several distinct haploid parasite genomes; the number of distinct genomes per infected human is termed the **Multiplicity of Infection** (MOI). The MOI is a key component in the determination of the dispersion of specific genotypes in various landscapes. The MOI factor also impacts the development of immunity to malaria, and it has been recognized as an important parameter for the monitoring and evaluation of malaria control interventions.

Key Aspects of Malaria Cannot Be Studied with Prevalent Paradigm

2 *Antigenic diversity*, defined as antigenic differences between parasites in a population, and **antigenic variation**, defined as the ability of a parasite to change antigens presented to the immune system during an infection, are central to the parasites ability to 1) infect previously exposed hosts, and 2) maintain a long-term infection in the face of the host immune response. Immune evasion facilitated by this parasite variability is a critical unaccounted parameter in the dynamics of parasite growth, and therefore, transmission.

Key Aspects of Malaria Cannot Be Studied with Prevalent Paradigm

3 **Asymptomatic blood-stage malaria infections** are even more common than symptomatic infections (estimated to be ten-fold in comparison), and these infections provide a major parasite reservoir for the continuous and persistent transmission of the parasite, with the resulting continued cyclical propagation of malarial disease, morbidity and mortality. Asymptomatic infected individuals harbor parasites in their blood, including the transmissible gametocytes.

A Shift in Paradigm

Inspired by : *Models for Predator-Prey Systems at Multiple Scales*, by **R. S. Cantrell** and **C. Cosner**. SIAM Review, Vol. 38, No. 2 (Jun., 1996), pp. 256-286Published by: Society for Industrial and Applied Mathematics. Stable URL: `http://www.jstor.org/stable/2132880`

A Shift in Paradigm

What is important is NOT to eliminate mosquitoes. What is important is to eliminate *Plasmodium*. Consider the following populations:

- Human: A set $H_i = \{1, 2, ..., I\}$.
- Mosquito: A set $M_j = \{1, 2, ..., J\}$.
- *Plasmodium*: A set of classes $P = \{p_{nkl}\}$ representing *Plasmodium* population density in organism n of different genotypes k and different life stages l.

A Shift in Paradigm

$$\dot{p}_{ik1} = \sum_{n=1}^{J} \lambda_{ji} h(d_{ij}) p_{nk1} - \tau_2 p_{ik1} - \tau_3 p_{ik1} - \omega_1 \frac{p_{ik1} e_i}{1 + \gamma_1 p_{ik1}}$$

$$\dot{p}_{ik2} = \tau_2 p_{ik1} + \phi_2 p_{ik2} \left(1 - \frac{p_{ik2} + p_{ik3}}{C_L}\right) - \tau_4 p_{ik2} - \omega_2 \frac{p_{ik2} e_i}{1 + \gamma_2 p_{ik2}}$$

$$\dot{p}_{ik3} = \tau_3 p_{ik1} + \phi_3 p_{ik3} \left(1 - \frac{p_{ik2} + p_{ik3}}{C_L}\right) - \zeta_4 p_{ik3} - \omega_3 \frac{p_{ik3} e_i}{1 + \gamma_3 p_{ik3}}$$

$$\dot{p}_{ik4} = \tau_4 p_{ik2} + \zeta_4 p_{ik3} + \phi_5 p_{ik5} \left(1 - \frac{p_{ik4}}{C_M}\right) - \tau_5 p_{ik4} - \tau_6 p_{ik4} - \omega_4 \frac{p_{ik4} e_i}{1 + \gamma_4 p_{ik4}}$$

$$\dot{p}_{ik5} = \tau_5 p_{ik4} + \phi_5 p_{ik5} \left(1 - \frac{p_{ik5}}{C_{RBC}}\right) + \rho \left(\sum_{s=1, s\neq j}^{K} p_{is5} - p_{ik5}\right) - \omega_5 \frac{p_{ik5} e_i}{1 + \gamma_5 p_{ik5}}$$

$$\dot{f}_{ik} = \frac{1}{2} \tau_6 p_{ik4} \left(1 - \frac{f_{ik} + m_{ik}}{C_G}\right) - \sum_{n=1}^{J} \lambda_{ij} h(d_{nj}) f_{nk} - \omega_f \frac{p_{ikf} e_i}{1 + \gamma_f p_{ikf}}$$

$$\dot{m}_{ik} = \frac{1}{2} \tau_6 p_{ik4} \left(1 - \frac{f_{ik} + m_{ik}}{C_G}\right) - \sum_{n=1}^{J} \lambda_{ij} h(d_{nj}) m_{nk} - \omega_m \frac{p_{ikm} e_i}{1 + \gamma_m p_{ikm}}$$

$$\dot{e}_i = \sum_{l=1}^{1..5, f, m} \kappa_l \frac{p_{ikl} e_i}{1 + \gamma_l p_{ikl}} - \epsilon e_i$$

$$\dot{p}_{jk1} = \sum_{q=1}^{I} \lambda_{ij} h(d_{ij}) \left(f_{qk} + m_{qk}\right) - \tau_1 p_{jk1} - \delta_6 \left(f_{qk} + m_{qk}\right)$$

Quantifying movement

- A *gravity model* quantifies the amount of movement between two communities k and j, and hence the transient likelihood of transmission exerted by hosts in location j on hosts in location k, is proportional to $N_j^{\tau_1} N_k^{\tau_2} / d^{\rho}$, where N_j is population in center j, and d_{jk} is the distance between centers j and k; τ_1, τ_2, and ρ are positive constants. A low-dimensional manifold can be recosntructed with gravity model information.
- A *niche model*, i.e. a species distribution model, can be constructed to determine likelihood of presence of vectors. Mosquito dispersal can be modeled using reaction-diffusion equations. Ecological features can be used in a pattern classification scenario to determine geographic areas that have similar diffusivity. These areas can be identified with diffusion isoclines. The dispersal of mosquitoes between two points follows geodesics in this diffusion space; this informs ecological corridors.

Implications

Implications of this approach:

- The functional space for population dynamics is **NOT** geographic.
- The discrete diffusion model can approximate the continuous diffusion model in this functional space under proper (realistic) assumptions, i.e. each island belongs to a low-dimensional manifold in which diffusion can be studied via the Laplace-Beltrami operator.
- This approach allows us to account for the large variability in *Plasmodium* genotypes. It allows us to incorporate individual immune response, and evaluate the global population of *Plasmodium*.
- This model is significantly easier to calibrate as compared to SEIR models. The parameters needed can be easily estimated from (non-trivial) experimental measures.

Results

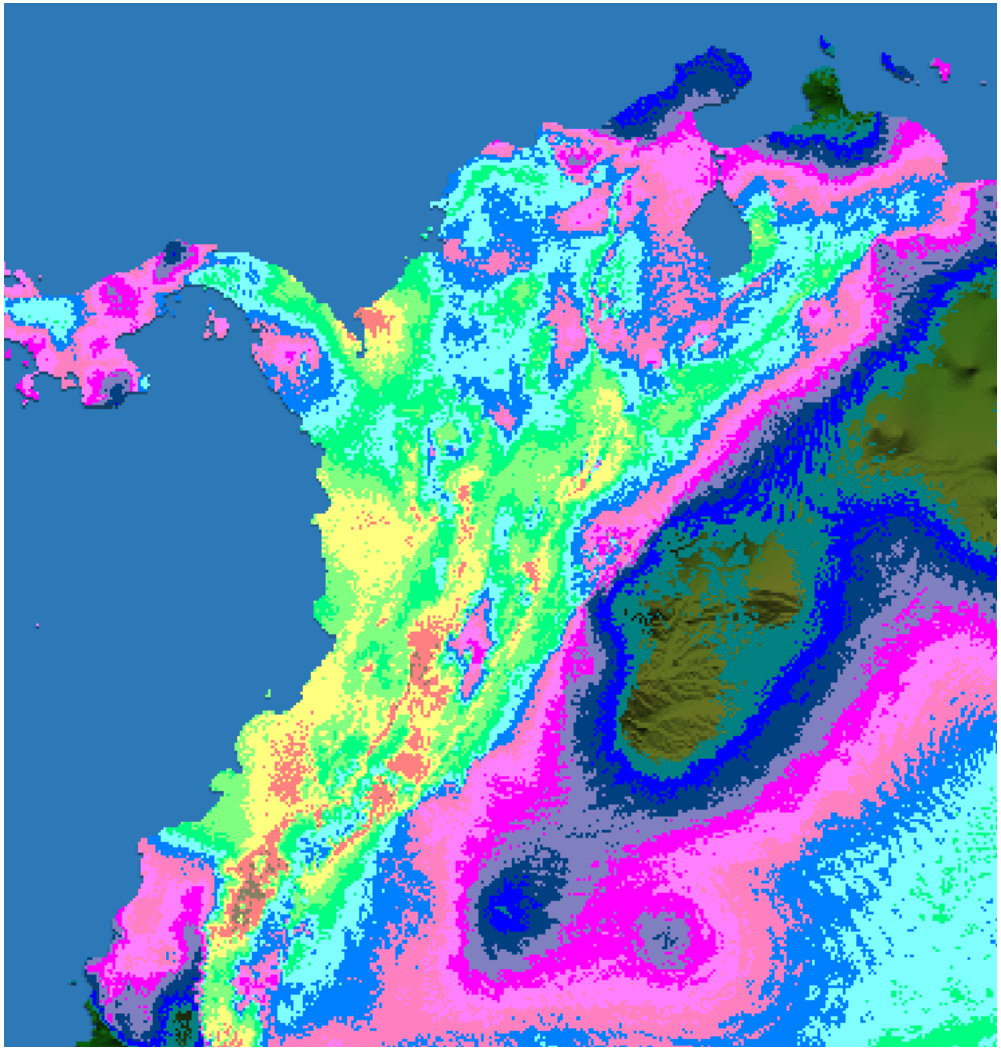


Image source (2012): `CLAIMProject(ICEMR)`

Results

OBSERVATION: Dockery, Hutson, Mischaikow, Pernarowski (1998) proved that with haploid genetics, and a small rate of mutation, the only nontrivial equilibrium is a population dominated by the slowest diffusing phenotype. This might explain observed asymptomaticity (*current direction of research*).

Thanks for your attention,

and Happy Birthday Chris!

JBG