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Dynamics of the antibody-*T.cruzi* competition during Chagas infection: Prognostic relevance of intracellular replication

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A recently proposed model for the competitive parasite-antibody interactions in Chagas disease is extended by separately describing the parasitic intracellular and extracellular phases. The model solutions faithfully reproduce available population data and yield predictions for parasite-induced cardiac cell damage.

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I. INTRODUCTION

Chagas disease is an endemic disease widespread in Latin America, with a total exposed population estimated at 60 million [1]. Its causative agent is the protozoan parasite *Trypanosoma cruzi*, which is transmitted by a bloodsucking insect of the subfamily *Triatominae*, or by blood transfusion. Upon infection, the initial acute phase of the disease, characterized by a transient parasitemia, ensues. Many years, even decades, after the initial infection, around 25% of the infected individuals develop a chronic inflammatory disease, with cardiovascular and/or gastrointestinal involvement. The heart pathology is characterized by myocarditis that leads to the development of heart failure and arrhythmia. At present there is no effective vaccine against this disease, whose social and economic effects are well documented [1,2].

The *T. cruzi* life cycle presents three main morphological stages. Replicating epimastigotes are found in the insect vector, while an intracellular reproductive form (amastigote), and a blood-circulating infective form (trypomastigote) are identified in the vertebrate host. In the host, the circulating trypomastigotes invade cells at bite wound sites, where they differentiate into intracellular amastigotes. These amastigotes multiply by binary fission, filling the cell. Then they burst out of the cell after a new differentiation, being released into the bloodstream as trypomastigotes. The circulating parasites can infect cells in a variety of tissues and start replicating at new infection sites. Replication resumes when the trypomastigotes enter another cell or are ingested by another vector.

The contribution of the physics literature to the analysis of the immune response to pathogen agents, ranging from the study of the HIV infection dynamics [3] to the modeling of the immune response to tumor growth [4], is significant. However, little effort has been devoted to the mathematical modeling of the various aspects of Chagas disease. This is surprising, since modeling could illuminate the relation between the microscopic mechanisms and the clinical expression of the disease. An important exception is the work of Nelson and Velasco-Hernández, who put forward a model of cell-mediated response to *T. cruzi* to describe the late pathogenesis stages and the possible role played by autoimmunity in determining the disease outcome [5].

We recently presented a model for the acute phase of the infection that predicts all possible outcomes of the disease: healing, death, and chronic infection, with stationary or quasicyclical populations [6–8]. This model was used to investigate diverse situations of interest, such as the action of parasite-released decoys, the influence of immune reaction delays, and the effects of an increase in the antibody efficiency [8].

Very good agreement was obtained [6,7] by comparing the predictions of our model with the data of El Bouhdidi *et al.* [9] and Truyens *et al.* [10]. However, small systematic discrepancies remain between the predicted evolution of the number of parasites and the observations. In this paper we will show that the agreement can be substantially improved if the reproductive process is explicitly modeled.

Using experimental infections in mice, Andersson *et al.* showed that both the parasite and the host genotypes are important in determining the eventual outcome of the *T. cruzi* infection [11]. Cummings and Tarleton reached a similar conclusion, adding that parasite localization in the chronic stage also depends on the parasite-mouse strain combination [12]. Andersson and co-workers stressed that parasite persistence is a necessary, but probably not a sufficient, condition for the emergence of chronic Chagas disease [11]. In fact, cardiac damage is likely to stem both from direct parasite action and from a misdirected reaction of the immune system [13,14]. The link between *T. cruzi* persistence and disease severity is strengthened by the observation that reinfections produce greater cardiac damage than infections [15]. Our model yields an estimate of the size of direct parasitical action and helps us to identify crucial parameters for determining cellular damage.

II. THE MODEL

Our assumptions about antibody dynamics are similar to those in the original model [8].

(i) There are N different antibody species $a_i(t)$ capable of mediating parasite removal.

(ii) There are N fixed values $a_{i,0}$ representing a continuous source exactly compensating for the inactivated antibody molecules in the absence of parasites.

(iii) The generation of antibodies at γ_i is induced by the presence of parasites.

(iv) The antibody loss due to binding with the parasites is quantified by the coefficients α_i.

Then we can write the evolution equation for the antibody species i as

$$\dot{a}_i(t) = (1/\tau_i)[a_{i,0} - a_i(t)] + \gamma_i n(t) - \alpha_i a_i(t) n(t), \qquad (1)$$

where τ_i is the intrinsic lifetime of antibodies belonging to species i, and $n(t)$ the parasite population. We also assume that the removal efficiency α_i is described by a smoothly increasing function of time [7], $\alpha_i(t) = \alpha_{A,i} + \alpha_{B,i}(1 - \exp \times[-t/T_i])$, where T_i is a "learning time."

To describe the parasite reproduction process, we introduce a new variable r, which represents the number of invaded cells. Its evolution is given by the equation,

$$\dot{r}(t) = \zeta n(t) - \eta r(t), \qquad (2)$$

where the *infectivity* ζ is the rate at which a circulating parasite penetrates into a host cell to initiate replication and the *cytotoxicity* η is the probability per unit time that an infected cell will burst due to the big number of parasites in its interior. Therefore, the circulating parasite production depends on the infected cell population. As a consequence, the circulating parasite evolution equation is,

$$\dot{n}(t) = \eta N_r r(t) - n(t) \sum_{i=1}^{N} \alpha_i(t) a_i(t) - \zeta n(t), \qquad (3)$$

with N_r being the mean number of trypomastigotes emerging from a ruptured cell. The parameters η and N_r can be easily related to the mean amastigote duplication time Ω: $\Omega = (\ln 2 / \ln N_r)(1/\eta)$.

For simplicity, we first study the $N=1$ case. By setting the time derivatives in the previous equation system equal to zero and writing $\alpha = \alpha_A + \alpha_B$, we obtain two sets of steady-state solutions

$$\overline{a_1} = a_0, \quad \overline{n_1} = 0, \quad \overline{r_1} = 0 \qquad (4)$$

and

$$\overline{a_2} = \frac{(N_r - 1)\zeta}{\alpha},$$

$$\overline{n_2} = \frac{(N_r - 1)\zeta - \alpha a_0}{\alpha\tau[\gamma - \zeta(N_r - 1)]}, \qquad (5)$$

$$\overline{r_2} = \frac{\zeta}{\eta}\overline{n_2}.$$

Here the first solution corresponds to host healing: the parasite and infected cell populations are completely eliminated. The second solution, which corresponds to chronic disease, exhibits an interesting situation: while the steady state populations of parasites and antibody molecules depend on the mean number of parasites released in a cell burst, but not on the mean incubation time ($\sim 1/\eta$), the opposite occurs with the number of infected cells. As expected, if the mean number of parasites emerging from the ruptured cell is lower than one, $N_r < 1$, only the healing solution is possible. Numerical analyses indicate that, at short times, $a(t)$ is smaller in the cases of large infectivity ζ: intracellular parasites do not activate the humoral reaction. Later on, the curves corresponding to different values of ζ cross each other because the low level of antibodies at short times allows for an increase in the circulating parasite number, which in turn stimulates antibody production, leading towards the steady state. If ζ is high, it is likely that increases in $a(t)$ fail to control the parasitemia.

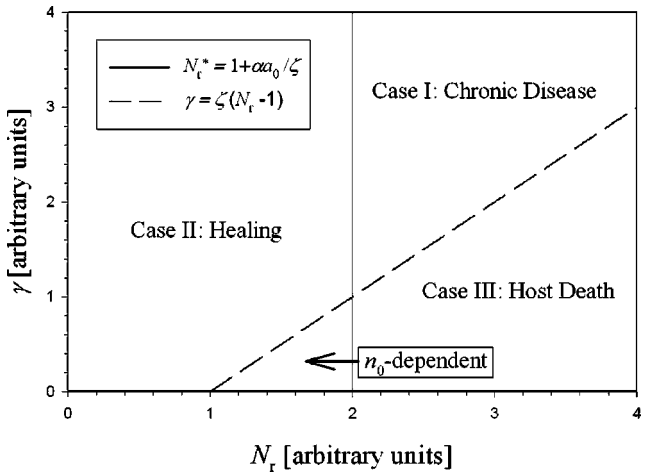

FIG. 1. γ-N_r phase diagram describing the outcome of the parasite infection. Here, we chose $\alpha = 0.1$, $\zeta = 1$, $\tau = 1$, and $a_0 = 10$. The outcome depends on the initial conditions only in the lower triangular zone.

Studying the stability of the steady-state solutions by the use of the Routh-Hurwitz criterion [16], we found the same three possible outcomes as in the simpler model: healing, chronic disease, and host death. To apply the criterion, we linearly perturb Eqs. (1)–(3) around a given steady-state solution and define suitable matrices [16] using the resulting coefficients. The signs of the corresponding determinants determine the parameter domain where the perturbation decays. The results of the parasitic invasion are best described by constructing a phase diagram in the plane defined by the parameters γ and N_r (Fig. 1). It is interesting to compare this diagram with that corresponding to the original model, where the parasite generation rate was used as the abscissa [8]. The main differences are: (i) the phase boundary between the surviving (healing and chronic) and host death cases starts at a nonzero value of N_r, not at the origin; (ii) its slope has changed: in fact, the equation for this phase boundary is $\gamma = \zeta(N_r - 1)$, which means that the value of the infectivity ζ is crucial to determine the infection outcome [from Eq. (5) we also see that the steady state parasite number $\overline{n_2}$ is a monotonically increasing function of ζ]; (iii) the borderline between the chronic and healing cases is now located at $N_r^* = 1 + \alpha a_0/\zeta$ (increasing the immune system efficiency or decreasing the infectivity enhances the chances of healing). In this way, the triple point where the three cases meet is located at $\gamma = \alpha a_0$, as in the original model [8]. Note that there is a region (the lower triangle in Fig. 1) where the outcome

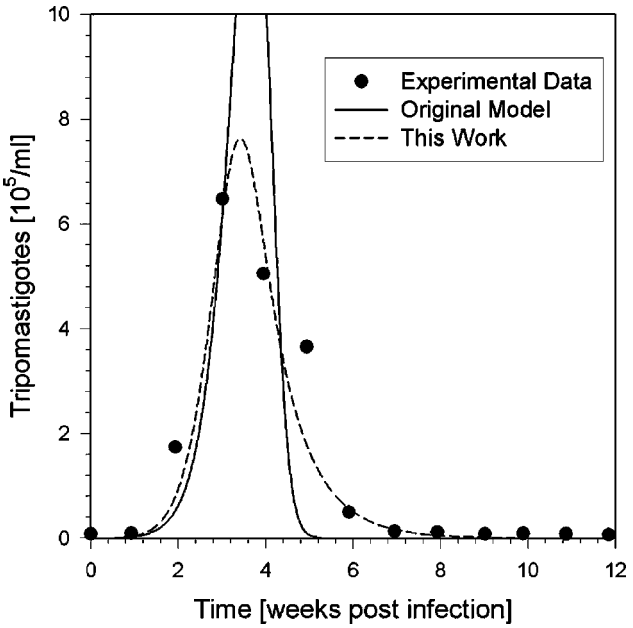

FIG. 2. Comparison of the extended model with its original version and experimental data from El Bouhdidi *et al.* [9].

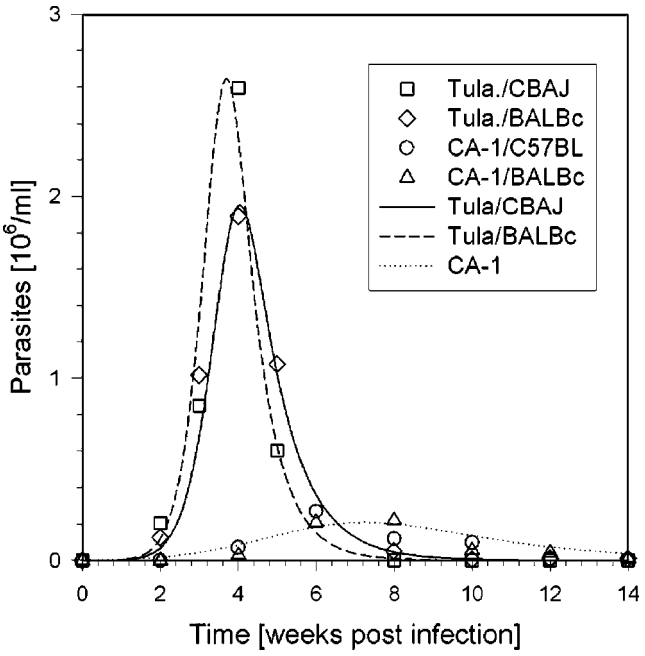

FIG. 3. Comparison of the extended model with the experimental data from Andersson *et al.* [11].

depends on the size of the parasite inoculation.

III. RESULTS

To compare the predictions of the extended model with those of the original version, we performed a fit of the experimental data for Bagg Albino (BALB/c) mice infected with *T. cruzi* parasites (Tehuantepec strain) from El Bouhdidi *et al.* [9]. Three antibody species, IgM, IgG1, and IgG2a were included in the model. The parameters were chosen to show the closest visual agreement between the experimental data and the model predictions. We obtained $N_r=13.8$, $\zeta=2.1[1/w]$, $\eta=2.1[1/w]$, and $n_0=100[1/ml]$, keeping the antibody parameters as in the original model [6].

In Fig. 2 we compare the fits obtained with the original and present models. It is evident that the new version yields a better fit to the evolution of the parasite population, especially towards the end of the acute period (the sum of the square residuals is reduced to a 10% of the value corresponding to the original model). Other criteria (Chi-square, Akaike information criterion) confirm that the extended model generates substantially better fits. The fits to the antibody populations (not shown for brevity) are visually indistinguishable from those obtained with the original model [6]. In that model, the increment of the number of antibodies and their increasing efficiency generate a fast decrement of the number of parasites. In the extended model, the infected cells represent a source of new parasites that weakens this effect, allowing for longer parasite survival, hence the longer $n(t)$ tail.

We have also successfully fitted the parasite data from Andersson *et al.* [11], who used various parasite strains (Tulahuen and CA-1) and mice (CBA/J and BALB/c). Their conclusion that both the genotypes of the parasite and the host play a role in the outcome of Chagas disease is evident from Fig. 3, where the infection with the CA-1 strain exhibits a later and much milder parasitosis than the infection with the Tulahuen strain, although the mice were infected with 10^4 parasites of the CA-1 strain but only 50 parasites of the Tulahuen strain. As seen from Fig. 3, there is excellent agreement between the model predictions and the experimental data for both strains. Fit parameters are presented in Table I. We considered that the parasites were controlled by exactly the same antibodies as in the preceding fit, with the same parameters, except for those in the table.

With the help of the data in Ref. [11] we can assess the damage produced in the host through cell destruction. Figure 4 shows the evolution of the number of infected cells (r) for the parameter values used in Fig. 3. Remarkably, the number of cells infected by the "mild and late" parasite strain, CA-1, is much higher than the number corresponding to the

TABLE I. Parameters corresponding to the fit to the experimental data from Andersson *et al.* [11]. ζ, η and γ_i are measured in w^{-1}. Here w stands for weeks.

Strain/Mice	N_r	ζ	η	n_0	γ_{IgM}	γ_{IgG1}	γ_{IgG2a}
Tula./CBAJ	12.1	2.5	2.5	50	$6.7\ 10^9$	$2.7\ 10^{11}$	$8.3\ 10^{11}$
Tula./BALB/c	14	2.3	2.0	50	$6.7\ 10^9$	$2.7\ 10^{11}$	$8.3\ 10^{11}$
CA-1/both	2.2	23.5	1.8	10000	$6.7\ 10^9$	$2.7\ 10^{11}$	$8.3\ 10^{11}$

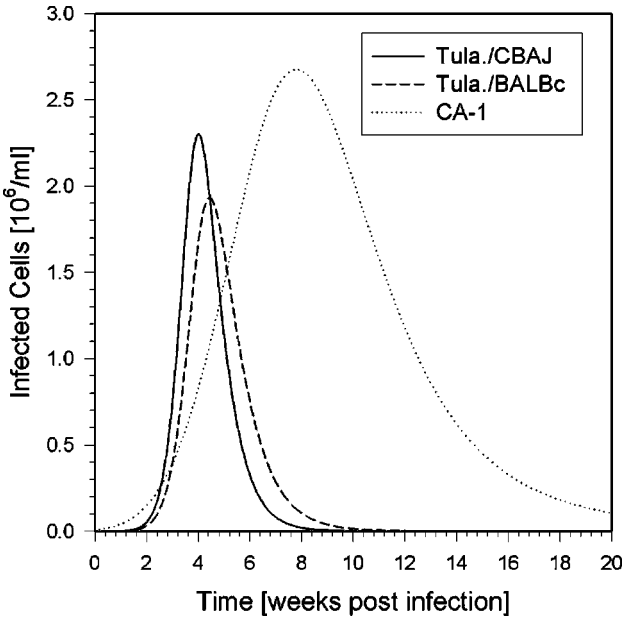

FIG. 4. Evolution of the infected cell population obtained with the parameters used to fit the experimental data of Andersson *et al.* [11].

"strong" strain. This is consistent with our previous analysis [6] and with the observations of Andersson and co-workers. These authors found that the mice infected with the CA-1 strain developed a severe inflammatory disease accompanied by massive fibrosis, dying at 9–10 months postinfection [11]. The mice infected with the Tulahuen strain also developed myocarditis but of less severity and with no sign of fibrosis.

The ratio ζ/η for the CA-1 strain is higher than for the Tulahuen strain. In Ref. [6] we compared *T. cruzi* and viral infections, applying a criterion due to Arnaout and Nowak [17] to understand the immune pattern generated by the parasite. We predicted that damage in the chronic phase would be inversely related to strain virulence and, following Ref. [17], that it would be generated by cellular immunity. We therefore propose to consider the ratio ζ/η as a strong indicator of virulence. When $\zeta/\eta<1$, the strain is more cytotoxic than infective, leading to high parasitemias and direct tissue damage; surviving hosts are likely to heal or to suffer only a mild chronic mainly inflammatory disease. If $\zeta/\eta>1$, the opposite occurs: the strain is more infective than cytotoxic, leading to mild acute phases, but with longer periods of detectable even if low parasitemias. In Fig. 1 the areas corresponding to cases I and III grow with increasing ζ, strengthening the hypothesis that the longer the parasite stays in the host, the greater the possibility of chronic disease or death. In this kind of infection, parasite persistence is determined by a relatively large $\bar{r}$, thus resulting in a weaker humoral response. Note that when ζ increases but η is fixed, a substantial reduction of the healing domain ensues, and the disease is driven more easily towards chronicity.

We can also estimate that the accumulated parasite-induced cell damage during the chronic stage is proportional to $Y\eta\bar{r}=Y\zeta\bar{n}$, with Y being the time elapsed from the end of the acute stage. Note also that the steady-state antibody population $\bar{a}$ is proportional to the parasite infectivity ζ. Since in the chronic stage $\bar{n}$ is small, for weakly infective strains (such as Tulahuen) the level of specific antibodies would be small (low or even undetectable positives) with few infected cells, excluding strong cellular immunity but with a real possibility of prolonged humoral reactions and mild cardiopathy. On the contrary, high positive antibodies titers would be found after the mild acute infections with weakly cytotoxic but very infective strains (such as CA-1), which retain high $\bar{r}$ and may give rise to intense accumulated cellular immune damage.

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