Results from Prior NSF Support

A Objectives

Our Specific Aims are to

1. Develop and parameterize models of *T. gondii* behavior for epithelial, muscle, neuron, and [immune response cell] *in vivo*

2. Combine cell population model into a cell community model to describe organ level processes and (b) link gut, muscle, brain, and vascular organs together. Use to guide and fit to *in vitro* data.

3. Between Host Model

A direct outcome of our research will be the ability to ...

B Background

C Preliminary Results

D Research Design & Methods

In order to develop an cohesive and biologically based model of *T. gondii* infection at the within and between host scales, we combine and nest different models together. This separation of modeling scales allows us to both develop and parameterize a model that takes into account intracellular, tissue, organ, host, and epidemilogical scale processes.

For example, in Specific Aim 1 we begin by constructing a simple tissue level model. The tissue level model uses ordinary and partial differential equations (ODE and PDE, respectively) to model the dynamics of the parasite, uninfected and infected host cells of a single type (e.g. epilthelial or muscle cells), and an indicator of the immune response state of the local tissue such as IFγ level (Figure **??**). As part of Specific Aim 2, our tissue level model will be expanded to include multiple cell types and, thus, model the dynamics at the level of an 'organ' such as the gut, skeletal muscle, or brain. In addition, these multiple organ level models will, in turn, be coupled together to model the dynamics of the infection at the individual host scale to varying degrees of sophistication (Figure **??**). Finally, for Specific Aim 3 ...

Specific Aim 1: Development and Parameterization of Tissue Model

Model Formulation: In order to describe the dynamics of an infection at the level of a single tissue (i.e. where there is only one host cell type), we begin by assuming that in the absence of the infection, the density of uninfected cells X_0 is determined by a density dependent production rate $r(X_0)$ and background mortality d_X and defining the time scale as a where, in general a_0 is time at which an infected cell first arrived in the focal tissue. (See Table **??** for definitions of all symbols used in the tissue level model.) We classify infected host cells based on whether they contain *T. gondii* in the tachyzoite or bradyzoite state which we indicate using the subscript $i \in \{T, B\}$, respectively, Thus, we let X_T and X_B represent the densities of host cells infected by a tachyzoite containing PV or a bradyzoite containing cyst. We structure the infected cells X_T and X_B by both the age of infection a and size of the parasite population within the cell s and use PDEs to describe their behavior. Because the overall sizes of a tachyzoite and bradyzoites are similar, we can estimate s empirically for any given cell based on the the volume of its PV or cyst. We assume that s grows according to the growth functions g_T and g_B which can be affected by both s

and other factors, such as the immune response state of the tissue Z (see below). The densities of infected cells X_T and X_B are reduced by the background cell removal rate d_X as well as PV and cyst bursting rates b_T and b_B, respectively. Cell bursting results in the release of free parasites into the tissue. We assume that b_T and b_B can vary between cell types, parasite strain, and Z. For example, b_T may increase rapidly with s, thus effectively limiting the maximum size of a PV, while b_B may stay relatively constant over a large range of s values. The densities of infected cells are also altered by stage conversion of tachyzoites into bradyzoites within the cell. We model this as the conversion of $X_T(a,s)$ into $X_B(a,s)$ which occurs at rate c_{TB}. As with bursting, we let c_{TB} vary depending on the cell type, parasite strain, s, and Z. For example, the conversion rate from X_T to X_B in epithelial tissues is negligible while the conversion rate in muscle tissues is substantial. Further, in general we expect c_{TB} to increase with the size s of the PV. Based on experimental data [CITATION], we assume that immune response clearance of infected cells is negligible.

Experimental data also indicates that bradyzoites rapidly convert to tachyzoites right after cell bursting [CITATION]. As a result, we assume that bradyzoites released when X_B cells burst are immediately converted into to free tachyzoites. This means that all newly infected cells are initially in the X_T class and that any X_B cells are the result of stage conversion. Uninfected cells X_0 become infected when a free parasite P encounters, enters, and successfully establishes itself within the host cell. Because the immune response state of the tissue Z can alter the state of the host cell, interfering with the parasite's ability to establishment an infection, we define h as the probability a newly ingressed parasite is able successfully infect a host cell and assume it is a function of Z. Free parasites are also removed from the tissue at a background mortality rate d_P and, unlike infected cells, through immune response mediated mortality d_{PZ}.

Regarding the immune response Z, modeling the immune response of a host to a pathogen could be an entire research program in and of itself and is outside the scope of this proposal. Thus, for our work we treat the immune response dynamics as a forcing function $f(a)$ whose stereotypical behavior is determined by the host genotype, parasite strain, and tissue type and location. Thus the dynamics of $Z(a)$ are largely independent from the dynamics of the other, non-immune response model components. [NEED ADDITIONAL DISCUSSION OF HOW WE WILL RELATE DIFFERENT COMPONENTS OF THE IMMUNE RESPONSE TO EACH OTHER] Information on immune response dynamics already exist at various scales, including the entire host as well as specific tissues and organs such as muscle [CITATIONS], blood [CITATION], and brain [CITATIONS] In our *in vivo* experiments, only a single aspect of the immune response will be mainipulated at a time. As we combine models in later formulations, we will include multiple components.

More formally, our tissue level model can be written as,

$$
\begin{aligned}
\frac{dX_0}{dt} &= \lambda\left(X_0\right) - \left(k_{PX}P + d_X\right)X_0 \\
\frac{dP}{dt} &= \sum_{i\in\{T,B\}} \int_1^{s_{i,\max}} s\, b_i(s,Z) X_i\left(a,s\right) ds - \left(k_{PX}X_0 + d_P + d_{PZ}(Z)\right)P \\
\frac{\partial X_T}{\partial a} + \frac{\partial}{\partial s}\left(g_T(s) X_B(a,s)\right) &= -\left(d_X - c_{TB}(s,Z)\right)X_T(a,s) \\
\frac{\partial X_B}{\partial a} + \frac{\partial}{\partial s}\left(g_B(s) X_B(a,s)\right) &= -\left(d_X + c_{TB}(s,Z)\right)X_T(a,s) \\
\frac{dZ}{dt} &= f(a)
\end{aligned}
$$

Symbol	Definition
a	Age of the infection time scale
s	Size of parasite population within an infected cell.
$X_0(a)$	Density of uninfected host cells at time a
$P(a)$	Density of free tachyzoites at time a
$X_T(a,s)$	Density of host cells infected by tachyzoites population of size s at time a.
$X_B(a,s)$	Density of host cells infected by bradyzoites population of size s at time a.
$Z(a)$	Immune response level at time a
$b_T(s,Z)$	Bursting rate of tachyzoite containing cells X_T as a function of s and Z.
$b_B(s,Z)$	Bursting rate of bradyzoite containing cells X_T as a function of s and Z.
k_{PX}	Rate at which free parasite P encounter uninfected cells X_0.
g_T, g_B	Intracellular population growth rate of tachyzoite and bradyzoites, respectively.
$h(Z)$	Probability of PV formation by an invading tachyzoite as a function of Z.
d_X & d_P	Background mortality rates of host cells X and free tachyzoites P, respectively.
$d_{PZ}(Z)$	Immune response mediated clearance of free tachyzoites.
c_{TB}	Conversion rate of tachyzoite containing cells X_T into bradyzoite containing cells X_B.

Table 1: Symbol definitions for tissue level model. Could reduce text size and/or column width and then wrap text around this to save space.

with a boundary condition for Equation (**??**) of

$$h(Z)k_{PX}X_0(a) = g\left(s_{T,\min}\right)X_T\left(a, s_{T,\min}\right).$$

Where $s_{i,\max}$ ($i \in \{T,B\}$) represents the maximum PV or cyst size possible, a value indirectly determined by the growth functions g_T and g_B and the host cell mortality rate d_X.

Model Parameterization Because of our tissue model assumes there's only one cell type, we can use time series data collected from *in vivo* experiments using cell cultures to parameterize key aspects of it. For example, by analyzing samples of from the cell culture, we will be able to estimate

1. Bursting rate $b_i, i \in \{T,B\}$
2. Conversion rate rate c_{TB}
3. PV formation probability $h(Z)$

Specific Aim 2: Organ and Within-Host Modeling

Limitations to our Work

Timeline of Proposed Research

Relationship of Proposed Work to Long-Term Goals

Figure 1: Illustration of SEMPPR's ability to accurately predict ϕ using parameters $\mathbf{\Lambda}$ generated from a simple MCMC algorithm and Eqn. (2).

E Broader Impacts

Box 1: Calculating the Likelihood of a Parameter Set $\mathbf{\Lambda}$

If we are interested in first estimating the set of parameters $\mathbf{\Lambda}$ used to calculate η we can treat the protein production rate of a gene ϕ as a nuisance parameter and integrate over it. Combining Eqn. (**??** with the assumption that $\phi \sim \text{Exp}(\zeta)$, the probability of observing a sequence fixed in a population as a function of $\mathbf{\Lambda}$ is,

$$a + b = c \tag{1}$$

Formally, Eqn. (1) represents the likelihood of $\mathbf{\Lambda}$ given a codon sequence. Thus, the total likelihood of $\mathbf{\Lambda}$ given the n observed gene sequences within a genome is simply,

$$\text{Lik}(\mathbf{\Lambda}|Z) = \prod_{i=1}^{n} P(Z|\mathbf{\Lambda}). \tag{2}$$

Whether likelihood function of Eqn. (2) is analyzed directly or, as we propose, weighted by a prior distribution, it provides method for estimating $\mathbf{\Lambda}$ using genomic data alone. These $\mathbf{\Lambda}$ values, in turn, can be used to predict ϕ (see Figure 1).