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DISPARATE DISEASE OUTCOMES IN CHRONIC INFECTION: THE ROLE OF INTRA-HOST VARIABILITY

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Abstract: We recently developed a model of *Mycobacterium marinum* (Mm) transmission dynamics in aquatic animals in [1]. Mm is a close genetic relative to the bacterium that causes human TB, and affects marine mammals on the same scale and with similarly varied disease presentation. It is evident that for a mathematical model to agree with laboratory infection studies and common observations, it is necessary to address the disparate outcomes explicitly, namely, the large pool of chronically but asymptomatically infected individuals, and individuals with acute infections. Here, we demonstrate that we can improve upon the agreement between the model and data by taking a simpler (fewer cohorts of fish), but more biologically meaningful modeling approach. We briefly also demonstrate that this phenomenological approach, particularly in conjunction with experiments, may be useful to provide support for or against hypotheses of underlying processes driving this and potentially other infections with a large pool of chronically infected individuals.

AMS Subject Classification: 92C99, 92D30
Key Words: progression variability, intra-host model, *Mycobacterium marinum*, physiologically structured models

1. Introduction

Mycobacteria can produce a wide spectrum of disease presentation, ranging from latent infections to active acute disease [5, 12]. The vast majority of

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infected individuals do not present TB symptoms throughout their lives [5, 11, 12], and only a small subset ($\sim$0.1%) will develop acute disease [5, 12]. Acute TB remains the leading cause of mortality by a single infectious agent because of the large size of the Mtb-infected population, killing approximately 2 million annually [3, 5, 11]. Medical factors (age, sex, nutrition, etc.) cannot explain the differences seen in humans and other animals, as high variability in colonization was still seen in studies in which these postulated variables were controlled [10]. Therefore, studying the difference in disease outcomes, mechanisms underlying these differences, and modeling the large chronic cohort accurately is an important undertaking.

Mycobacterium marinum (Mm) is a close genetic relative to *Mycobacterium tuberculosis*, the etiological agent of human TB, and provides an attractive alternative to study mycobacterial infections as it grows faster and poses less of a risk to researchers. The magnitude of the human TB burden is paralleled by a variety of mycobacterial pathogens in fish, and in particular by *Mycobacterium marinum* (Mm) [2, 4, 5, 6, 7], which is known to infect at least 200 fish species in marine and fresh water environments [4, 5, 9]. Annually, fish mycobacteriosis costs billions of dollars in combined losses to the wild-caught fisheries, to aquaculture-raised fish, to the aquarium trade and to research colonies [7, 8, 9].

We developed a Mm infection transmission model within a food network [1], as experiments have indicated the likelihood of multiple oral transmission routes via consumption of infected food items. One route involves the consumption of mosquito larvae carrying Mm in their gut, which readily eat Mm, and are a natural food source for small fish, including medaka. Not only is this infection route a plausible natural mechanism, but it has been seen to be effective in the lab. We chose to use a discrete number of physiological groups to reflect differences in individual susceptibility to infection, effectiveness of immune response, feeding behavior, etc. structured by intra-host bacterial burden. Fish within these groups are considered to be identical. In [1], we demonstrated that these physiological differences are necessary to reproduce observed data (the time course of deaths of fish that had been fed 'meals' of larvae carrying Mm).

In this work we demonstrate a marked improvement in the agreement between the model and data using fewer physiological groups by modifying the intra-host progression rate functions to be based on more biologically meaningful courses of progression. We further demonstrate the potential of this phenomenological-type modeling approach to be used in conjunction with experiments to elucidate key steps of the pathogen-immune response dynamics critical to understanding Mm infections. Further studies using a similar approach may prove useful in the understanding of other infections with a large

chronic pool and highly variable disease outcomes, such as human TB.

2. A Simple *Mycobacterium Marinum* Infection Model

The full Mm transmission model in [1] is structured by bacterial load x, which can change over several orders of magnitude during the course of infection, from $x_{\min}$ the smallest bacterial load corresponding to the successful establishment of a Mm colony, past the chronic asymptomatic stage to the acute infection stage. We assume there is a maximum bacterial load $x_{\max}$, above which no fish can survive. Therefore, we study solutions on a log-scale ($z = \log(x)$), where z takes values in $\mathcal{Z} = [z_{\min}, z_{\max}]$.

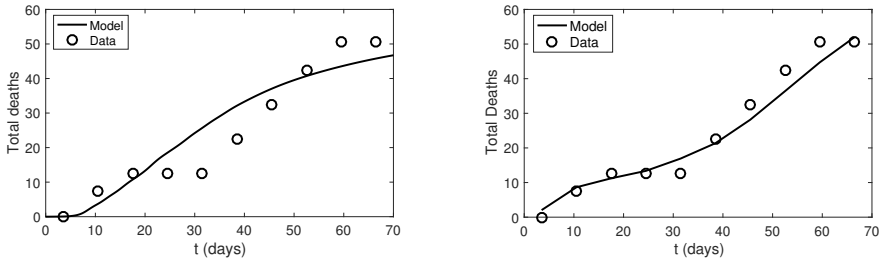
To study the experimental situation in which susceptible fish $S^i(t)$ of physiological group $i = 1, ..., m$ were fed Mm carrier mosquito larvae at rate cM, the model can be reduced to

$$\begin{aligned}\frac{dS^i}{dt} &= -\mu S^i - \nu\eta cMS^i,\\ \frac{\partial I^i}{\partial t} &= -\left(\frac{\partial}{\partial z}\left\{\frac{1}{\ln 10}\frac{1}{10^z}g^i I^i\right\} + \mu f_u I^i\right),\end{aligned}$$

where $I^i(t, z)$ is the density of infected fish at time t and log-bacterial load z. The effective infection rate is the product $\nu\eta$, where ν is the (per Mm) infectivity rate via this route, and η is the number of Mm per typical carrier larva M. Infections exacerbate death due to natural causes (at per capita rate μ) by the factor f_μ. Infection progresses at the rate $g^i(t, z, M) = \beta^i(z) + \sigma c\eta \exp\{-\alpha 10^z\}M$, where $\beta^i(z)$ is the intra-host progression due to the interplay between Mm colonization of internal organs and the host's immune system, and the remaining term is the progression of the infection by subsequent meals of carrier larvae (also termed exogenous reinfection), with effective infection rate σ. Any possible retardation in feeding rate due to infection is represented by the factor $\exp\{-\alpha 10^z\}$. The initial conditions are $S^i(t_0) = S_0^i$ and $I^i(t_0, z) = 0$. The boundary condition, or the rate of new infections, is given by $\frac{1}{\ln 10}\frac{1}{10^z}g^i I^i|_{z_{\min}} = \nu\eta cMS^i$. Since most infection modes are irrelevant in this experimental scenario, several terms can be neglected that appear in the full model in [1] so most subscripts and superscripts in the original model have been omitted.

In the scenario studied here, the fish were fed 5 carrier mosquito larvae on days $\{t_j\}_{j=1}^7 = \{0, 3.5, 7, 13, 20, 24, 28\}$ for $j = 1, ..., 7$ to induce infection. We implement this mathematically as taking $M \equiv 1$, and a piecewise constant

feeding rate ($c(t) = 5$ for $t \in [t_j, t_{j+1})$ and $c(t) = 0$ elsewhere). Then each meal is given by $\int_{t_j}^{t_{j+1}} c(s)Mds = 5$. The only differences among physiological subgroups of fish were reflected in the progression functions $\beta^i(z)$, which we took to be simple exponential functions $\beta^i(z) = b_i 10^z$ for $i \in \{1, ..., m\}$ in our initial model development efforts. To achieve the agreement seen in Figure 1a, and for the bacterial loads of the sacrificed fish to span the observed ranges, it was necessary to take several ($m = 6$) physiological classes. Thereby, we demonstrated that the additional complexity of more than one physiological class was required for a model to reproduce even basic qualitative observed behavior, or the variable disease outcomes.



(a) Previous model (b) Improved model

Figure 1: Total cumulative deaths as observed when fish were fed carrier mosquito larvae, and as computed from model solutions of (a) the mycobacterial model above as in [1], and (b) of the same model with modifications as described in Section 3.

3. Model Improvements

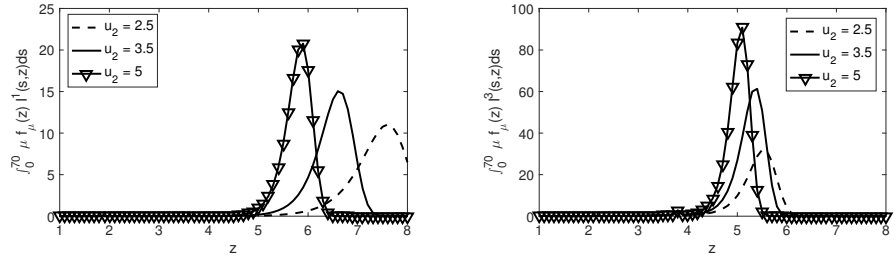
While the agreement between the original model and data was encouraging as a first attempt, we are motivated to improve upon these results. An obvious way to do so would be to simply increase the number of physiological groups, but this would result in an increase in model complexity without a corresponding gain in understanding. Instead, we modify the intra-host progression and death rate functions based on hypotheses and their resulting phenomena.

Upon closer inspection, it became clear that the death rate of the infected fish $\mu f_\mu(z)$ in the original model resulted in too many deaths of fish at 'low' bacterial loads (that would be associated with only chronic or asymptomatic

infection). Adjusting parameter values in the previous form of $f_\mu(z)$, the extent to which the death rate is exacerbated by infection, would easily result in fewer deaths at lower and medium bacterial loads. However, this also results in too few deaths at high bacterial loads, which is problematic as it effectively allows a non negligible amount of fish to survive past $z_{\max}$. We take the form

$$f_\mu(z) = 1 - \chi_{[z>z_c]} \left\{ 1 - \exp\left(u_1 \frac{z - z_c}{z_{\max} - z_c} \right)^{u_2} \right\}, \quad u_2 \geq 1,$$

which, with $u_2 = 1$ and $z_c = z_{\min}$, reduces to that of the original model. The disease-related death rate for values of $u_2 > 1$ is lower at low bacterial loads and higher as z increases for a fixed value of u_1. We also included the use of a characteristic function $\chi_{[z>z_c]}$, so that death due to infection below some critical bacterial load z_c does not occur at all. This is in accordance with the idea that there is some 'tipping point' in infection, below which no discernible effect on their lifespan is observed. The inclusion of both of these features results in model solutions that agree with observed phenomena as can be seen in Figure 2, which contains the total deaths of infected fish that progress to symptomatic infections (and disease-related death) as a function of their bacterial loads. The deaths of only chronically asymptomatically infected fish are not affected by this parameter and therefore are not shown in Figure 2.



(a) $i = 1$ (b) $i = 3$

Figure 2: Total deaths $\int_0^t \mu f_\mu(z) I^i(s,z) ds$ of fish as a function of (log-)bacterial load z at the final time $t = 70$ for (a) the fastest progressing group $i = 1$ and for (b) the group ($i = 3$) that progresses to symptomatic infection only after several Mm doses for different values of u_2.

A key feature of this data set is the lag in deaths observed around 17-32 days which we reasonably assume to be reflective of chronically infected fish

that would otherwise not progress to a more severe infection and/or death without additional doses of Mm (meals of carrier larvae). It is important that a model of Mm dynamics reproduces this feature as this chronically infected pool in natural populations likely plays an important role in the persistence and impact of mycobacterial infections.

The exponential functions used in previous efforts cannot be used to reproduce this lag as the bacterial load simply continues to increase in all fish once infected, albeit at different rates. The incorporation of a time delay in either the (per capita) infection rate $\nu\eta c(t-\tau)M$ or the rate of acceleration due to subsequent meals $\sigma\eta c(t-\tau)M$ would likely result in better agreement. However, such a model is substantially less tractable. More importantly, while the inclusion of this feature would likely result in the reproduction of this observed phenomena, it would not be based on biologically plausible theories concerning disease progression that would result in this phenomena.

We consider phenomenological models of three commonly observed courses of infection:

1. quick progressione to acute infected state and death, $\beta^1(z) = b_1 10^z$.
2. initial infection controlled, 'long-term' chronic state:
$$\beta^2(z) = b_2(z - z_{\min})e^{-b_3(z-z_{\min})}.$$
3. initial infection controlled, possible symptomatic infection upon subsequent dosing (later meals of carrier larvae):
$$\beta^3(z) = b_4(z - z_{\min})e^{-b_5(z-z_{\min})} + \chi_{[z>z_c]}b_6(z - z_c).$$

Most parameter values are unknown to the best of the authors' knowledge, and were simply chosen so that the overall number of infections in model solutions were on the same scale as the experimental data. With the parameter values in Table 1, the agreement between the data and the cumulative deaths computed from model solutions is notably improved, as shown in Figure 1b. Further improvement in the agreement between the model and this and other data sets will be pursued in future studies.

4. Simulation Studies

To demonstrate the utility of this phenomenological model as a potentially useful tool to gain underlying insight into underlying principles, we study the

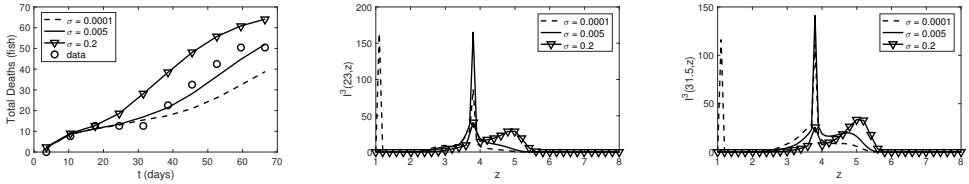
Parameter	Units	Value	Parameter	Units	Value
$z_{\min}$	log(bact)	1	$z_{\max}$	log(bact)	8
z_c	log(bact)	4.5	μ	$\frac{1}{[\text{time}]}$	$\frac{1}{1600}$
u_1	N/A	6	u_2	N/A	2.2
η	$\frac{[\text{bact}]}{[\text{mosq}]}$	2.4×10^3	ν	$\frac{[\text{fish}]}{[\text{bact}]}$	2.5×10^{-5}
b_1	$\frac{\log(\text{bact})}{\text{time}}$	5	b_2	$\frac{\log(\text{bact})}{\text{time}}$	100
b_3	N/A	1	b_4	$\frac{\log(\text{bact})}{\text{time}}$	215
b_5	N/A	0.05	b_6	$\frac{\log(\text{bact})}{\text{time}}$	1000
σ	none	5×10^{-3}			

Table 1: Model parameters and corresponding units to produce solution in Figure 1b.

effect of changes in parameter values on observable model quantities. Focusing on the time course of deaths of infected fish, and the density of infected fish with chronic asymptomatic infections that may progress to a symptomatic state ($i = 3$) as a function of log-bacterial load, we illustrate similarities and differences in the effects of changing two parameters.

Figure 3 contains these observable outcomes with different values of σ, the degree to which the infection is accelerated by each subsequent Mm dose (via consumption of an effective carrier larvae meal by an infected fish). For the lowest value of σ ($\sigma = 0.0001$) used here, there is a cohort of fish whose infections remain in the lowest bacterial load ranges. With the medium and highest values of σ, however, there is no such cohort and the infections either progress to a medium (below the tipping point z_c) severity, or the infections worsen past the tipping point z_c and quickly progress. An increase in the value of σ results in a greater proportion of the infected fish with severe infections, and correspondingly more deaths.

The effect of changing z_c, the bacterial load at which the tipping point occurs, is shown in Figure 4. Increasing the value of z_c results in a smaller proportion of fish with infections that progress to the most severe stages, or highest bacterial load ranges, an effect directly opposite that of increasing σ. If these two parameters have identical but opposite effects on solutions, it would suggest a high degree of correlation between them and the unlikelihood of the identifiability of both from observations. However, increasing z_c further does



(a) $\mathcal{I}(t;\mu f_{\mu}(z))$ (b) $I^3(20,z)$ (c) $I^3(31.5,z)$

Figure 3: In (a) is the total (cumulative) number of deaths $\mathcal{I}(t;\mu f_{\mu}(z)) = \sum_{i=1}^{3}\int_0^t\int_{\mathcal{Z}}\mu f_{\mu}(x)I^i(s,x)dx\,ds$ of fish in all groups using three values of σ ($\sigma = 0.0001$, $\sigma = 0.05$, and $\sigma = 0.2$). The panels (b) and (c) contain the densities of infected fish in the third physiological class $i = 3$ at $t = 20$, and at $t = 31.5$, respectively.

not result in the small cohort of fish that remain in the least severe stages, or lowest bacterial load ranges (Figures 4b and 4c), in contrast to such a cohort in Figures 3b and 3c for the lowest value of σ.

That these differences are observable experimentally suggests that the model can be used in conjunction with experiments to provide support for or against working hypotheses of events governing disease progression. For example, we may be able to deduce whether a critical tipping point in bacterial load exists and understand its role in the large variability observed in disease outcomes. Additionally, we may be able to determine whether, or to what degree, re-infection by subsequent doses (or, exogenous reinfection in a natural setting) plays an important role in the activation of chronic or latent infections. Further studies along these lines have the potential to reveal critical insight that may form the basis of future therapeutic strategies targeting human TB and perhaps other chronic infections. Further, it is reasonable to expect that the model may be calibrated to a population of fish, providing information as to the distribution of progression (as represented by the progression rate functions). Such knowledge would provide the basis for population level studies, allowing researchers to anticipate any reduction in acute infections and death as a result of any intervention measures.

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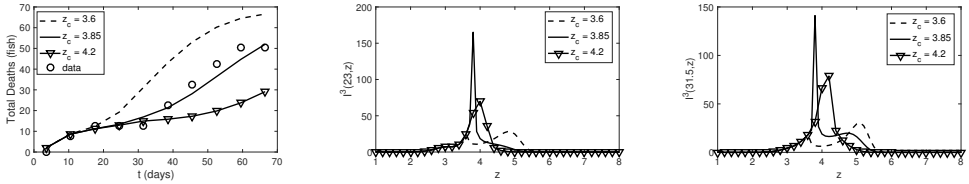

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