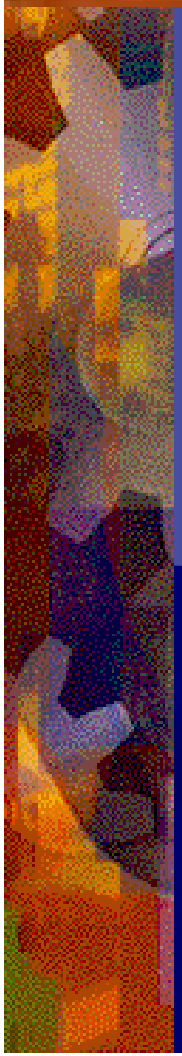

Computational model of NOS/TGF-Beta1/Plasmodia System in humans and mosquitoes

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Malaria

- One of the world's top 10 deadliest diseases
- Affects 350-500 million people every year
- Kills 2 million people every year, especially those in third-world countries
- A protozoan from the genus *Plasmodium*

Transmission of Parasite

- The plasmodia infects a female *Anopheles* mosquito.
- The parasite invades and multiplies in the mosquito's midgut, soon causing spillovers into the mosquito's open circulatory system. The parasite then easily spreads throughout the mosquito's body (including its salivary gland).
- As the mosquito feeds on human blood, it injects its own parasite-containing saliva into the human bloodstream.
- The mosquito also ingests blood components including immune-modulating factors from the human that surprisingly affect mosquito biology, including cytokine transforming growth Factor beta-1 (TGF-Beta1).

Purpose

- Create a model that accurately simulates the dynamics of the NOS/TGF-Beta1/Plasmodia system in a mosquito-mammal environment.
- Understand ideas that may lead to improved methods of malaria control and therapy, including modulation of TGF-Beta1.

Key Chemicals

- Nitric Oxide (NO) serves primarily two purposes in this model:
  - Kills the malaria parasite in mosquitoes and in humans.
  - Activates TGF-Beta1 in mosquitoes and in humans.
- Transforming Growth Factor-Beta1 (TGF-B1) is a central immune-modulating cytokine that is elevated in humans with malaria. It, however, plays different roles in mosquitoes and in humans:
  - Induces the production of NO in mosquitoes
  - Inhibits the production of NO in humans

Important Variables

- Mosquito
  - P_s : amount of parasites
  - N_s: amount of NO
  - T_s: amount of active TGF-Beta1
  - L_s: amount of latent TGF-Beta1
  - Z_s: amount of cysts
  - X_s: amount of mediator X, which inhibits NO
- Human
  - P_m: amount of parasites
  - N_m: amount of NO
  - T_m: amount of active TGF-Beta1

P_s

- Parasites form into cysts at a certain rate (-)
- NO kills P_s (-)

$$\frac{dP_s}{dt} = -\mu_c P_s - k_{nps} P_s N_s$$

T_s

- N_s activates L_s to T_s (+)
- Natural decay rate (-)

$$\frac{dT_s}{dt} = k_{tts} L_s N_s - \mu_{ts} (T_s - T_{T\_\min\_s})$$

N_s

- Natural decay rate (-)
- Induced by P_s (+)
- Induced by T_s (+)
- Inhibited by chemical mediator, X (-)

$$\frac{dN_s}{dt} = -\mu_{ns}(N_s - N_{N\_\min\_s}) + \frac{k_{tp}(T_s + P_s)}{1 + T_s + P_s + k_x X_s}$$

L_s

- Natural decay rate (-)
- L_s is activated to T_s (-)

$$\frac{dL_s}{dt} = (L_{s0} - L_s)\mu_{ls} - k_{tts} L_s N_s$$

Z_s

- Parasites form into cysts at a certain rate (+)

$$\frac{dZ_s}{dt} = \mu_c P_s$$

X_s

- Inhibits itself (-)
- Induced by N_s (+)

$$\frac{dX_s}{dt} = (-X_s + N_s)/\tau$$

P_m

- Growth rate (+)
- N_m kills P_m (-)

$$\frac{dP_m}{dt} = k_{gpm} P_m \left(1 - \frac{P_m}{P_{mm}}\right) - \frac{\lambda_m k_{npm} P_m N_m}{1 + \alpha_{npm} N_m}$$

T_m

- Natural decay rate (-)
- Induced by N_m (+)

$$\frac{dT_m}{dt} = -\mu_{tm}(T_m - T_{T\_\min\_m}) + \frac{k_{nsm}N_m}{1+\alpha_{nsm}N_m}$$

N_m

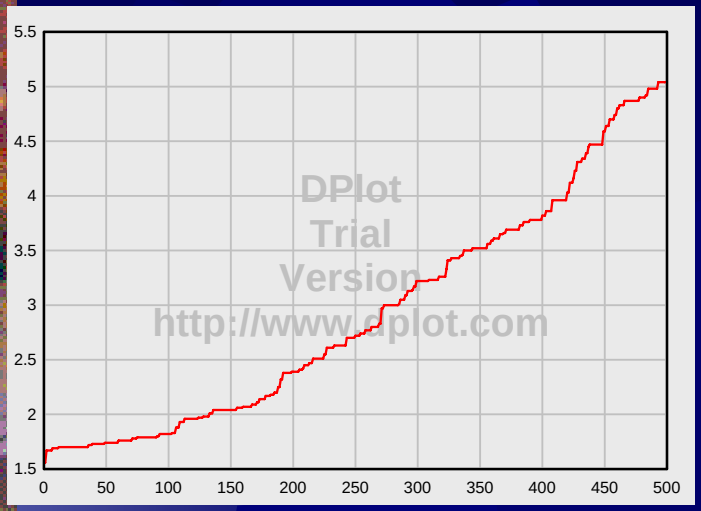
- Induced by P_m (+)
- Inhibited by T_m (-)
- Natural decay rate (-)

$$\frac{dN_m}{dt} = \frac{k_{pnm} P_m}{1 + k_{tnm} T_m} - \mu_{nm} (N_m - N_{N\_\min\_m})$$

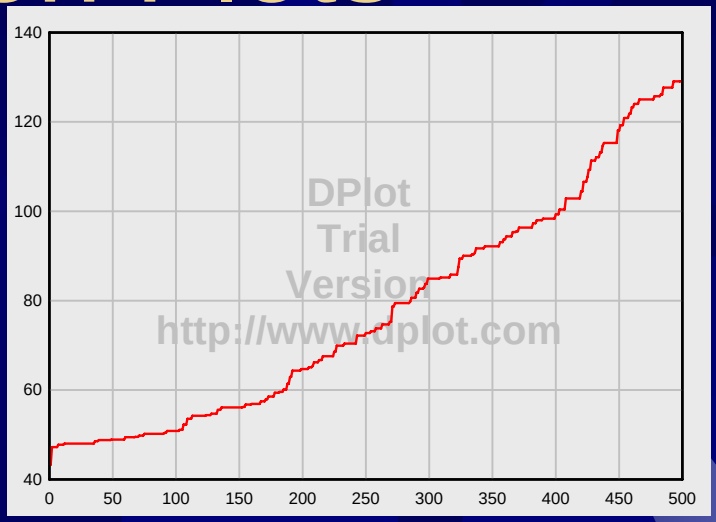
Java Simulation

- Individual dynamics depend on previous equations
- Simulation specifics
  - 100 humans, 200 mosquitoes
  - 500 time steps
- Runge-Kutta method
- Simulation is a stochastic process
  - Depends on the random number generator and a given probability, which decides whether the mosquitoes and humans interact.

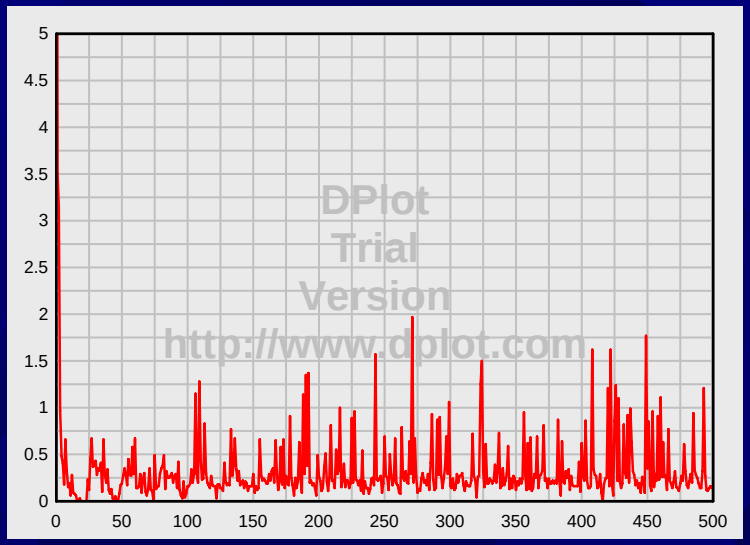
Simulation Plots



Z_s

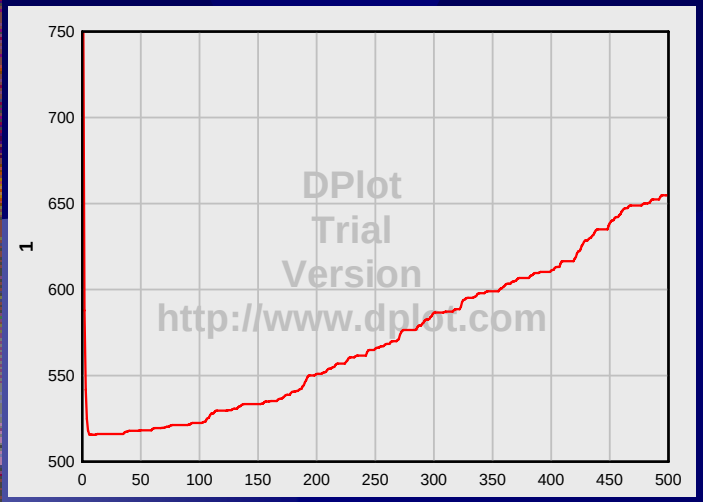


P_m

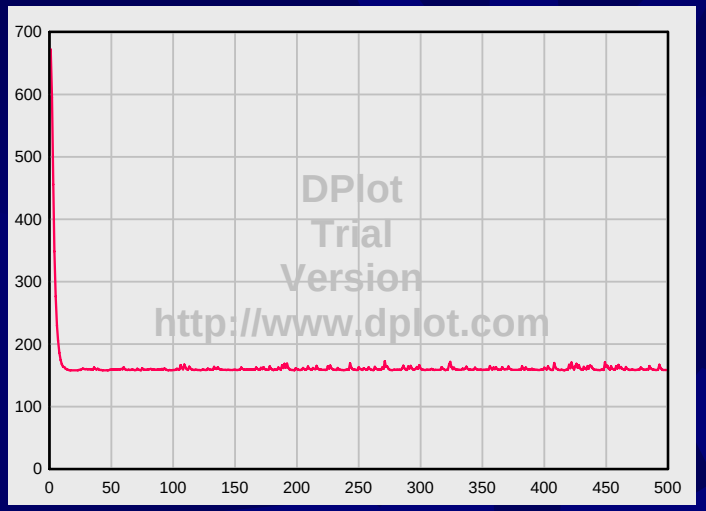


T_s

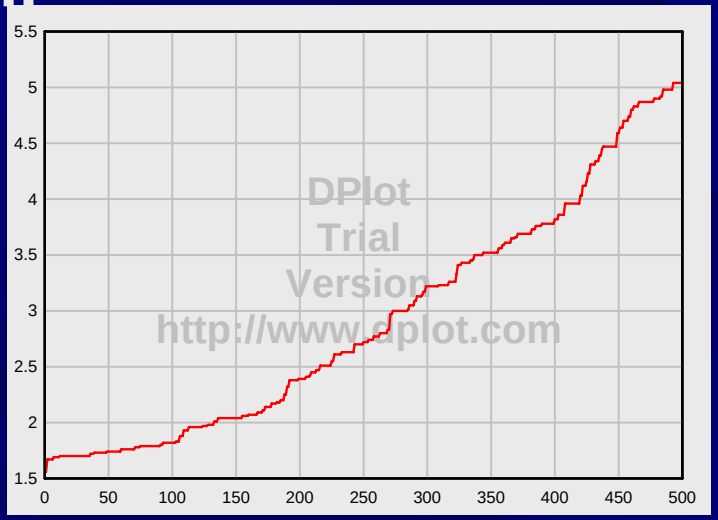
Simulation Plots Continued



T_m

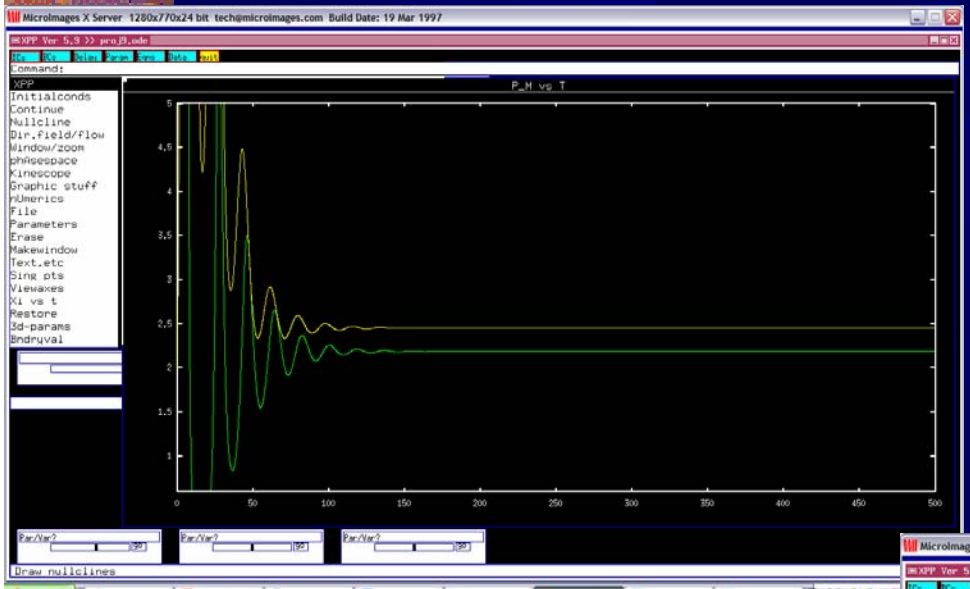


N_s



N_m

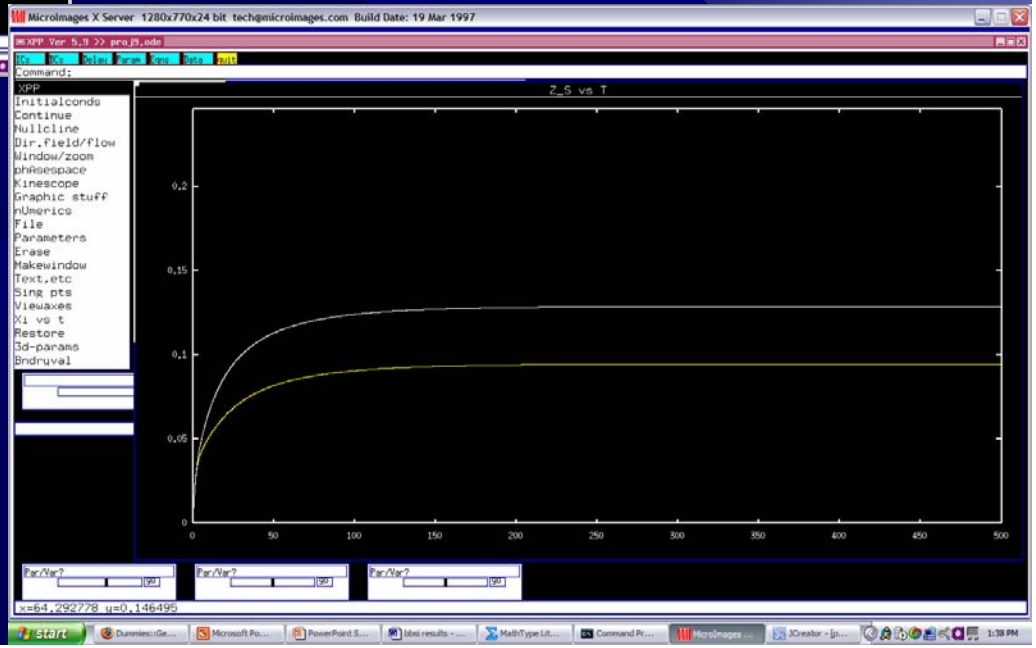
Effect of raising TGF in mosquitoes and mammals



Mammal

Yellow: Mu_tm=0.1

Green: Mu_tm=0.6

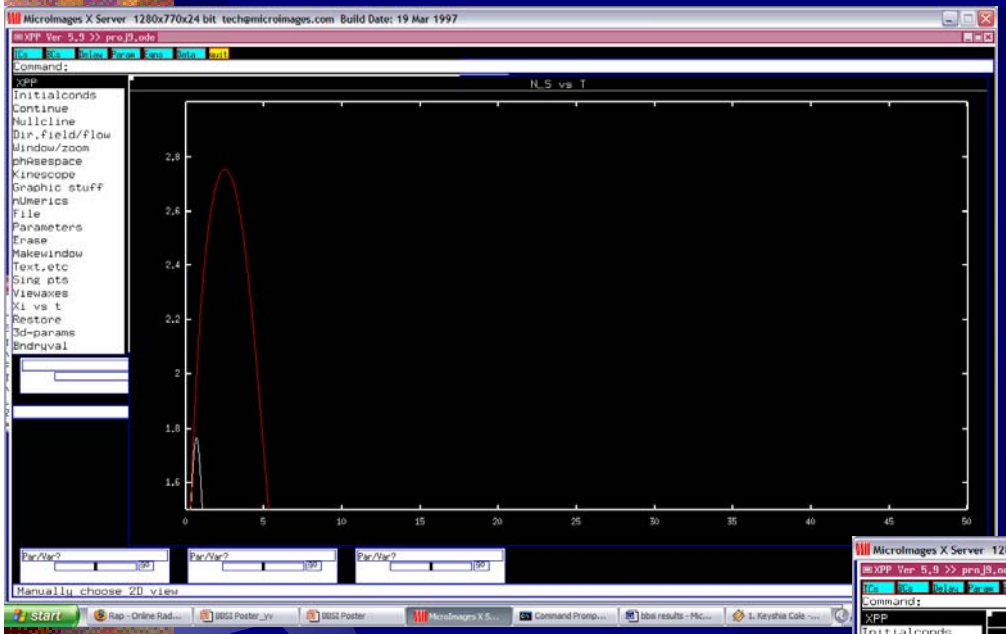


Mosquito:

Yellow: T_s=10, L_s=100

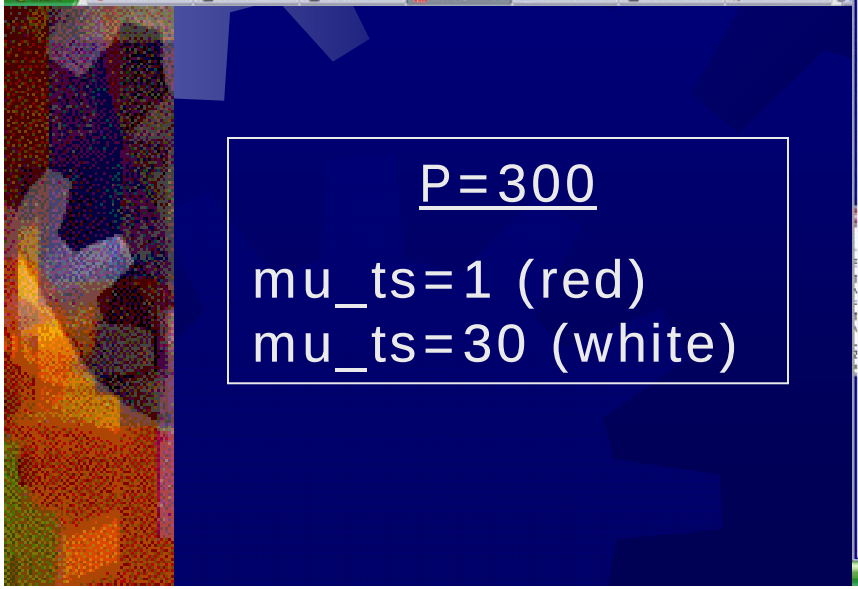
White: T_s=1, L_s=100

Saturation of Parasite Effects on NOS induction by TGF



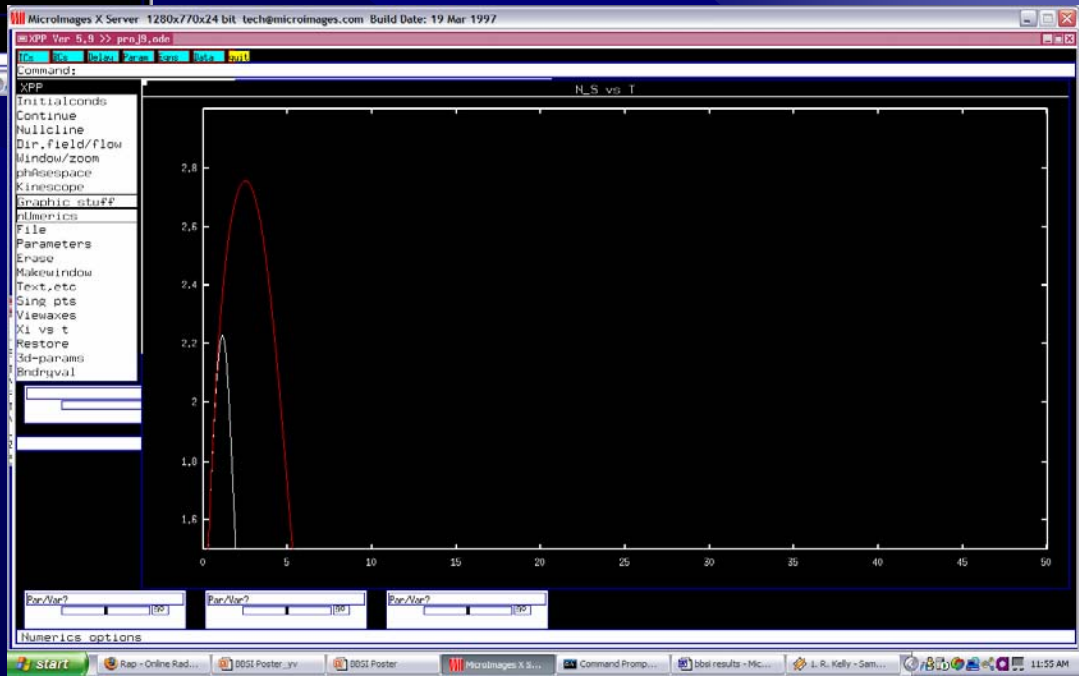
P=1

mu_ts=1 (red)
mu_ts=30 (white)



P=300

mu_ts=1 (red)
mu_ts=30 (white)



Conclusion

- We have successfully modeled the system with two sets of differential equations.
- A Java simulation has been written to model the individual dynamics as well as the population dynamics.

Limitations

- However, at this point in our research, the model is not complete: the specific parameters for the model have not yet been pinned down.
- As a result, the numbers produced in the simulation have little significance, and we are only able to produce qualitative results.

Future Research

- Once we are finally confident in our parameters, however, we will be able to easily produce reliable quantitative results (plug and chug into Java simulation).

Acknowledgements

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5) Dr. Shirley Luckhart, UC-Davis

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