Modeling Mammal-Mosquito Parasite system incorporating TGF-Beta1 Protein and Nitric Oxide

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Introduction

As one of the world's Top 10 Deadliest Diseases, Malaria affects 350-500 million people every year, kills approximately 2 million people every year, and especially in third-world countries, has progressed to become a very serious problem.

The trouble begins when the Malaria parasite, a Protozoan from the family Plasmodium, infects one of two hosts: human beings or female Anopheles mosquitoes. Once the female Anopheles mosquito is infected, the malaria parasite will invade and multiply in the mosquito's liver cells and red blood cells [1]. Due to a large level of Nitric Oxide, the mosquito's vascular permeability enlarges significantly, causing spillovers into the mosquito bloodstream [4]. Once the malaria parasite is in the bloodstream, the parasite easily spreads throughout the mosquito's body (including its salivary gland). Once the mosquito feeds on its human prey, while taking its blood meal the mosquito 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 [2].

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 and TGF-Beta1. In addition to increasing vascular permeability in the mosquito, the critical function of Nitric Oxide in this system is simply to kill the malaria parasite and to induce production of TGF-Beta1 [4]. The TGF-Beta1 (Transforming Growth Factor beta-1) protein, however, plays different roles in the mosquitoes and in the humans. In mosquitoes, TGF-Beta1 induces the production of Nitric Oxide. However, in humans, TGF-Beta1 actually inhibits the production of Nitric Oxide [1]. This fact is highly significant because while in the mosquito, Nitric Oxide and TGF-Beta1 grow in a positive feedback loop, in humans, the growth of Nitric Oxide is limited by TGF-Beta1, so the Nitric Oxide may therefore, not be able to kill as many malaria parasites.

In an effort to understand this convoluted malaria life cycle, this project will attempt to model the transmittance of malaria, TGF-Beta1, and Nitric Oxide between mosquitoes and humans. If we are able to successfully model this system of differential equations and choose accurate constants, we will be close to understanding the correct range of Nitric Oxide and TGF-Beta1 levels needed (in the humans and mosquitoes) to suppress the malaria situation at an optimum level.

Methods

Taking into account this system's considerable breadth and complicity, this system had to be split into two parts: the mosquito subsystem (denoted s for "skeeter" and the mammalian subsystem (denoted m for "mammal").

Mosquito Subsystem

In the mosquito subsystem, our model holds five main differential equations that summarize the change in five main variables: the number of parasites in the mosquito (P_s), the amount of active TGF-Beta1 protein in the mosquito (T_s), the amount of Nitric Oxide in the mosquito (N_s), the amount of latent TGF-Beta1 protein in the mosquito (L_s), and finally, the number of cists in the mosquito (Z_s). The number of parasites in the mosquito bloodstream depends positively on the parasite's growth rate (it grows logistically), and it depends negatively on the amount of Nitric Oxide (which of course kills the parasite) and the rate that the parasites escape into cists. The amount of active TGF-Beta1 protein in the mosquito bloodstream depends positively on the amount of Nitric Oxide, the rate at which latent TGF-Beta1 is converted into active TGF-Beta1, and the amount TGF-Beta1 protein received from the mammal during the bloodmeal; TGF-Beta1 only depends negatively on its own decay rate. The amount of Nitric Oxide in the mosquito bloodstream depends positively on the number of parasites and the amount of active TGF-Beta1, but negatively on its own decay rate and on the rate at which it kills parasites (because of course when killing a parasite, the Nitric Oxide molecule sacrifices itself). The amount of latent TGF-Beta1 protein in the mosquito bloodstream depends positively on the TGF-Beta1 obtained from the mammal during bloodfeeding, and depends negatively on the rate at which latent TGF-Beta1 is converted into active TGF-Beta1. The number of cists in the mosquito bloodstream depends positively on the number of parasites in the bloodstream, and negatively on its own decay rate and on itself (the formation of too many cists will lead to several cists bursting). All five of these differential equations may be viewed below in Figure 1.

Mammalian Subsystem

Compared to the mosquito subsystem, the mammalian subsystem is relatively less complicated. Instead of five differential equations, the mammalian subsystem holds three differential equations describing the number of parasites (P_m), the amount of active TGF-Beta1 (T_m), and the amount of Nitric Oxide (N_m) in the mammalian bloodstream. The amount of latent TGF-Beta1 is not included in the mammalian subsystem because in mammals, it is assumed that there is an infinite supply of latent TGF-Beta1. The number of cists in the mammalian subsystem were also omitted because cists, of course, grow in mosquitoes, not in mammals.

The number of malaria parasites in the mammalian bloodstream depends positively on the parasite's growth rate (grows logistically) and the number of cists in the malaria's bloodstream, but also depends negatively on the amount of Nitric Oxide. The amount of active TGF-Beta1 depends positively on the conversion rate (from latent TGF-Beta1 to active TGF-Beta1) and the amount of Nitric Oxide, but depends negatively on its own decay rate. Although the differential equation of TGF-Beta1 in the mosquito depends on the TGF-Beta1 obtained from the human during bloodfeeding, the differential equation for TGF-Beta1 in the mammal does not depend on the TGF-Beta1 obtained from the mosquito during bloodfeeding. This is strictly because of the size difference between the mammal and the mosquito – any additional TGF-Beta1 in the mammal will not make more than an infinitesimal change, whereas additional TGF-Beta1 in the mosquito might make a significant change. Finally, the amount of Nitric Oxide in the mammalian bloodstream depends positively on the number of parasites in the bloodstream, but depends negatively on its own decay rate, on the rate at which it kills

parasites (the more parasites Nitric Oxide kills, the more molecules of Nitric Oxide are sacrificed), and on the amount of active TGF-Beta1. Again, this is the main difference between the mosquito model and the mammalian model (that TGF-Beta1 induces Nitric Oxide in mosquitoes but inhibits production of Nitric Oxide in mammals), and the true inspiration for this project. These differential equations may be seen below in Figure 2.

Figure 1 (Mosquito)

$$\frac{dP_s}{dt} = k_{gps}P_s(1-\frac{P_s}{P_{ss}}) - \frac{\lambda_s k_{nps}P_s N_s}{1+\alpha_{nps}N_s} - \beta P_s$$

$$\frac{dT_m}{dt} = k_{tt*s}L_s N_s - \mu_{ts}T_s + rT_m$$

$$\frac{dN_s}{dt} = -\frac{k_{nps}P_s N_s}{1+\alpha_{nps}N_s} - \mu_{ns}N_s + k_{pn}P_s + \frac{k_{tns}T_s}{1+\alpha_{tns}T_s}$$

$$\frac{dL_s}{dt} = (L_{s0} - L_s)M_{ls} - k_{tt*s}L_s N_s$$

$$\frac{dZ_s}{dt} = \gamma_b P_s - qZ_s - \mu_z Z_s$$

For convenience in variable choice, this model takes close reference to a previous system modeled by Dr. Ermentrout regarding anti-inflammatory response [3].

Figure 2 (Mammal)

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

$$\frac{dT_m}{dt} = -\mu_{tm}T_m + \frac{k_{nsm}N_m}{1+\alpha_{nsm}N_m}$$

$$\frac{dN_m}{dt} = \frac{k_{pnm}P_m}{1+k_{pnm}T_m} - \mu_{nm}(N_m - N_{N\_\min}) - \frac{k_{npm}P_m N_m}{1+\alpha_{npm}N_m} - \frac{\gamma_{npm}N_m^2}{1+\varepsilon_{nm}N_m^2}$$

Summary

Now that the mosquito-mammal system has been modeled, only the constants are left to be filled in. After looking at the numerous experiments done by Dr. Vodovotz's

team, we will carefully select all the proper constants for our model. Finally, when running our simulation, we will need to take another factor into account: the timing of the bloodmeals. Considering that TGF-Beta1 is detected in the midgets for about 12 hours (the time when Nitric Oxide has the best chance to hit the parasite) and that parasites feed every 3 days, the simulation will last about approximately 24-48 hours. After countless simulations are run for a wide range of values, there will hopefully be ample data indicating the optimum levels of each factor of the simulation.

References

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3. 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.

4. Meeting with Dr. Vodovotz