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

Neil Parikh[1], Dr. Bard Ermentrout[2], Ian Price[2], Dr. Shirley Luckhart[3], Dr. Yoram Vodovotz[4,5]

[1]*Bioengineering & Bioinformatics Summer Institute, Dept. of Computational Biology, University of Pittsburgh, 15260*

[2]*Department of Mathematics, University of Pittsburgh, 15260*

[3]*Department of Medical Microbiology and Immunology, University of California-Davis, 95616*

[4]*Department of Surgery and* [5]*Center for Inflammation and Regenerative Modeling, University of Pittsburgh, 15213*

Background/Intro.

As one of the world's top 10 deadliest diseases, malaria affects 350-500 million people every year and kills approximately 2 million people every year especially in third-world countries.

The malaria parasite, a protozoan from the genus *Plasmodium*, infects a female *Anopheles* mosquito. Once the mosquito is infected, 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. It is through this mosquito transmission that malaria is quickly spread from human to human. As the CDC states, in malaria, the mosquito is merely a "vector"; while it transmits the disease, it is not affected by the parasite. It is now recognized that in this process, the mosquito also ingests blood components including immune-modulating factors from the human that surprisingly affect mosquito biology. One of these factors is the cytokine transforming growth Factor beta-1 (TGF-Beta1), which is a central immune-modulating cytokine that is elevated in humans with malaria.

Although humans are usually concerned with the growth and movement of malaria between humans and mosquitoes, there are a few additional factors to consider in our system: nitric oxide (NO) and TGFbeta1. The critical functions of NO in this system are to kill the malaria parasite and to induce production of TGF-Beta1. The TGF-Beta1 protein, however, plays different roles in the mosquitoes and in the humans. In mosquitoes, TGF-Beta1 generally induces the production of NO, while generally inhibiting the production of NO in humans. This fact is highly significant because while NO and TGF-Beta1 grow in a positive feedback loop in the mosquito, in humans the growth of NO is limited by TGF-Beta1.

In an effort to understand this complex set of interactions, this project will attempt to model the transmittance of malaria and TGF-Beta1 between mosquitoes and humans, as well as the role of NO in this process. If we are able to successfully model this system of differential equations and choose accurate constants, we will gain insights that may allow for improved methods of malaria control and therapy, including modulation of TGFbeta1.

Method

This system had to be split into two parts: the mosquito subsystem and the mammalian subsystem. Then, we conducted a population experiment using a model simulation written in Java.

Java Simulation

- Simulation had 200 mosquitoes and 100 mammals
- Dynamics of each object depend on these equations
- Simulation is a stochastic process; depends on random number generator, which decides whether the mosquitoes and mammals interact.
- Individual objects (mosquitoes/mammals) are updated once every time step (500 time steps total).

Macro Model

S = susceptible humans

I = infected humans

J = I + TGF blockers

M = uninfected mosquito

P = Infected mosquito

T = P + TGF blocker

$$S' = (1-S)\mu_s - \alpha TS - PS$$
$$I' = \alpha TS + PS - \mu_s I - rI$$
$$J' = rI - \mu_s J$$
$$M' = (1-M)\mu_i - IM - \beta JM$$
$$P' = IM - \mu_i P$$
$$T' = \beta JM - \mu_i T$$

Micro Model

P_s =Parasites in mosquito

T_s =Active TGF in mosquito

N_s =NOS in mosquito

L_s =Latent TGF in mosquito

Z_s =Cysts in mosquito

X_s =Parasites in mosquito

P_m =Parasites in mammal

T_m =TGF in mammal

N_m =NOS in mammal

$$\frac{dP_s}{dt} = -\mu_c P_s - k_{nps} P_s N_s$$
$$\frac{dT_s}{dt} = k_{tts} L_s N_s - \mu_{ts}(T_s - T_{T\_\min\_s})$$
$$\frac{dN_s}{dt} = -\mu_{ns}(N_s - N_{N\_\min\_s}) + \frac{k_{tp}(T_s + P_s)}{1 + T_s + P_s + k_x X_s}$$
$$\frac{dL_s}{dt} = (L_{s0} - L_s)\mu_{ls} - k_{tts} L_s N_s$$
$$\frac{dZ_s}{dt} = \mu_c P_s$$
$$\frac{dX_s}{dt} = (-X_s + N_s)/\tau$$

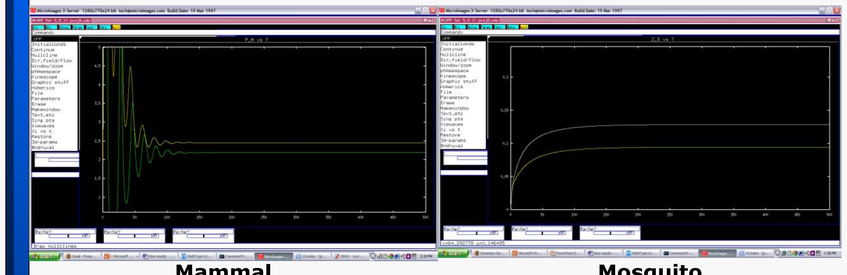
Micro Model (Mosquito Subsystem)

$$\frac{dP_m}{dt} = k_{gpm} P_m \left(1 - \frac{P_m}{P_{mm}}\right) - \frac{\lambda_m k_{npm} P_m N_m}{1 + \alpha_{npm} N_m}$$
$$\frac{dT_m}{dt} = -\mu_{tm}(T_m - T_{T\_\min\_m}) + \frac{k_{nsm} N_m}{1 + \alpha_{nsm} N_m}$$
$$\frac{dN_m}{dt} = \frac{k_{pnm} P_m}{1 + k_{tnm} T_m} - \mu_{nm}(N_m - N_{N\_\min\_m})$$

Micro Model (Mammal Subsystem)

Results

Effect of raising TGF in mosquitoes and mammals



Mammal

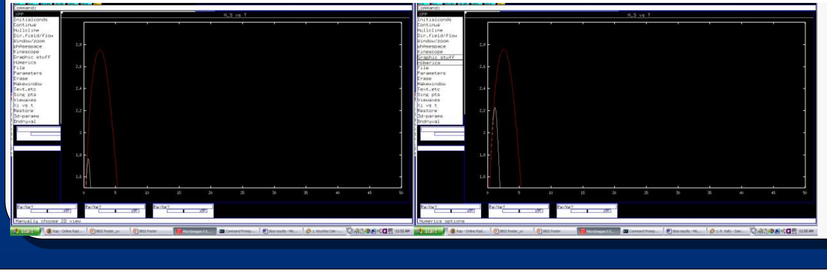
Mu_tm=0.1 (yellow; Mu_tm=0.6 (green)

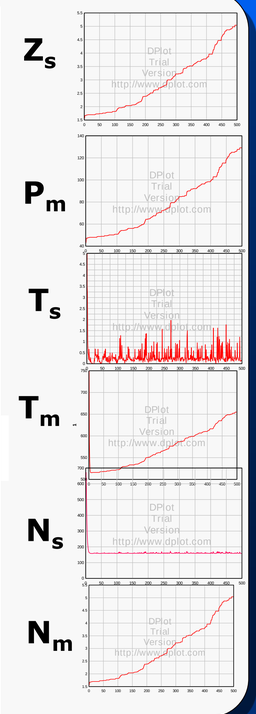
Mosquito

T_s=10, L_s=100 (yellow), T_s=1, L_s=100 (white)

Saturation of Parasite Effects on NOS induction by TGF

Left: P=1, mu_ts=1 (red), mu_ts=30 (white); Right: P=300, mu_ts=1 (red), mu_ts=30 (white)





Conclusion

At this point in the study, we have successfully modeled the system with two sets of differential equations (six for mosquitoes and three for mammals). In addition, a Java simulation has been written to accurately model the individual dynamics as well as the population dynamics. 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. Once we are finally confident in our parameters, however, we will be able to produce reliable quantitative results.

Acknowledgements

The national BBSI program (http://bbsi.eeicom.com) is a joint initiative of the NIH-NIBIB and NSF-EEC, and the BBSI @ Pitt is supported by the National Science Foundation under Grant EEC-0234002.

1) Dr. Bard Ermentrout
2) University of Pittsburgh
3) Ian Price, Graduate Student at U. of Pitt.
4) Dr. Yoram Vodovotz, U. of Pitt.
5) Dr. Shirley Luckhart, UC-Davis

References

Akman-Anderson, L., Vodovotz, Y., Zamora, R., and Luckhart, S. "Bloodfeeding as an Interface of Mammalian and Arthropod Immunity." Unpublished work.

"CDC - Malaria." CDC. 15 June 2007 <http://www.cdc.gov/malaria/>.

Paul REL, Bonnet S, Boudin C, Tchuinkam T, Robert V. Aggregation in malaria parasites places limits on mosquito infection rates. *Infection, Genetics and Evolution*. ;In Press, Corrected Proof.

Reynolds, A., Rubin, J., Clermont, G., Day, J., Vodovotz, Y., and Ermentrout, G. "A reduced mathematical model of the acute inflammatory response: I. Derivation of model and analysis of anti-inflammation." *Journal of Theoretical Biology*. 242 (2006): 220-236.