Modeling Malaria Pathogenesis: The Double-Edged Sword of Nitric Oxide

Austerman, R.J.,[*†‡] M.R. Crusoe,[1] I. Malenica,[†‡] J.I. Lindsay,[1] P. Salmon,[‡] M. McCaughan,[*] T. Farahani,[*] Y. Kuang[‡] and J.D. Nagy[‡1]

[*]ASU School of Life Sciences. [†]Barrett Honors College at ASU. [‡]ASU School of Mathematical and Statistical Sciences. [1]SCC Department of Life Sciences.

Introduction

The precise cause of morbidity and mortality from malaria is variable and not completely understood. Clark *et al.* (2003, 2004) emphasize similarities between malaria pathogenesis and conditions leading to general inflammation. They note that *Plasmodium falciparum* infection correlates with increases in plasma concentration of pro-inflammatory cytokines. These cytokines up-regulate the enzyme inducible nitric oxide synthase (iNOS) which in turn leads to increased levels of nitric oxide. Nitric oxide acts as an anti-inflammatory agent, perhaps calming the pathogenic inflammation, but may also be directly cytotoxic to cells. Here we introduce a novel model of malaria pathogenesis based upon Clark's hypothesis. Our work extends the model presented by Iggidr *et al.* (2006). Similar to their model, ours tracks parasitized and non-parasitized erythrocytes and free merozoites while adding a feedback loop for the host's immune response and its interactions with iNOS.

Model

$$\begin{cases} \frac{dx}{dt} = \Lambda - \mu_x x - \beta m x - \frac{\alpha j^s}{\gamma^s + j^s} x \\ \frac{dy}{dt} = \beta m x - \mu_y y - \frac{\alpha j^s}{\gamma^s + j^s} y \\ \frac{dm}{dt} = r\mu_y y - \mu_m m - \beta m x \\ \frac{df}{dt} = a y(t-\tau) e^{-jk} - \mu_f f \\ \frac{dj}{dt} = bf - \mu_j j \end{cases}$$

Variable	Interpretation	Units
x	concentration of healthy red blood cells	cells/μL
y	concentration of infected red blood cells	cells/μL
m	concentration of free merozoites	cells/μL
f	concentration of TNF	pM
j	concentration of iNOS	pM

Table 1. Model parameters and default values.

Parameter	Interpretation	Value	Units
Λ	Rate of erythropoesis	26,560	cells/(μL*hr)
μ_x	Removal rate of RBCs via spleen	0.0083	1/hr
β	Contact (infection) rate between merozoites and healthy RBCs	8×10^{-6}	μL/(cells*hr)
μ_y	Removal rate of infected red blood cells	0.025	1/hr
r	Number of free merozoites released per bursting RBC	24	cells
μ_m	Death rate of free merozoites	60	1/hr
α	Maximum percentage of RBCs killed via spleen due to NO induced Na^+-K^+-ATPase damage (supremum of hill function)	0.8	1/hr
γ	Threshhold for dramatic NO induced Na^+-K^+-ATPase damage (offset of hill function)	1	pM
s	Speed at which $\alpha \to 100$ once Υ is reached (steepness of hill function)	2	N/A
a	Default rate of TNF upregulation	10	pM/(cells*hr)
k	TNF downregulation due to feedback of NO	0.1	1/pM
μ_f	Rate of TNF degradation	3.47	1/hr
μ_j	Rate of iNos degradation	0.347	1/hr
b	iNOS upregulation rate due to TNF	1	1/hr
τ	Delay of TNF effect onset	2	hr

Mathematical Analysis

Result 1: *All solutions with positive initial conditions remain positive and bounded for all time.*

Result 2: *Consider a simplified model in which TNF-mediated immunopathology is described by simple mass action instead of a Hill function. Let*

$$R_0 = \frac{\beta\Lambda(r-1)}{\mu_m \mu_x}.$$

Then the disease-free equilibrium,

$$\{x, y, m, f, j\} = \{\Lambda/\mu_x, 0, 0, 0, 0\},$$

is locally asymptotically stable if and only if

$$R_0 < 1.$$

Otherwise it is unstable, and a chronic infection—either constant or cyclical—results.

Numerical Analysis

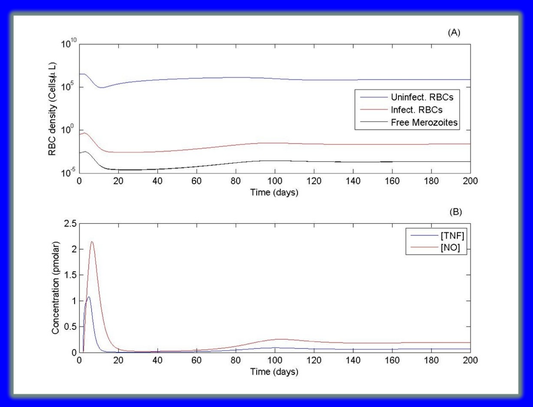

Figure 1. An example of chronic malaria infection. (a) Erythrocyte and merozoite dynamics. (b) TNF and NO dynamics.

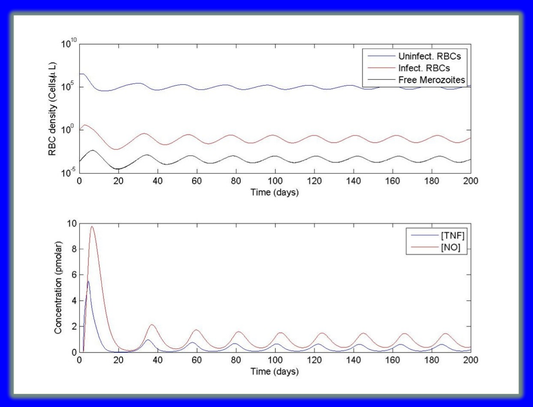

Figure 2. Sustained oscillations. Parameters at default except $\beta = 8\times10^{-4}$.

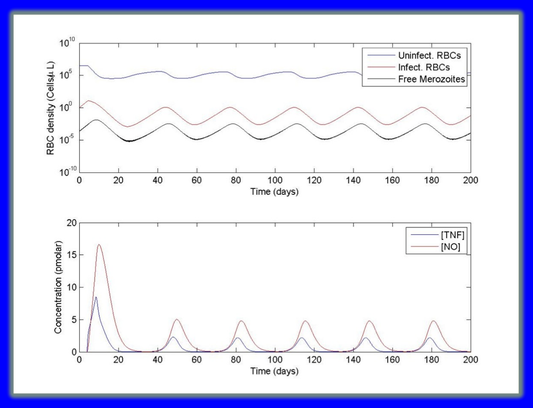

Figure 3. Oscillations associated with the time delay. Parameters as in fig. 2 except that $\tau = 4$.

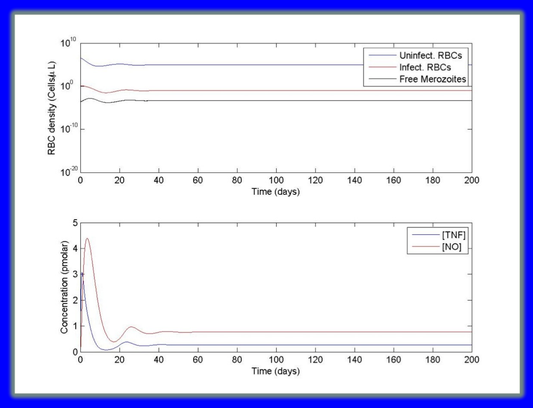

Figure 4. Oscillations associated with the time delay. Parameters as in fig. 2 except that $\tau = 0$.

Conclusion: *Oscillations in parasitemia and immunopathology are caused by a physiologically relevant time delay in TNF release in response to parasite antigens, primarily parasite GPIs.*

Future work

The next steps of our research focus on completing parameterization of the model and continuing to validate our model from a biological standpoint. Dynamics of model are not entirely worked out. Figures 1-4 are a very small portion of the data our model can generate. In addition, we will assess whether the effects of TNF can explain the differential mortality between *P. falciparum* and *P. vivax*. Toward this end, we plan to alter parameter values according to different characteristics of *falciparum* and *vivax* malaria, run simulations, and observe the differences between species. We recognize that the model form we present here represents a first approximation to the problem. Once the model presented here is fully analyzed, we plan to incorporate more realistic representations of the immunopathology of malaria to further explore Clark *et al.*'s hypothsis.

Literature Cited

Clark, I.A. *et al.* (2004) Pathogenesis of malaria similar conditions. *Clinical Microbiology Reviews* **17**: 509-539.

Iggidr, A. *et al.* (2006) Global analysis of new malaria intrahost models with a competitive exclusion principle. *SIAM J. Appl. Math.* **67**: 260-278.

Tumwiine J. *et al.* (2008) On global stability of the intra-host dynamics of malaria and the immune system. *Journal of Mathematical Analysis and Applications* **341**: 855-869.