

# Mathematical modelling of immune response against *Trypanosoma cruzi*

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## Summary

- Introduction
- Model formulation
- Analysis of the general model
- Isolated action of the humoral response
- Isolated action of the cellular response
- Numerical simulations
- Conclusion

# Introduction

- *Trypanosoma cruzi* is the causative agent of American trypanosomiasis (Chagas' disease)
- It is transmitted by various species of bloodsucking triatomine insects
- Forms of transmission include consumption of uncooked food contaminated with faeces from infected bugs, congenital transmission, blood transfusion, organ transplantation, and accidental laboratory exposure
- *T. cruzi* infection is a zoonosis, and humans are merely unfortunate hosts
- 10 to 12 million people are infected with *T. cruzi*
- Up to 45,000 persons die each year of Chagas' disease

# Chagas' disease

*Model formulation   Analysis of the general model   Isolated action of the humoral response   Isolated action of the cellular response   Numerical simulation*

- The insects become infected by sucking blood from animals or humans that have circulating trypomastigotes
- The injected parasites multiply in the midgut of the insects as epimastigotes
- In the hindgut transform into infective metacyclic trypomastigotes that are discharged with the feces at the time of subsequent blood meal
- The parasites enter a variety of host cell types and multiply in the cytoplasm after transformation into amastigotes
- When multiplying amastigotes fill the host cell, they differentiate into trypomastigotes (occurring about 24 hours), and the cell ruptures
- The parasite released invades local tissues or spreads hematogenously to distinct sites, this initiating further cycles of multiplication

# Immune response

Model formulation Analysis of the general model Isolated action of the humoral response Isolated action of the cellular response Numerical simulation

- In experimental models, both CD4 and CD8 T cells have been shown to be important for resistance to *T. cruzi*
- Lysis of infected macrophages by CD8-positive, cytotoxic T cells may be an important mechanism of host defense
- CD4 T cells are also necessary to generate the specific antibody that contributes to parasite clearance
- Both types of T cells produce cytokines, principally interferon gamma (IFN- $\gamma$ ), capable of activating macrophages to kill intracellular amastigotes
- The pathogenicity of experimental *T. cruzi* infections has been linked to the induction of immunosuppressive cytokines by the parasite following infection, which inhibit the macrophage activation capability of IFN- $\gamma$
- Humoral (from activated B, plasma cells) and cellular (from CD8-positive, cytotoxic T cells) responses are promoted by the action of CD4 T cells in order to subdue *T. cruzi* infection

# Model formulation

# Assumptions

Model formulation Analysis of the general model Isolated action of the humoral response Isolated action of the cellular response Numerical simulation

- Cytokines act on activation and differentiation of T-cells into Th1 and Th2 by cytokines – Proportional to the number of *T. cruzi*
- We do not include every cell potentially involved (macrophages, NK cells, eosinophils, etc.) in the immune response
- Neither CD4 T cells as well as dendritic cells are considered
- The recruitment (migration) and proliferation of immune response cells are simply proportional to parasites quantity
- We assume that B and CD8 T cells are activated proportionally to the parasite circulating in the blood, as well as their proliferation
- Apoptosis is not considered (easy to be taken into account in numerical simulations)



# Variables

*Model formulation* *Analysis of the general model* *Isolated action of the humoral response* *Isolated action of the cellular response* *Numerical simulation*

- $T$  → Circulating trypanosomes in the blood stream
- $H$  → Susceptible host cells
- $I$  → Infected host cells
- $B$  → Inactivated B cells
- $B_a$  → Activated B cells – Plasma cells
- $C$  → Inactivated CD8 T cells
- $C_a$  → Activated CD8 T cells – Cytotoxic cells

# Parameters I

Model formulation Analysis of the general model Isolated action of the humoral response Isolated action of the cellular response Numerical simulation

- $\tau$  → Average number of *T. cruzi* released by one infected cell
- $n$  → Average number of *T. cruzi* penetrating one susceptible cell
- $\alpha$  → Infection rate
- $\lambda_H$  → Host cells replenishing rate
- $\lambda_B$  → B cells replenishing rate (bone marrow)
- $\lambda_C$  → CD8 T cells replenishing rate
- $\mu_T$  → *T. cruzi* mortality rate
- $\mu_H$  ( $\mu_I$ ) → Susceptible cells mortality rate (infected cells)
- .....

# Parameters II

Model formulation Analysis of the general model Isolated action of the humoral response Isolated action of the cellular response Numerical simulation

- .....
- $\mu_B$  ( $\mu_B^d$ )  $\rightarrow$  B cells mortality rate (additional)
- $\mu_C$  ( $\mu_C^d$ )  $\rightarrow$  CD8 T cells mortality rate (additional)
- $\gamma_B$   $\rightarrow$  B cells activation rate
- $\gamma_C$   $\rightarrow$  CD8 T cells activation rate
- $\delta_B$   $\rightarrow$  Plasma cells proliferation rate
- $\delta_C$   $\rightarrow$  Cytotoxic cells proliferation rate
- $\beta$   $\rightarrow$  Cytotoxic response rate
- $\varepsilon$   $\rightarrow$  Humoral response rate

# Dynamical system

Model formulation Analysis of the general model Isolated action of the humoral response Isolated action of the cellular response Numerical simulation

$$\left\{ \begin{array}{l} \frac{d}{dt} T = \tau (\mu_H + \mu_I) I - \mu_T T - n\alpha TH - \varepsilon B_a T \\ \frac{d}{dt} H = \lambda_H - \mu_H H - \alpha TH \\ \frac{d}{dt} I = \alpha TH - (\mu_H + \mu_I) I - \beta I C_a \\ \frac{d}{dt} B = \lambda_B - \mu_B B - \gamma_B BT \\ \frac{d}{dt} B_a = \gamma_B BT - (\mu_B + \mu_B^d) B_a + \delta_B B_a T \\ \frac{d}{dt} C = \lambda_C - \mu_C C - \gamma_C CT \\ \frac{d}{dt} C_a = \gamma_C CT - (\mu_C + \mu_C^d) C_a + \delta_C C_a T \end{array} \right.$$

- Simple, but has seven equations!!

# Analysis of the general model

# Trivial equilibrium point

Model formulation Analysis of the general model Isolated action of the humoral response Isolated action of the cellular response Numerical simulation

- $P^0 = (0, H_0, 0, B_0, 0, C_0, 0)$ , where  $H_0$ ,  $B_0$  and  $C_0$  are

$$\begin{cases} H_0 &= \frac{\lambda_H}{\mu_H} \\ B_0 &= \frac{\lambda_B}{\mu_B} \\ C_0 &= \frac{\lambda_C}{\mu_C} \end{cases}$$

- Populational average amount of host cells and immune system cells found in an individual free of *T. cruzi* infection
- The trivial equilibrium  $P^0$  is locally asymptotically stable (LAS) when  $\alpha < \alpha_0$ , where

$$\alpha_0 = \frac{\mu_T \mu_H}{(\tau - n) \lambda_H} = \frac{\mu_T}{(\tau - n) H_0}$$

- Global stability ( $\alpha \leq \alpha_0$ ) using Lyapunov function  $V = \tau I + T$

# Non-trivial equilibrium point

Model formulation Analysis of the general model Isolated action of the humoral response Isolated action of the cellular response Numerical simulation

## ■ Dimensionless parameters:

$$\left\{ \begin{array}{llll} \lambda'_H = \frac{\lambda_H}{\mu_H} = H_0; & \lambda'_B = \frac{\lambda_B}{\mu_B} = B_0; & \lambda'_C = \frac{\lambda_C}{\mu_C} = C_0; & \\ \alpha' = \frac{\alpha}{\mu_H}; & \alpha'_0 = \frac{\alpha_0}{\mu_H}; & \beta' = \frac{\beta}{\mu_H + \mu_I}; & \varepsilon' = \frac{\varepsilon}{\mu_T}; \\ \gamma'_B = \frac{\gamma_B}{\mu_B}; & \gamma'_C = \frac{\gamma_C}{\mu_C}; & \delta'_B = \frac{\delta_B}{\mu_B + \mu_B^d}; & \delta'_C = \frac{\delta_C}{\mu_C + \mu_C^d}; \\ \mu_{Bd} = \frac{\mu_B}{\mu_B + \mu_B^d}; & \mu_{Cd} = \frac{\mu_C}{\mu_C + \mu_C^d}; & \mu_{HT} = \frac{\mu_H}{\mu_T}; & \mu_{HI} = \frac{\mu_H}{\mu_H + \mu_I} \end{array} \right.$$

# Non-trivial equilibrium point

Model formulation Analysis of the general model Isolated action of the humoral response Isolated action of the cellular response Numerical simulation

- $P^*$  has coordinates:

$$\left\{ \begin{array}{l} \bar{H} = \frac{H_0}{1 + \alpha \bar{T}} \\ \bar{I} = \frac{\mu_{HI} \alpha H_0 \bar{T}}{(1 + \alpha \bar{T})(1 + \beta \bar{C}_a)} \\ \bar{B} = \frac{B_0}{1 + \gamma_B \bar{T}} \\ \bar{B}_a = \frac{\mu_{Bd} \gamma_B B_0 \bar{T}}{(1 + \gamma_B \bar{T})(1 - \delta_B \bar{T})} \\ \bar{C} = \frac{C_0}{1 + \gamma_C \bar{T}} \\ \bar{C}_a = \frac{\mu_{Cd} \gamma_C C_0 \bar{T}}{(1 + \gamma_C \bar{T})(1 - \delta_C \bar{T})} \end{array} \right.$$

- $\bar{T}$  is the positive solution of the equation

$$f(\bar{T}) = \bar{T} \times g(\bar{T})$$



# Non-trivial equilibrium point

Model formulation   Analysis of the general model   Isolated action of the humoral response   Isolated action of the cellular response   Numerical simulation

- The fifth degree  $f(\bar{T})$  and third degree  $g(\bar{T})$  polynomials are:

$$\begin{cases} f(\bar{T}) &= \left[ \left( \frac{\alpha}{\alpha_0} - 1 \right) - \alpha \bar{T} \right] (1 - \delta_B \bar{T}) (1 - \delta_C \bar{T}) (1 + \gamma_B \bar{T}) (1 + \gamma_C \bar{T}) \\ g(\bar{T}) &= \beta \gamma_C C_0 (1 - \delta_B \bar{T}) (1 + \gamma_B \bar{T}) (1 + \alpha \bar{T}) + \varepsilon \gamma_B B_0 (1 - \delta_C \bar{T}) (1 + \alpha \bar{T}) \\ &\quad + \beta \varepsilon \gamma_C C_0 \gamma_B B_0 (1 + \alpha \bar{T}) \bar{T} + n \alpha \beta \mu_{HT} \gamma_C C_0 H_0 (1 - \delta_B \bar{T}) (1 + \alpha \bar{T}) \end{cases}$$

- $P^*$  to be biologically feasible, by inspecting  $\bar{B}_a$  and  $\bar{C}_a$ , must obey:

$$\begin{cases} \bar{T} < T_B = \frac{1}{\delta_B} \\ \bar{T} < T_C = \frac{1}{\delta_C} \end{cases}$$

- $\alpha > \alpha_0$  – A unique positive solution  $\bar{T}$  in the range  $(0, \delta)$ , with  $\delta = \min \{ (\alpha - \alpha_0) / \alpha \alpha_0, 1 / \delta_B, 1 / \delta_C \}$
- Two special cases – Humoral and cellular responses acting isolated

# Local stability

- Characteristic equation is

$$h_1(\beta, \varepsilon) + \beta \times h_2 + \varepsilon \times h_3 = 0,$$

- The functions  $h_1(\beta, \varepsilon)$ ,  $h_2$  and  $h_3$  are

$$\left\{ \begin{array}{l} h_1(\beta, \varepsilon) = (\mu_C + \mu_C^d - \delta_C \bar{T} + \psi) (\mu_C + \gamma_C \bar{T} + \psi) (\mu_B + \mu_B^d - \delta_B \bar{T} + \psi) (\mu_B + \gamma_B \bar{T} + \psi) [\alpha \bar{T} (\mu_H + \mu_I + \beta \bar{C}_a + \psi) (\mu_T + \varepsilon \bar{B}_a + \psi) + (\psi + \mu_H + \mu_I + \mu_T + \varepsilon \bar{B}_a + \beta \bar{C}_a + n \alpha \bar{H}) (\mu_H + \psi) \psi] \\ h_2 = \bar{I} \tau (\mu_H + \mu_I) (\mu_B + \mu_B^d - \delta_B \bar{T} + \psi) (\mu_B + \gamma_B \bar{T} + \psi) (\mu_H + \alpha \bar{T} + \psi) [(\gamma_B \bar{B} + \delta_B \bar{B}_a) (\mu_B + \psi) + \gamma_B \delta_B \bar{B}_a \bar{T}] \\ h_3 = \bar{T} (\mu_C + \mu_C^d - \delta_C \bar{T} + \psi) (\mu_C + \gamma_C \bar{T} + \psi) (\mu_H + \mu_I + \beta \bar{C}_a + \psi) (\mu_H + \alpha \bar{T} + \psi) [(\gamma_C \bar{C} + \delta_C \bar{C}_a) (\gamma_C + \psi) + \gamma_C \delta_C \bar{C}_a \bar{T}] \end{array} \right.$$

# Isolated action of the humoral response

# Case 1 – Humoral response only

Model formulation Analysis of the general model Isolated action of the humoral response Isolated action of the cellular response Numerical simulation

- African trypanosomes do not have an intracellular form and multiply as trypomastigotes that circulate in the mammalian blood stream and other extracellular spaces
- Humoral response acting isolated –  $\beta = 0$

$$\left\{ \begin{array}{l} \frac{d}{dt}T = \tau\alpha TH - \mu_T T - \varepsilon B_a T \\ \frac{d}{dt}H = \lambda_H - \mu_H H - \alpha TH \\ \frac{d}{dt}B = \lambda_B - \mu_B B - \gamma_B BT \\ \frac{d}{dt}B_a = \gamma_B BT - (\mu_B + \mu_B^d) B_a + \delta_B B_a T \end{array} \right.$$

# Non-trivial equilibrium point

Model formulation Analysis of the general model Isolated action of the humoral response Isolated action of the cellular response Numerical simulation

- $P^*$  has coordinates:

$$\begin{cases} \bar{H} &= \frac{H_0}{1 + \alpha\bar{T}} \\ \bar{B} &= \frac{B_0}{1 + \gamma_B\bar{T}} \\ \bar{B}_a &= \frac{\mu_{Bd}\gamma_B B_0\bar{T}}{(1 - \delta_B\bar{T})(1 + \gamma_B\bar{T})}, \end{cases}$$

- $\bar{T}$  is solution of the equation

$$\frac{\left(\frac{\alpha}{\alpha_0} - 1\right) - \alpha\bar{T}}{1 + \alpha\bar{T}} = \frac{\varepsilon\gamma_B B_0\bar{T}}{(1 - \delta_B\bar{T})(1 + \gamma_B\bar{T})}.$$

- All equations can be retrieved from general model by letting  $\beta = 0$  and  $n = 0$

# Local stability

- The characteristic equation is

$$0 = \varepsilon \bar{T} (\mu_H + \alpha \bar{T} + \psi) [\gamma_B \bar{B} (\mu_B + \psi) + \delta_B \bar{B}_a (\mu_B + \gamma_B \bar{T} + \psi)] \\ + (\mu_B + \mu_B^d - \delta_B \bar{T} + \psi) (\mu_B + \gamma_B \bar{T} + \psi) \\ \times [\alpha \bar{T} (\mu_T + \varepsilon \bar{B}_a + \psi) + (\mu_H + \psi) \psi].$$

- Written as  $\psi^4 + \sum_{i=1}^4 a_i \psi^{4-i} = 0$ , with the coefficients  $a_i$ :

$$\left\{ \begin{array}{l} a_1 = (\mu_H + \alpha \bar{T}) + (\mu_B + \gamma_B \bar{T}) + (\mu_B + \mu_B^d - \delta_B \bar{T}) \\ a_2 = (\mu_B + \mu_B^d - \delta_B \bar{T}) [(\mu_H + \alpha \bar{T}) + (\mu_B + \gamma_B \bar{T})] + (\mu_H + \alpha \bar{T}) (\mu_B + \mu_B^d - \delta_B \bar{T}) \\ \quad + \alpha \bar{T} (\mu_T + \varepsilon \bar{B}_a) + \varepsilon \bar{T} (\gamma_B \bar{B} + \delta_B \bar{B}_a) \\ a_3 = (\mu_H + \alpha \bar{T}) (\mu_B + \gamma_B \bar{T}) (\mu_B + \mu_B^d - \delta_B \bar{T}) + [(\mu_B + \gamma_B \bar{T}) + (\mu_B + \mu_B^d - \delta_B \bar{T})] \\ \quad \times \alpha \bar{T} (\mu_T + \varepsilon \bar{B}_a) + \varepsilon \bar{T} (\gamma_B \bar{B} + \delta_B \bar{B}_a) [(\mu_H + \alpha \bar{T}) + \mu_B] + \varepsilon \gamma_B \delta_B \bar{T} \bar{B}_a \\ a_4 = \alpha \bar{T} (\mu_T + \varepsilon \bar{B}_a) (\mu_B + \gamma_B \bar{T}) (\mu_B + \mu_B^d - \delta_B \bar{T}) + \varepsilon \bar{T} (\mu_H + \alpha \bar{T}) \\ \quad \times [\mu_B (\gamma_B \bar{B} + \delta_B \bar{B}_a) + \gamma_B \delta_B \bar{T} \bar{B}_a]. \end{array} \right.$$

- All the Routh-Hurwitz conditions are satisfied: (1)  $a_1 > 0$ , (2)  $a_3 > 0$ , (3)  $a_4 > 0$  and (4)  $a_1 a_2 a_3 > a_3^2 + a_1^2 a_4$

# Isolated action of the cellular response

## Case 2 – Cellular response only

Model formulation Analysis of the general model Isolated action of the humoral response Isolated action of the cellular response Numerical simulation

- Cellular response acting isolated –  $\varepsilon = 0$

$$\left\{ \begin{array}{l} \frac{d}{dt} T = \tau (\mu_H + \mu_I) I - \mu_T T \\ \frac{d}{dt} H = \lambda_H - \mu_H H - \alpha T H \\ \frac{d}{dt} I = \alpha T H - (\mu_H + \mu_I) I - \beta I C_a \\ \frac{d}{dt} C = \lambda_C - \mu_C C - \gamma_C C T \\ \frac{d}{dt} C_a = \gamma_C C T - (\mu_C + \mu_C^d) C_a + \delta_C C_a T \end{array} \right.$$



# Non-trivial equilibrium point

Model formulation   Analysis of the general model   Isolated action of the humoral response   Isolated action of the cellular response   Numerical simulation

- $P^*$  has coordinates:

$$\left\{ \begin{array}{l} \bar{H} = \frac{H_0}{1 + \alpha\bar{T}} \\ \bar{I} = \frac{\mu_{HI}\alpha H_0\bar{T}}{(1 + \alpha\bar{T})(1 + \beta\bar{C}_a)} \\ \bar{C} = \frac{C_0}{1 + \gamma_C\bar{T}} \\ \bar{C}_a = \frac{\mu_{Cd}\gamma_C C_0\bar{T}}{(1 - \delta_C\bar{T})(1 + \gamma_C\bar{T})}, \end{array} \right.$$

- $\bar{T}$  is solution of the equation

$$\frac{\left(\frac{\alpha}{\alpha_0} - 1\right) - \alpha\bar{T}}{1 + \alpha\bar{T}} = \frac{\beta\gamma_C C_0\bar{T}}{(1 - \delta_C\bar{T})(1 + \gamma_C\bar{T})}.$$

- All equations can be retrieved from general model by letting  $\varepsilon = 0$  and  $n = 0$  (or,  $\tau \gg n$ )

# Local stability

Model formulation Analysis of the general model Isolated action of the humoral response Isolated action of the cellular response Numerical simulation

- The characteristic equation is

$$0 = (\mu_C + \mu_C^d - \delta_C \bar{T} + \psi) (\mu_C + \gamma_C \bar{T} + \psi) [\alpha \bar{T} (\mu_H + \mu_I + \beta \bar{C}_a + \psi) (\mu_H + \mu_I + \beta \bar{C}_a) (\mu_H + \psi) \psi] + \beta \bar{I} \tau (\mu_H + \mu_I) (\mu_H + \alpha \bar{T} + \psi) [(\gamma_C \bar{C} + \delta_C \bar{C}_a) (\gamma_C + \psi) + \gamma_C \delta_C \bar{C}_a]$$

- The Routh-Hurwitz conditions of  $\psi^5 + \sum_{i=1}^5 a_i \psi^{5-i} = 0$  are: (1)  $a_i > 0$  ( $i = 1, 2, 3, 4, 5$ ), (2)  $a_1 a_2 a_3 > a_3^2 + a_1^2 a_4$ , and (3)  $(a_1 a_4 - a_5) (a_1 a_2 a_3 - a_3^2 - a_1^2 a_4) > a_5 (a_1 a_2 - a_3)^2 + a_1 a_5^2$
- The condition (3) can be written as  $a_3 (a_1 a_2 - a_3) > a_1^2 a_4$ , and, when all coefficients are positive ( $a_i > 0$ , for  $i = 1, \dots, 5$ ), then an implicit condition is  $a_1 a_2 > a_3$
- This is not satisfied for a sufficiently higher values of  $\delta_C$ . Limit cycles appear

# Numerical simulations

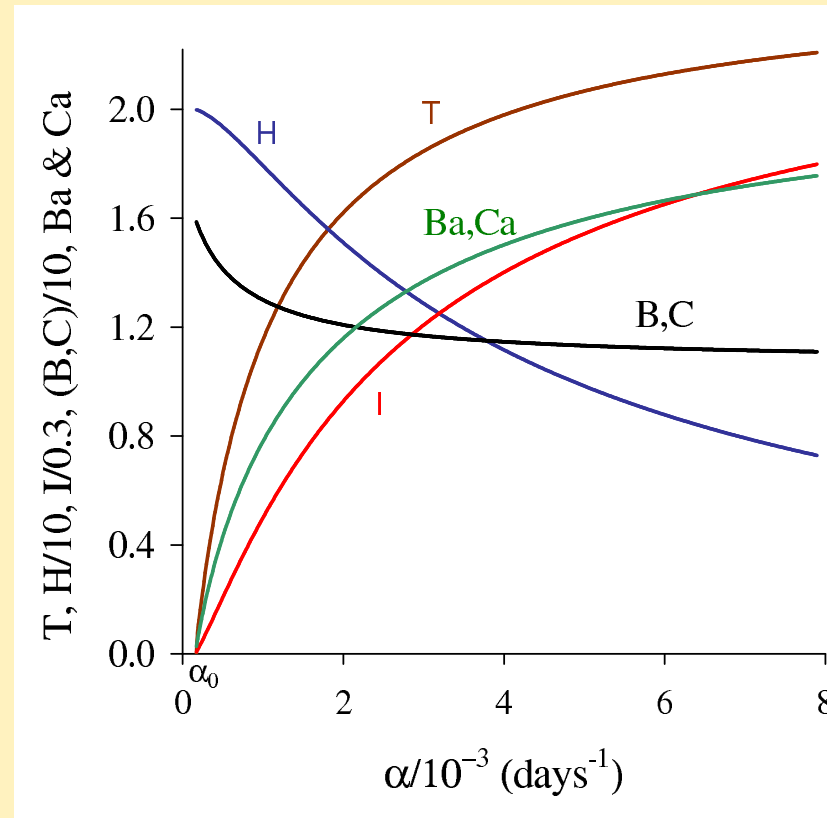
# Values of parameters

Model formulation Analysis of the general model Isolated action of the humoral response Isolated action of the cellular response Numerical simulation

- $\tau \rightarrow 20$
- $n \rightarrow 1$
- $\alpha \rightarrow 3 \times \alpha_0$
- $\lambda_H \rightarrow 0.2$
- $\lambda_B \rightarrow 0.8$
- $\lambda_C \rightarrow 0.8$
- $\mu_T \rightarrow 0.06$
- $\mu_H(\mu_I) \rightarrow 0.01 (0.05)$
- $\mu_B(\mu_B^d) \rightarrow 0.05 (0.2)$
- $\mu_C(\mu_C^d) \rightarrow 0.05 (0.2)$
- $\gamma_B \rightarrow 0.01$
- $\gamma_C \rightarrow 0.01$
- $\delta_B \rightarrow 0.05$
- $\delta_C \rightarrow 0.05$
- $\beta \rightarrow 0.1$
- $\varepsilon \rightarrow 0.1$

# Bifurcation diagram – I

Model formulation Analysis of the general model Isolated action of the humoral response Isolated action of the cellular response Numerical simulation

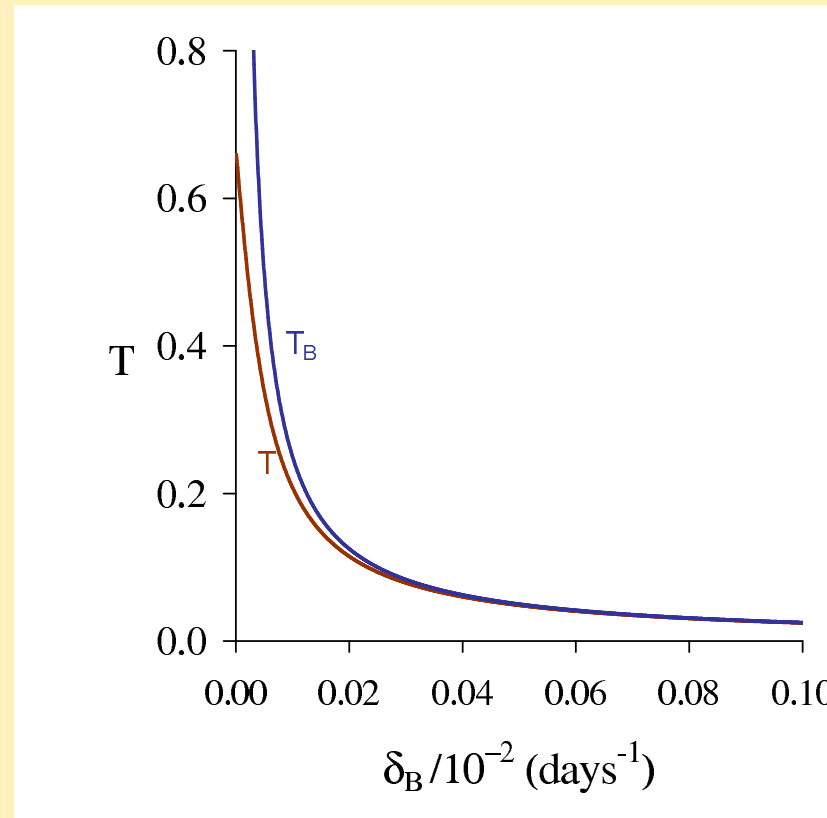


The bifurcation diagram of  $\bar{T}$ , plus all other variables, varying  $\alpha$ . A unique positive solution

The scales of vertical and horizontal axes must be multiplied by the factors shown in the legends to obtain the actual values (for instance,  $\bar{H}$  must be multiplied by the factor 10)

# Bifurcation diagram – II

Model formulation Analysis of the general model Isolated action of the humoral response Isolated action of the cellular response Numerical simulation

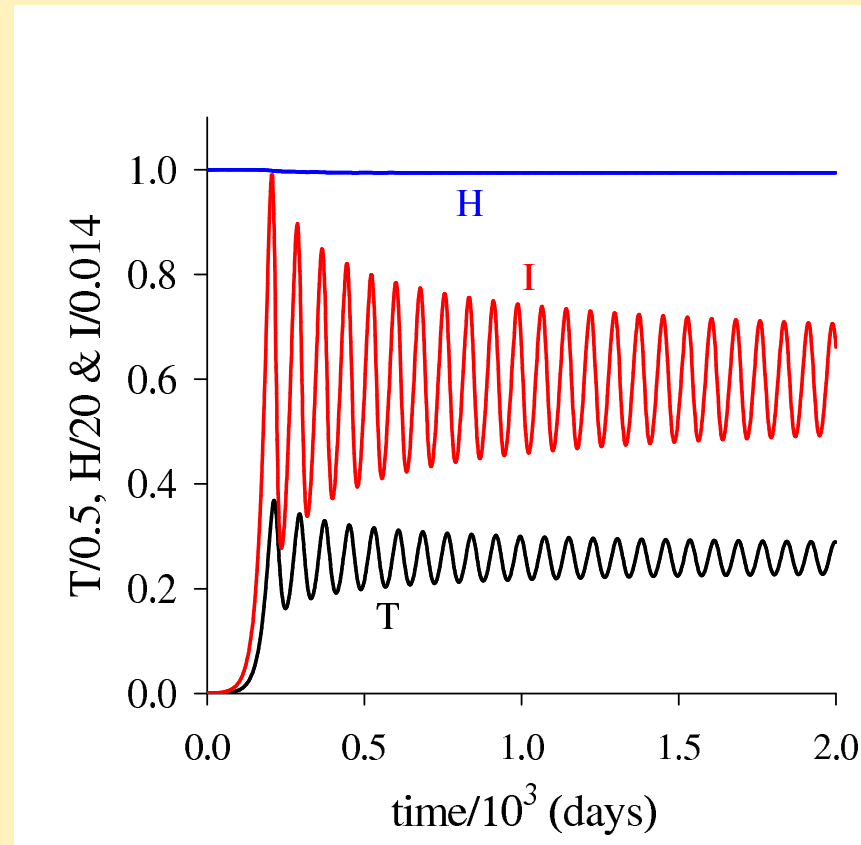


The bifurcation diagram of  $\bar{T}$  and the upper bound  $T_B$  as function of  $\delta_B$ . A unique positive solution

The scales of vertical and horizontal axes must be multiplied by the factors shown in the legends to obtain the actual values (for instance,  $\bar{H}$  must be multiplied by the factor 10)

# Dynamical trajectories – Ia

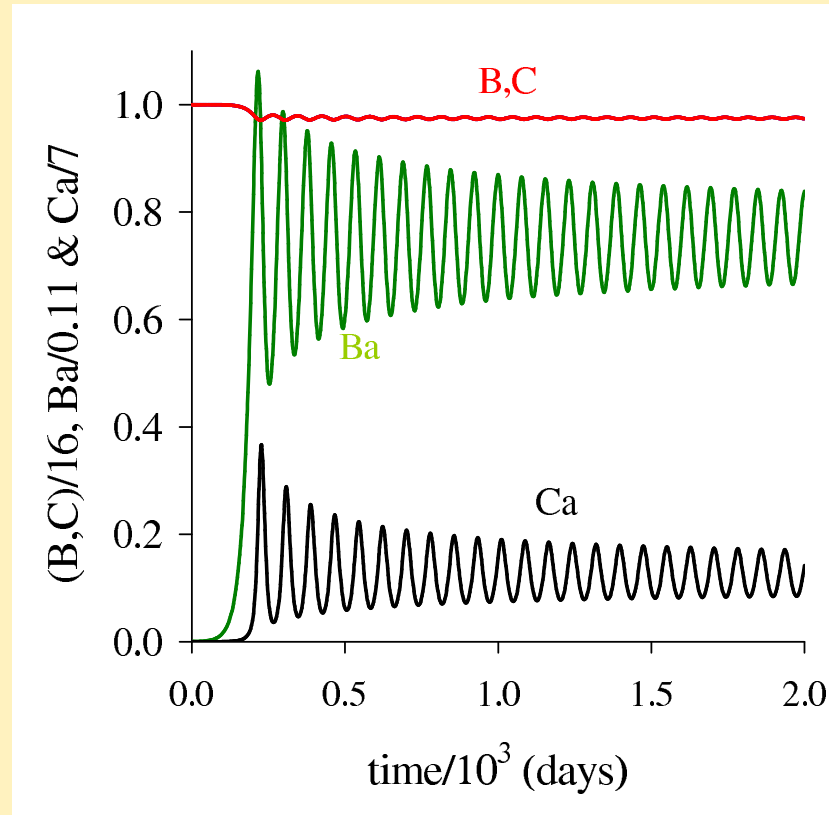
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Dynamical trajectories of *T. cruzi* infection, except  $\delta_C = 1.75$ : The interaction of parasite with host cells ( $T$ ,  $H$  and  $I$ ). Regular oscillations occur. The scales of vertical and horizontal axes must be multiplied by the factors shown in the legends to obtain the actual values.

# Dynamical trajectories – Ib

Model formulation Analysis of the general model Isolated action of the humoral response Isolated action of the cellular response Numerical simulation

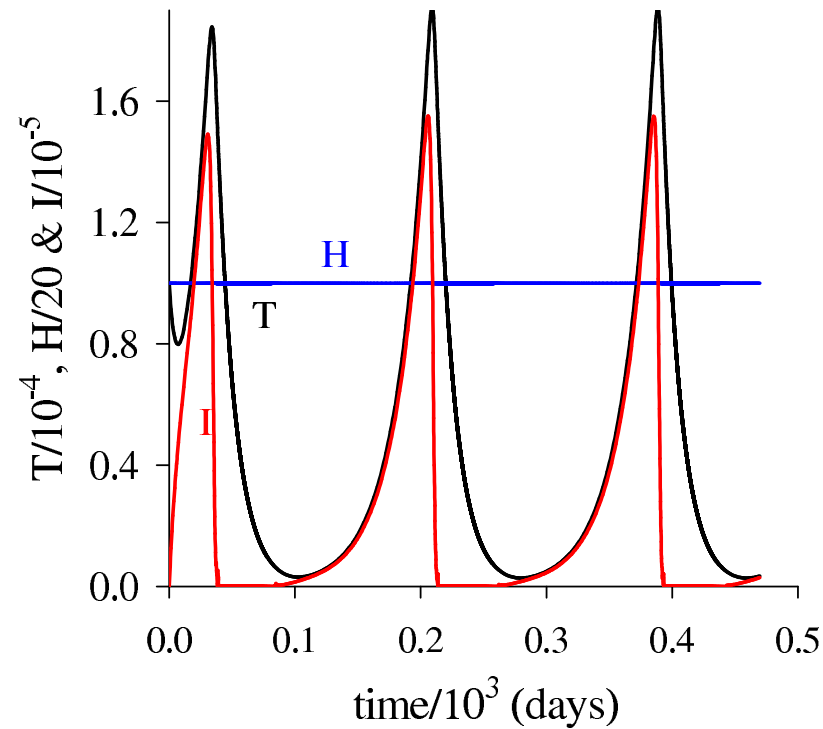


Dynamical trajectories of *T. cruzi* infection, except  $\delta_C = 1.75$ : The immune response cells ( $B$ ,  $B_a$ ,  $C$  and  $C_a$ ). Regular oscillations occur  
The scales of vertical and horizontal axes must be multiplied by the factors shown in the legends to obtain the actual values



# Dynamical trajectories – IIa

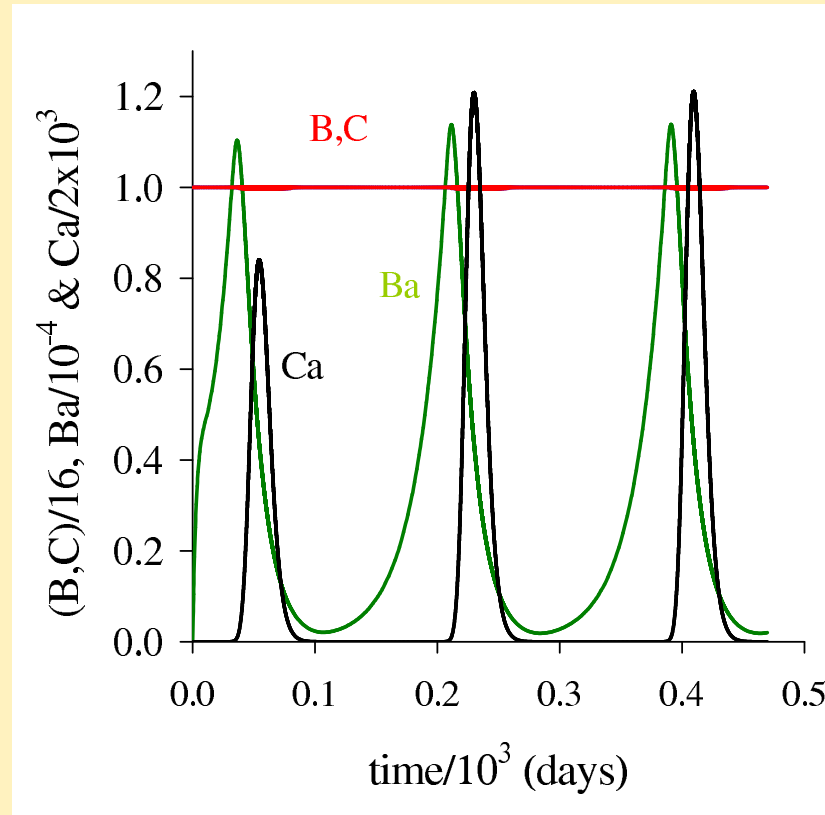
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Dynamical trajectories of *T. cruzi* infection, except  $\delta_C = 5 \times 10^3$ : The interaction of parasite with host cells ( $T$ ,  $H$  and  $I$ ). Regular oscillations occur. The scales of vertical and horizontal axes must be multiplied by the factors shown in the legends to obtain the actual values.

# Dynamical trajectories – IIb

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Dynamical trajectories of *T. cruzi* infection, except  $\delta_C = 5 \times 10^3$ : The immune response cells ( $B$ ,  $B_a$ ,  $C$  and  $C_a$ ). Regular oscillations occur. The scales of vertical and horizontal axes must be multiplied by the factors shown in the legends to obtain the actual values.

# Conclusion

# Conclusion

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- The joint action of humoral and immune responses control *T. cruzi* infection. In general, parasitemia is contained at a lower but persistent level by immune responses, which can fluctuate in a weak humoral response. The model showed that sustained oscillations occurred when humoral response is less strong than cellular response
- Cellular response seems to be more effective (by killing infected cells) than humoral response. But the latter is important to avoid sustained oscillations
- After a strong immune response, effector cells must commit suicide in order to avoid self damage
- The model showed that immune response alone was not able to fade out *T. cruzi* infection, when the reproducibility of this parasite is greater than 1 ( $R_0 > 1$ ). Biologically, however, we can define a critical level of circulating parasites below which they can be considered eliminated

**Thank You**