Stochastic Model of the Dynamics of Chagas Disease in Urban Scenarios

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Abstract

Chagas disease (American Trypanosomiasis) is one of the most significant health problems in Latin America, both for its high morbidity/mortality rate and for its difficult control because of the natural transmission through hematophagus triatomine insects. As a consequence of migration waves in recent decades, the infection has considerably expanded from rural endemic areas to urban centers. The incorporation of infected individuals into cities, most of whom are asymptomatic and unaware of their infected condition, increases the risk of congenital or transfusional transmission. The so-called *urban Chagas*, which involves only the human population, is an emerging problem in American, European, Australian and Japanese cities. The objectives of this work were to develop and apply a stochastic model that will allow researchers to explain the dynamics of the disease in urban scenarios and thus obtain a higher degree of approximation to the real sanitary situation. This model was formulated as a continuous-time Markov chain. We deduced a stochastic differential equation system by using the method of generating functions, using expressions of conditional probabilities. This system provides the expected numbers of individuals in each stage of the disease. Based on official data and laboratory and clinical information, we run a simulation in Buenos Aires city (Argentina).

Keywords: expected number, generating function, Markov process, temporal dynamics.

1.Introduction

Chagas disease, or American Trypanosomiasis, is caused by the protozoan *Trypanosoma cruzi* (Kinestoplastida, Trypanosomatidae). The incorporation into cities of infected individuals -most asymptomatic and unaware of their infected condition- increases the risk of spreading the infection. The so-called *urban Chagas*, which involves only inter-human transmission – mainly by the congenital and transfusional routes- is an emerging problem in Latin American cities and in more than a dozen countries in America, Europe, Australia and Japan (WHO, 2010).

The natural evolution of the disease has been divided into three stages: acute, chronic indeterminate and chronic with determinate pathology (WHO, 2002; Storino, 2010). Individuals in the acute stage show high peripheral blood parasitemia, but, in most cases, the symptoms are nonspecific and disappear spontaneously after two months. Therefore, almost all the infected individuals enter the chronic indeterminate period, which may last for 20-30 years or even for a lifetime. Detection of infection at this stage is limited because it is characterized by being asymptomatic. It is estimated that one-third of these individuals evolve towards the chronic with determinate pathology stage, which affects them in the productive stage of their lives, with high morbidity and mortality. The antiparasitic drugs available are used mostly until the first years of the chronic indeterminate stage because evidence about its action at the chronic with pathology stage is controversial (Muñoz et al. 2011).

The main objetive of this work was to develop a stochastic model for the dynamics of Chagas disease in urban scenarios, which can be operated to describe and forecast the spread of the infection. The model proposed was applied in a real scenario. This work is a continuation of two graduate theses (Fabrizio, 2009, 2011)

2. Materials and Methods

The progress of the disease over time was modeled as a continuous-time Markov chain because, when the present stage is known, the probability of any future behavior of the process is not altered by additional knowledge about the past behavior (Bharucha-Reid, 1960; Karlin, 1975; Feller, 1980). Thus, the behavior in time t depends only on the behavior in the preceding time $t - h$.

The stage and the number of susceptible individuals and individuals in the acute, chronic indeterminate and chronic with determinate pathology stages were denoted $H_S(t) = H_S$, $H_A(t) = H_A$, $H_I(t) = H_I$, and $H_P(t) = H_P$, respectively. The number of individuals in each stage was considered as a random variable, because the dispersion behaves essentially as a stochastic process. The model is based on the following assumptions: (i) migratory movements are generated by individuals in any stage (except by those in the acute stage because of the short duration of the stage) at constant levels; (ii) birth rates of susceptible babies are directly proportional to H_S , H_I, and H_P and birth rates of babies infected with *T. cruzi* are directly proportional to infected individuals in both chronic stages; birth to mothers in the acute stage is not considered because of the short duration of the stage; iii) cure rates of individuals H_A and H_I, rates of evolution of the infection and mortality rates are proportional to the number of individuals in each outlet compartment; iv) the rates of transmission through blood transfusion are directly proportional to the number of individuals in each stage of the infection. Table 1 presents the events and their rates.

Thus, we define, for example, the probability of birth of an infected individual in an infinitesimal time $(t + h)$ as

$$P\left\{\begin{array}{l} H_S(t+h)=H_S, H_A(t+h)=H_A+1, H_I(t+h)=H_I, H_P(t+h)=H_P / H_S(t)=H_S, \\ H_A(t)=H_A, H_I(t)=H_I, H_P(t)=H_P \end{array}\right\}$$
$$= h\,\beta_{AI}\,H_I(t) + h\,\beta_{AP}H_P(t) + o(h)$$

We considered $P\{two\ or\ more\ changes\ in\ (t,t+h)\} = o(h)$, so multiple events occur with negligible probability and can be ignored. In all the cases, $o(h)$ is an infinitesimal of an order lower than h, i.e., $\lim_{h\to 0}\frac{o(h)}{h} = 0$. The probability that the system is in any stage at the time $t + h$ is the sum of the probabilities of each of the processes postulated in Table 1. Using conditional probabilities, we obtain the following expression:

$$P_{H_S,H_A,H_I,H_P}(t+h) =$$
$$P\left\{\begin{array}{l} H_S(t+h)=H_S, H_A(t+h)=H_A, H_I(t+h)=H_I, H_P(t+h)=H_P / H_S(t)=H_S-1, H_A(t)=H_A, \\ H_I(t)=H_I, H_P(t)=H_P \end{array}\right\}.$$
$$P_{H_S-1,H_A,H_I,H_P}(t) +$$
$$P\left\{\begin{array}{l} H_S(t+h)=H_S, H_A(t+h)=H_A, H_I(t+h)=H_I, H_P(t+h)=H_P / H_S(t)=H_S-1, H_A(t)=H_A+1, \\ H_I(t)=H_I, H_P(t)=H_P \end{array}\right\}.$$
$$P_{H_S-1,H_A+1,H_I,H_P}(t) +$$
$$P\left\{\begin{array}{l} H_S(t+h)=H_S, H_A(t+h)=H_A, H_I(t+h)=H_I, H_P(t+h)=H_P / H_S(t)=H_S-1, H_A(t)=H_A, \\ H_I(t)=H_I+1, H_P(t)=H_P \end{array}\right\}.$$
$$P_{H_S-1,H_A,H_I+1,H_P}(t) +$$
$$P\left\{\begin{array}{l} H_S(t+h)=H_S, H_A(t+h)=H_A, H_I(t+h)=H_I, H_P(t+h)=H_P / H_S(t)=H_S+1, H_A(t)=H_A-1, \\ H_I(t)=H_I, H_P(t)=H_P \end{array}\right\}.$$
$$P_{H_S+1,H_A-1,H_I,H_P}(t) +$$
$$P\left\{\begin{array}{l} H_S(t+h)=H_S, H_A(t+h)=H_A, H_I(t+h)=H_I, H_P(t+h)=H_P / H_S(t)=H_S+1, H_A(t)=H_A, \\ H_I(t)=H_I, H_P(t)=H_P \end{array}\right\}.$$
$$P_{H_S+1,H_A,H_I,H_P}(t) +$$

$$P\left\{\begin{matrix} H_S(t+h)=H_S, H_A(t+h)=H_A, H_I(t+h)=H_I, H_P(t+h)=H_P / H_S(t)=H_S, H_A(t)=H_A-1, \\ H_I(t)=H_I, H_P(t)=H_P \end{matrix}\right\}.$$

$$P_{H_S,H_A-1,H_I,H_P}(t)+$$

$$P\left\{\begin{matrix} H_S(t+h)=H_S, H_A(t+h)=H_A, H_I(t+h)=H_I, H_C(t+h)=H_C / H_S(t)=H_S, H_A(t)=H_A+1, \\ H_I(t)=H_I-1, H_P(t)=H_P \end{matrix}\right\}.$$

$$P_{H_S,H_A+1,H_I-1,H_P}(t)+$$

$$P\left\{\begin{matrix} H_S(t+h)=H_S, H_A(t+h)=H_A, H_I(t+h)=H_I, H_P(t+h)=H_P / H_S(t)=H_S, H_A(t)=H_A+1, \\ H_I(t)=H_I, H_P(t)=H_P \end{matrix}\right\}.$$

$$P_{H_S,H_A+1,H_I,H_P}(t)+$$

$$P\left\{\begin{matrix} H_S(t+h)=H_S, H_A(t+h)=H_A, H_I(t+h)=H_I, H_P(t+h)=H_P / H_S(t)=H_S, H_A(t)=H_A, \\ H_I(t)=H_I-1, H_P(t)=H_P \end{matrix}\right\}.$$

$$P_{H_S,H_A,H_I-1,H_P}(t)+$$

$$P\left\{\begin{matrix} H_S(t+h)=H_S, H_A(t+h)=H_A, H_I(t+h)=H_I, H_P(t+h)=H_P / H_S(t)=H_S, H_A(t)=H_A, \\ H_I(t)=H_I+1, H_P(t)=H_P-1 \end{matrix}\right\}.$$

$$P_{H_S,H_A,H_I+1,H_P-1}(t)+$$

$$P\left\{\begin{matrix} H_S(t+h)=H_S, H_A(t+h)=H_A, H_I(t+h)=H_I, H_P(t+h)=H_P / H_S(t)=H_S, H_A(t)=H_A, \\ H_I(t)=H_I+1, H_P(t)=H_P \end{matrix}\right\}.$$

$$P_{H_S,H_A,H_I+1,H_P}(t)+$$

$$P\left\{\begin{matrix} H_S(t+h)=H_S, H_A(t+h)=H_A, H_I(t+h)=H_I, H_P(t+h)=H_P / H_S(t)=H_S, H_A(t)=H_A, \\ H_I(t)=H_I, H_P(t)=H_P-1 \end{matrix}\right\}.$$

$$P_{H_S,H_A,H_I,H_P-1}(t)+$$

$$P\left\{\begin{matrix} H_S(t+h)=H_S, H_A(t+h)=H_A, H_I(t+h)=H_I, H_P(t+h)=H_P / H_S(t)=H_S, H_A(t)=H_A, \\ H_I(t)=H_I, H_P(t)=H_P+1 \end{matrix}\right\}.$$

$$P_{H_S,H_A,H_I,H_P+1}(t)+$$

$$\{1-[\omega_{Si}+\beta_{SS}H_S(t)+\beta_{SI}H_I(t)+\beta_{SP}H_P(t)+\gamma_{AS}H_A(t)+\gamma_{IS}H_I(t)+\gamma_{SATA}H_A(t)+\gamma_{SATI}H_I(t)$$
$$+\gamma_{SATP}(H_S,H_A,H_I,H_P,t)+\omega_{Se}+\delta_S H_S(t)+\beta_{AI}H_I(t)+\beta_{AP}H_P(t)+\gamma_{AI}H_A(t)+\delta_A H_A(t)$$
$$+\omega_{Ii}+\gamma_{IP}H_I(t)+\omega_{Ie}+\delta_I H_I(t)+\omega_{Pi}+\omega_{Pe}+\delta_P H_P(t)]h\}.P_{H_S,H_A,H_I,H_P}(t)+o(h)$$

Table 1. Estimations of the parameters and references used for their calculation

Event	Parameter	References	Estimation
Immigration of H_S individuals	ω_{Si}	Censo Nacional de Población, Hogares y Vivienda (2001), WHO (2006)	132.051041
Birth of an H_S individual to an H_S mother	β_{SS}	Ministerio de Salud de la Nación (2009)	0.000041
Birth of an H_S individual to an H_I mother	β_{SI}	Rissio et al. (2009); Freilij et al. (2010)	0.000038
Birth of an H_S individual to an H_P mother	β_{SP}	Rissio et al. (2009); Freilij et al. (2010)	0.000019
Cure of an H_A individual	γ_{AS}	WHO (2002); Rissio et al. (2009); Freilij et al. (2010)	0.000667
Cure of an H_I individual	γ_{IS}	Andrade et al. (1996); Sosa-Estani et al. (1998); Rissio et al. (2009)	0.000018
Evolution of an H_S to an H_A individual by blood transfusion from an H_A individual	γ_{SATA}	Gobierno de la Ciudad de Buenos Aires (2012); WHO (2002)	0.000003
Evolution of an H_S to an H_A individual by blood transfusion from an H_I individual	γ_{SATI}	Gobierno de la Ciudad de Buenos Aires (2012); WHO (2002)	0.000009

Evolution of an H_S to an H_A individual by blood transfusion from an H_P individual	γ_{SATP}	Gobierno de la Ciudad de Buenos Aires (2012); WHO (2002)	0.000001
Emigration of H_S individuals	ω_{Se}	Censo Nacional de Población, Hogares y Vivienda (2001)	134.303938
Mortality of H_S individuals	δ_S	Ministerio de Salud de la Nación (2009)	0.000029
Birth of an infected individual to an H_I individual	β_{AI}	Rissio et al. (2009); Freilij et al. (2010)	0.000002
Birth of an infected human to an H_P individual	β_{AP}	Rissio et al. (2009); Freilij et al. (2010)	0.000001
Evolution of an H_A individual to an H_I individual	γ_{AI}	WHO (2002)	0.015833
Mortality of H_A individuals	δ_A	WHO (2002)	0.000446
Immigration of H_I individuals	ω_{Ii}	Censo Nacional de Población, Hogares y Vivienda (2001)	6.255049
Evolution of an H_I individual to an H_P individual	γ_{IP}	Storino (2010)	0.000096
Emigration of H_I individuals	ω_{Ie}	Censo Nacional de Población, Hogares y Vivienda (2001)	4.644155
Mortality of H_I individuals	δ_I	Storino et al. (2010)	0.000029
Immigration of H_P individuals	ω_{Pi}	Censo Nacional de Población, Hogares y Vivienda (2001)	0.695005
Emigration of H_P individuals	ω_{Pe}	Censo Nacional de Población, Hogares y Vivienda (2001)	0.516017
Mortality of H_P individuals	δ_P	Manzullo and Dairraidou (1991)	0.000303

Given the significance of each conditional probability, constituting the incremental ratio on the right side of the equation and taking limits $(h \to 0)$ on both sides, we obtain the system (2) of Kolmogorov´s forward equations.

$$\frac{dP_{H_S,H_A,H_I,H_P}(t)}{dt} = \omega_{Si}P_{H_S-1,H_A,H_I,H_P}(t) + \beta_{SS}(H_S-1)P_{H_S-1,H_A,H_I,H_P}(t) + \beta_{SI}H_I P_{H_S-1,H_A,H_I,H_P}(t)$$
$$\beta_{SP}H_P P_{H_S-1,H_A,H_I,H_P}(t) + \gamma_{As}(H_A+1)P_{H_S-1,H_A+1,H_I,H_P}(t) + \gamma_{IS}(H_I+1)P_{H_S-1,H_A,H_I+1,H_P}(t)$$
$$+ \gamma_{SATA}(H_A-1)P_{H_S+1,H_A-1,H_I,H_P}(t) + \gamma_{SATI}H_I P_{H_S+1,H_A-1,H_I,H_P}(t) + \gamma_{SATP}H_P P_{H_S+1,H_A-1,H_I,H_P}(t)$$
$$+ \omega_{Se}P_{H_S+1,H_A,H_I,H_P}(t) + \delta_P(H_S+1)P_{H_S+1,H_A,H_I,H_P}(t) + \beta_{AI}H_I P_{H_S,H_A-1,H_I,H_P}(t) + \beta_{AP}H_P P_{H_S,H_A-1,H_I,H_P}(t)$$
$$+ \gamma_{AI}(H_A+1)P_{H_S,H_A+1,H_I-1,H_P}(t) + \delta_A(H_A+1)P_{H_S,H_A+1,H_I,H_P}(t) + \omega_{Ii}P_{H_S,H_A,H_I-1,H_P}(t)$$
$$+ \gamma_{IP}(H_I+1)P_{H_S,H_A,H_I+1,H_P}(t) + \omega_{Ie}P_{H_S,H_A,H_I+1,H_P}(t) + \omega_{Pi}P_{H_S,H_A,H_I,H_P-1}(t) + \omega_{Pe}P_{H_S,H_A,H_I,H_P-1}(t)$$
$$+ \delta_P(H_P-1)P_{H_S,H_A,H_I,H_P+1}(t) - \omega_{Si} + \beta_{SS}H_S + \beta_{SI}H_I + \beta_{SP}H_P + \gamma_{AS}H_A + \gamma_{IS}H_I + \gamma_{SATA}H_P + \gamma_{SATI}H_I$$
$$+ \gamma_{IP}H_I + \omega_{Ie} + \delta_I H_I + \omega_{Pi} + \omega_{Pe} + \delta_P H_P]P_{H_S,H_A,H_I,H_P}(t)$$

In order to obtain the expected number of individuals in each stage we used the method of generating functions (Feller, 1980; Piskunov, 1983; Casella and Berger, 2002). The generating function for this model of four variables can be expressed as:

$$\varphi(a,b,c,d,t) = \sum_{H_S,H_A,H_I,H_P} a^{H_S}b^{H_A}c^{H_I}d^{H_P}P_{H_S,H_A,H_I,H_P}(t)$$

The expected values of the number of individuals in each stage of infection are:

$$E(H_S(t)) = \frac{\partial\varphi}{\partial a}\Big]_{a=b=c=d=1}, \quad E(H_A(t)) = \frac{\partial\varphi}{\partial b}\Big]_{a=b=c=d=1}, \quad E(H_I(t)) = \frac{\partial\varphi}{\partial c}\Big]_{a=b=c=d=1} \text{ and}$$
$$E(H_P(t)) = \frac{\partial\varphi}{\partial d}\Big]_{a=b=c=d=1} \qquad (3)$$

The system that provides those expected values is:

$$\frac{\partial}{\partial t}\frac{\partial\varphi}{\partial a} = (\omega_{Si}-\omega_{Se}) + (\beta_{SS}-\delta_S)\frac{\partial\varphi}{\partial a} + (\gamma_{AS}-\gamma_{SATA})\frac{\partial\varphi}{\partial b} + (\beta_{SI}+\gamma_{IS}-\gamma_{SATI})\frac{\partial\varphi}{\partial c} + (\beta_{SP}-\gamma_{SATP})\frac{\partial\varphi}{\partial d}$$

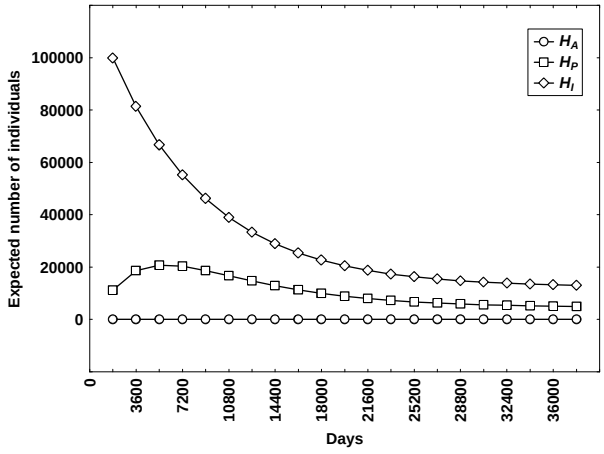
$$\frac{\partial}{\partial t}\frac{\partial \varphi}{\partial b} = (\gamma_{SATA} - \gamma_{AS} - \gamma_{AI} - \delta_A)\frac{\partial \varphi}{\partial b} + (\gamma_{SATI} + \beta_{AI})\frac{\partial \varphi}{\partial c} + (\gamma_{SATP} + \beta_{AP})\frac{\partial \varphi}{\partial d}$$
$$\frac{\partial}{\partial t}\frac{\partial \varphi}{\partial c} = (\omega_{Ii} - \omega_{Ie}) + \gamma_{AI}\frac{\partial \varphi}{\partial b} + (-\gamma_{IS} - \delta_I - \gamma_{IP})\frac{\partial \varphi}{\partial c}$$
$$\frac{\partial}{\partial t}\frac{\partial \varphi}{\partial d} = (\omega_{Pi} - \omega_{Pe}) + \gamma_{IP}\frac{\partial \varphi}{\partial c} - \delta_P\frac{\partial \varphi}{\partial d} \quad (4)$$

Integrating equations (4) with respect to time yields the expressions of the expected numbers of individuals in each stage.

3. Results

The model proposed was applied to Buenos Aires (Argentina), because this city is assumed to have only human-transmission, there is available information about the values of the parameters, and it presents a constant flow of infected individuals from endemic areas, such as Northern Argentine provinces and neighboring countries, including Bolivia and Paraguay. We assumed that Buenos Aires city was initially inhabited by three million inhabitants, 111,000 (3.7%) of whom were infected with *T. cruzi* (Ministerio de Salud de la Nación, 2009). We further assumed that, initially, 90% of the infected individuals were H_{I} and that the remaining 10% were H_{P}. Table 1 shows the estimated values of the parameters and the corresponding reference sources. The unit time considered for the parameter estimations was 1 day. Figure 1 describes the dynamics of the infection. Despite the linearization assumptions, we did not consider an excessive increase in population, even over a period of 100 years: the total population increased from 3 to 4.4 million people. The expected number of H_{I} was reduced not only by the favourable effect of the treatment and the non-appearance of new H_{A} but also by other removal causes such as emigration, mortality or progression of the disease increasing the number of H_{P} individuals. The number of H_{P} increased during the first eleven years possibly by the passage of the first H_{I}, but then decreased possibly by the reduction of H_{I}. Therefore, it is demonstrated that if model parameters are kept at their respective constant values, the population of Buenos Aires tends to an endemic equilibrium point at values of $H_A^* = 9$, $H_I^* = 12{,}200$ and $H_P^* = 4{,}456$.

Figure 1. Dynamics of the infection in Buenos Aires city



4. Conclusions

We present a stochastic model formulated as a continuous-time Markov chain. The model will allow researchers to explain the dynamics of Chagas disease in any scenario where the infection is transmitted only by the congenital and transfusional routes. A simulation for the first moments as a function of time was obtained using the method of generating functions. In applying the model to Buenos Aires city, we

concluded that, by maintaining the parameters at a constant level, an endemic equilibrium is established. While the percentage of infected individuals decreased from the initial 3.7% to 0.4% in 100 years, this decrease is only by dilution (due to an increase in the number of H_S). The important thing here is the establishment of a stable endemic equilibrium with about 16,700 chagasic people.

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