Schistosomiasis propagation in a circular habitat with endemic boundary

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Abstract: - A model of propagation for schistosomiasis within a circular habitat with endemic boundary is proposed. The model is a system of four linear and coupled reaction-diffusion equations derived from a double SIR model according with the life cycle of the disease. We apply the Laplace transform method making the inverse transform by means of the theorem of residues and a solution is given using computer algebra. We deduce the explicit form of the basic reproductive rate with effect of the endemic boundary from symbolic solution and some control measures are derived.

Key-Words: - Spatial SIR model, schistosomiasis model, Laplace transform, Residue Theorem, Computer algebra, Basic Reproductive Rate.

1 Introduction

Schistosomiasis is an important public health problem with 15,000 deaths in 2001 [1]. Globally, about 120 million of the 200 million are estimated to be symptomatic and 20 million are thought suffer severe consequences of the infection. The five species of flatworms that cause schistosomiasis are found in tropical countries Africa, Caribbean, eastern South American, east Asia and the Middle East [1].

The Fig.1 shows a simplified graph for schistosomiasis transmission. The solid lines represent the host (humans and snails) and the dotted lines represent the schistosoma at its different stages of development. The mechanism of transmission must be read from left to right. Initially one infected human emits schistosoma eggs to the environment. At the water, the eggs generate miracidia. Now, when a susceptible snail enters in contact with the miracidia, then the snail is converted to infected snail. The infected snails emit cercariae to the water and when a susceptible human enters in contact with the cercariae, then the susceptible human is converted to infected human. The new infected human begins to emit eggs and the cycle of transmission starts again.

We develop a spatial model for schistosomiasis inside of an habitat which is a finite circular region with endemic boundary, at the sense that the disease is always permanently present at the boundary or the disease is initially introduced from the boundary according to an exponential function and then from the boundary, the disease is propagated with a brownian movement towards the interior. The model is a system of four linear and coupled reaction-diffusion equations derived from a double SIR model for humans and snails, which is coupled by miracidia and cercariae.

Recently, environmental changes linked to water resources development, population movements and population growth have led to the spread of diseases to previously low or non endemic areas particularly Sub Saharan Africa, which suggest that a spatial model can be used [2].

In this work, we obtain the basic reproductive rate

with spatial effects for schistosomiasis, which is a typical disease with intermediate hosts and we compare this measure in endemic and pandemic conditions, which guides about prevention and control strategies. We solve the model using the Laplace transform technique implemented by computer algebra and the result is given in terms of Bessel functions.

As is well known, the basic reproductive rate denoted R_0, of SIR models of infectious diseases that are directly transmitted is given by [3].

$$R_0 = \frac{S_0 \beta}{\gamma}$$

where S_0 is the initial number of susceptible individuals, β is the constant of infection and γ is the constant of removal of infected individuals . The condition of occurrence of an epidemic is $R_0 > 1$. ( )

Similarly we can obtain R_0 for infectious diseases with hosts and vectors. Here, the constant of infection from vector to human is denoted $\beta_{v,h}$ and the constant of infection from human to vector is denoted $\beta_{h,v}$. The constant of removal of infected humans is denoted γ_h and the constant of removal of infected vectors is denoted γ_v. The basic reproductive rate for such indirectly transmitted disease is given by [3, 4].

$$R_0 = \frac{\beta_{v,h} \, \beta_{h,v} \, S_{h,0} \, S_{v,0}}{\gamma_h \, \gamma_v}$$

where $S_{h,0}$ is the initial number of susceptible humans and $S_{v,0}$ is the initial number of susceptible vectors.

2 The Mathematical Model

From the Fig. 1 we can formulate the following modified double SIR model [3, 5].

$$\frac{d}{dt} S_h(t) = -\beta_{C,h} \, S_h(t) \, C(t)$$

$$\frac{d}{dt} I_h(t) = \beta_{C,h} \, S_h(t) \, C(t) - \gamma_h \, I_h(t)$$

$$\frac{d}{dt} R_h(t) = \gamma_h \, I_h(t)$$

$$\frac{d}{dt} S_s(t) = -\beta_{M,s} \, S_s(t) \, M(t)$$

$$\frac{d}{dt} I_s(t) = \beta_{M,s} \, S_s(t) \, M(t) - \gamma_s \, I_s(t)$$

$$\frac{d}{dt} R_s(t) = \gamma_s \, I_s(t)$$

$$\frac{d}{dt} M(t) = \alpha_h \, I_h(t) - \gamma_M \, M(t)$$

$$\frac{d}{dt} C(t) = \alpha_s \, I_s(t) - \gamma_C \, C(t)$$

where ($S_h(t)$, $I_h(t)$, $R_h(t)$) are the numbers for humans and ($S_s(t)$, $I_s(t)$, $R_s(t)$) are the numbers for snails and ($M(t)$, $C(t)$) are respectively the numbers of miracidia and cercariae. The constant of infection from cercariae to humans is denoted $\beta_{C,h}$ and the constant of infection from miracidia to snails is denoted $\beta_{M,s}$. The constants of removal of infected humans, infected snails, miracidia and cercariae are denoted respectively (γ_h, γ_s, γ_M, γ_C). The rate of emission of eggs from the infected human is denoted α_h and the rate of emission of cercariae from the infected snail is denoted α_s. The corresponding basic reproductive rate is given by [3].

$$R_0 = \frac{\alpha_h \, \beta_{M,s} \, \alpha_s \, \beta_{C,h} \, S_{h,0} \, S_{s,0}}{\gamma_h \, \gamma_s \, \gamma_M \, \gamma_C}$$

The modified double SIR model for schistosomiasis can be converted to a spatial model if various diffusion terms are included for the various populations that are involved. The resultant spatial model has the form [4].

$$\frac{\partial}{\partial t} S_h(r, t) = D_h \, \Delta^2 S_h(r, t) - \beta_{C,h} \, S_h(r, t) \, C(r, t)$$

$$\frac{\partial}{\partial t} I_h(r, t) = D_h \, \Delta^2 I_h(r, t) + \beta_{C,h} \, S_h(r, t) \, C(r, t) - \gamma_h \, I_h(r, t)$$

$$\frac{\partial}{\partial t} R_h(r, t) = D_h \, \Delta^2 R_h(r, t) + \gamma_h \, I_h(r, t)$$

$$\frac{\partial}{\partial t} S_s(r, t) = D_s \, \Delta^2 S_s(r, t) - \beta_{M,s} \, S_s(r, t) \, M(r, t)$$

$$\frac{\partial}{\partial t} I_s(r, t) = D_s \, \Delta^2 I_s(r, t) + \beta_{M,s} \, S_s(r, t) \, M(r, t) - \gamma_s \, I_s(r, t)$$

$$\frac{\partial}{\partial t} R_s(r, t) = D_s \, \Delta^2 R_s(r, t) + \gamma_s \, I_s(r, t)$$

$$\frac{\partial}{\partial t} M(r, t) = D_M \, \Delta^2 M(r, t) + \alpha_h \, I_h(r, t) - \gamma_M \, M(r, t)$$

$$\frac{\partial}{\partial t} C(r, t) = D_C \, \Delta^2 C(r, t) + \alpha_s \, I_s(r, t) - \gamma_C \, C(r, t)$$

where all densities are given at point r at time t and the diffusion constants for human, snails, miracidia and cercariae are denoted respectively (D_h, D_s, D_M, D_C). The symbol Δ^2 represents the Laplacian operator. We assume a circular and finite habitat with endemic boundary like a more realistic picture of schistosomiasis transmission within a closed region.
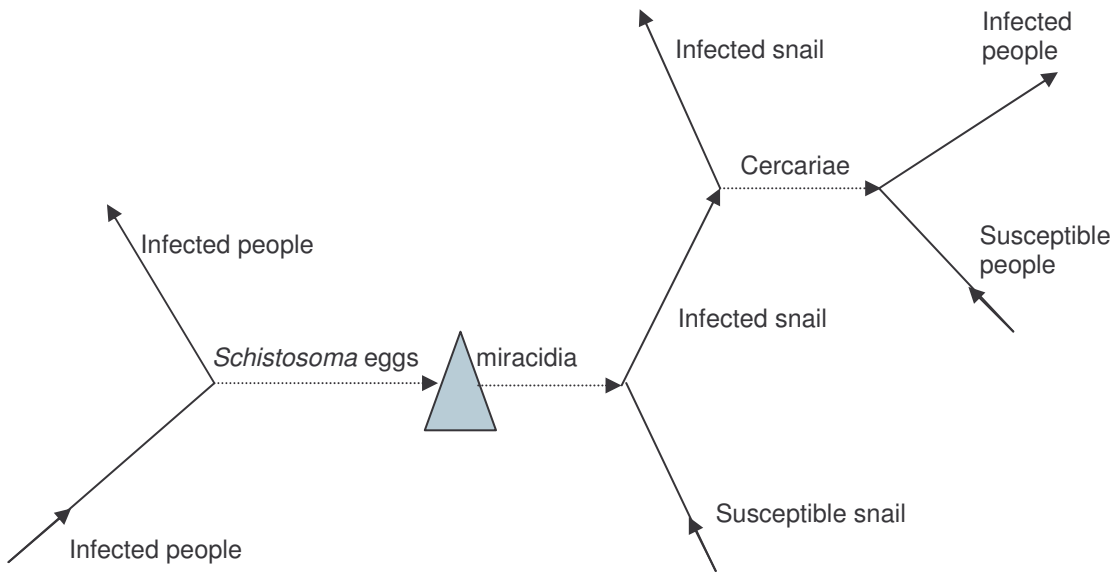
Figure 1. Life cycle of schistosomiasis

3 The Mathematical Problem

The spatial model is non linear and it can not be solved analytically. But when we are interested only with the beginning of the epidemics, this spatial model can be to reduced to the system of four linear and coupled equations of the diffusion-reaction type, which is given at the equations (1)-(4).

$$\frac{\partial}{\partial t} I_h(r,t) = D_h \Delta^2 I_h(r,t) + \beta_{C,h} S_{h,0} C(r,t) - \gamma_h I_h(r,t) \tag{1}$$

$$\frac{\partial}{\partial t} I_s(r,t) = D_s \Delta^2 I_s(r,t) + \beta_{M,h} S_{s,0} M(r,t) - \gamma_s I_s(r,t) \tag{2}$$

$$\frac{\partial}{\partial t} M(r,t) = D_M \Delta^2 M(r,t) + \alpha_h I_h(r,t) - \gamma_M M(r,t) \tag{3}$$

$$\frac{\partial}{\partial t} C(r,t) = D_C \Delta^2 C(r,t) + \alpha_s I_s(r,t) - \gamma_C C(r,t) \tag{4}$$

where $S_{h,0}$ and $S_{s,0}$ denote respectively, the initial density of susceptible human and the initial density of susceptible snails.

The equations (1)-(4) tell us, that humans, snails, miracidia and cercariae spread in the space by means of brownian movement and that the humans generate eggs that become miracidia, and then the miracidia invade to the snails and finally snails emit cercariae that infect to the humans and the cycle begins again.

The equations (1)-(4) must be complemented with certain initial conditions. Here we assume the following ones:

$$I_s(r,0) = 0 \tag{5}$$

$$M(r,0) = 0 \tag{6}$$

$$C(r,0) = 0 \tag{7}$$

$$I_h(r,0) = 0 \tag{8}$$

With a circular habitat of radius a, we use polar coordinates (r, Θ) and we assume perfect cylindrical symmetry, it is to say all densities are independent of Θ. With such assumptions, the Laplace operator takes the form

$$\Delta^2 u(r,t) = \frac{\left(\frac{\partial}{\partial r} u(r,t)\right) + r\left(\frac{\partial^2}{\partial r^2} u(r,t)\right)}{r} \tag{9}$$

where $u(r,t)$ is an arbitrary function.

The conditions of endemic boundary can be of the Dirichlet type or the Newman type. In the Dirichlet type a certain density of humans infected at the border is specified. For the Newman type, a certain flow of infected humans is specified at the border. Here only we consider the case of boundary condition of Dirichlet kind. More specifically, we consider the endemic boundary condition of the form

$$I_h(a,t) = f(t) \tag{10}$$

where $f(t)$ is an arbitrary function of t.

The problem that is tried to solve here, consists of the determination of the symbolic solution of the system of equations (1)-(4) with (5)-(10), so that the explicit

form of the basic reproductive rate for schistosiamisis in such spatial model can be obtained.

4 Problem Solution

Since our problem cannot be solved by means of the method of separation of variables, it is necessary to apply the Laplace Transform method making the inverse transform by means of the theorem of residues[6]. Since the equations (1)-(10) are too voluminous like being solved by hand with pencil and paper, it is necessary to apply some type of system of computer algebra that allows symbolic computation.

4.1. Method of Solution

A certain algorithm is used to solve (1)-(10). The inputs of the algorithm are the equations (1)-(4), the initial conditions (5)-(8); the boundary condition (10); and certain finitude condition for the solutions.

The output of the algorithm is the basic reproductive rate. The algorithm operates as it follows. The inputs are converted into transformed expressions by means of a Laplace transformer. The transformed expressions are processed by a certain Dsolver that generates the transformed solution. Next, this last, is processed by means of an inverser with residue theorem, and we obtain the explicit form of the solution. Finally using a stability analyzer, we deduce the explicit form of the basic reproductive rate and the algorithm is finished.

4.2. Results of Computations

Here, we consider the case when the function f(t) in the boundary condition (10) has the form

$$\text{f}(t) = \mu_b \, e^{(-\eta \, t)} \tag{11}$$

The equation (11) corresponds to the case when the density of humans infected on the boundary of the habitat, decays exponentially with time from an initial boundary density denoted μ_b.

Then, the solution of the equations (1)-(11), that is obtained using our algorithm for computer algebra, is given by

$$u_h(r, t) = u_{h, 1}(r, t) + u_{h, 2}(r, t) \tag{12}$$

where

$$u_{h, 1}(r, t) = \frac{e^{(-\eta \, t)} \mu_b \, J_0(\sqrt{\lambda(-\eta)} \, r)}{J_0(\sqrt{\lambda(-\eta)} \, a)} \tag{13}$$

$$u_{h, 2}(r, t) = \sum_{i=1}^{4} \left(\sum_{n=1}^{\infty} F_{i, n}(r, t) \right) \tag{14}$$

with

$$F_{i, n}(r, t) = \frac{2 \, e^{(S_{i, n} \, t)} \mu_b \, J_0\left(\dfrac{\alpha_n \, r}{a}\right) \alpha_n}{(S_{i, n} + \eta) J_1(\alpha_n) a^2 \left(\dfrac{d}{dS_{i, n}} \lambda(S_{i, n})\right)} \tag{15}$$

being $\lambda(s)$ a solution of the equation of fourth degree

$$K_1 \lambda(s)^4 + K_2 \lambda(s)^3 + K_3 \lambda(s)^2 + K_4 \lambda(s) + K_5 = 0 \tag{16}$$

and being $S_{i,n}$ the roots of the equation of fourth degree

$$s^4 + A_1 s^3 + A_2 s^2 + A_3 s - A_4 = 0 \tag{17}$$

The coefficients K at (16) and A at (17) are given at the appendix. Finally, $J_m(x)$ is the Bessel function of order m of the first kind, a is the radius of the circular habitat and α_n are the zeroes of J_0 [7], namely

$$J_0(\alpha_n) = 0 \tag{18}$$

and we use the following convention

$$\frac{d}{dS_{i, n}} \lambda(S_{i, n}) = \lim_{s \to S_{i, n}} \frac{d}{ds} \lambda(s) \tag{19}$$

4.3 Analysis of Results

As it is observed at the equation (12), the density of infected humans, consists of two summands. The first one is given at (13) and the second is given at (14) and (15). For $\eta > 0$, the first summand decays exponentially with the time and it does not represent any risk of pandemic. The second summand is also a sum of terms with exponential dependence on time and some of such terms can be exponentially increasing with the time and then a pandemic would be had. The condition so that a pandemic is generated is that (17) admits a positive real solution, it is to say that $A_4 > 0$, where A_4 is given at the appendix. This last condition can be rewritten as $R_{0,n} > 1$, where

$$R_{0, n} = \frac{S_{s, 0} \alpha_s \beta_{M, s} \alpha_h \beta_{C, h} S_{h, 0}}{\left(\gamma_C + \dfrac{\alpha_n^2 \delta_C}{a^2}\right)\left(\gamma_M + \dfrac{\alpha_n^2 \delta_M}{a^2}\right)\left(\gamma_s + \dfrac{\alpha_n^2 \delta_s}{a^2}\right)\left(\gamma_h + \dfrac{\alpha_n^2 \delta_h}{a^2}\right)} \tag{20}$$

The ground basic reproductive rate for schistosomiasis corresponds to n=1, with α_1=2.405, namely

$$R_{0,1} = \frac{S_{s,0}\,\alpha_s\,\beta_{M,s}\,\alpha_h\,\beta_{C,h}\,S_{h,0}}{\left(\gamma_C + \frac{5.8\delta_C}{a^2}\right)\left(\gamma_M + \frac{5.8\delta_M}{a^2}\right)\left(\gamma_s + \frac{5.8\delta_s}{a^2}\right)\left(\gamma_h + \frac{5.8\delta_h}{a^2}\right)} \tag{21}$$

The equation (21) can be rewritten as

$$R_{0,1} = \frac{R_0}{\left(1 + \frac{5.8\delta_C}{a^2\gamma_C}\right)\left(1 + \frac{5.8\delta_M}{a^2\gamma_M}\right)\left(1 + \frac{5.8\delta_s}{a^2\gamma_s}\right)\left(1 + \frac{5.8\delta_h}{a^2\gamma_h}\right)} \tag{22}$$

where R_0 is the basic reproductive rate of schistosomiasis for the purely temporal models without spatial effects ($\delta = 0$) or for the spatial models with infinite habitat ($a \longrightarrow \infty$), and is given by

$$R_0 = \frac{S_{s,0}\,\alpha_s\,\beta_{M,s}\,\alpha_h\,\beta_{C,h}\,S_{h,0}}{\gamma_C\,\gamma_M\,\gamma_s\,\gamma_h} \tag{23}$$

Now, for the case when $\eta = 0$, the equation (13) losses its dependence on time and can be considered as certain endemic configuration of the disease inside the habitat. The condition for such pan-endemic configuration exists is

$$0 < \lambda(0) \tag{24}$$

which is equivalent to $K_5(s=0) < 0$, where K_5 is given at the appendix. This last condition can be rewritten as $R_0 > 1$, where R_0 is given at (23). We conclude that the basic reproductive rate of disease corresponding to the endemic configuration coincides with the basic reproductive rate corresponding both to the purely temporal models as the spatial models with infinite habitat.

Finally, when $\eta < 0$, then (13) has exponential increasing with time and corresponds to the irruption of the pandemic without necessity of any kind of epidemic threshold. We can see from (22) and (23) that

$$R_{0,1} < R_0 \tag{25}$$

Now, from the perspective of the control measures, we have that the percentage of decreasing of the population of snails both to prevent the endemic state (13) as to control the epidemic state (14), are given, respectively by

$$P_{ende} = 1 - \frac{1}{R_0} \tag{26}$$

$$P_{epi} = 1 - \frac{1}{R_{0,1}} \tag{27}$$

From (25)-(27) we deduce that

$$P_{epi} < P_{ende} \tag{28}$$

it is to say the percentage of decreasing of snail population to prevent the endemic state is greater than the percentage of decreasing to prevent the epidemic state.

5 Conclusion

Our principal result is the equation (22) which gives the basic reproductive rate for schistosomiasis inside a circular habitat with endemic boundary. We observe that the effect of boundary consists on certain re normalization of the removal constants for the four populations due to the presence of diffusion terms. Such renormalization is positive and then the basic reproductive rate with boundary effects is less that the basic reproductive rate without boundary effects.

The computational method that was applied here, can be used to solve more complex spatial models of schistosomiasis transmission, as for example models with incorporate the effects of heterogeneity of all involved populations.

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Appendix. Coefficients of equations (16) and (17)

$$K_1 = \delta_C \delta_h \delta_s \delta_M, \quad K_2 = (\delta_h \delta_s \delta_M + \delta_C \delta_h \delta_s + \delta_C \delta_s \delta_M + \delta_C \delta_h \delta_M)s + \delta_C \delta_h \gamma_s \delta_M$$

$$+ \gamma_C \delta_h \delta_s \delta_M + \delta_C \gamma_h \delta_s \delta_M + \delta_C \delta_h \delta_s \gamma_M, \quad K_3 =$$

$$(\delta_h \delta_M + \delta_C \delta_M + \delta_C \delta_s + \delta_C \delta_h + \delta_s \delta_M + \delta_h \delta_s)s^2 + (\delta_C \gamma_h \delta_s + \delta_C \delta_h \gamma_M + \delta_h \gamma_s \delta_M$$

$$+ \gamma_C \delta_h \delta_M + \delta_C \delta_h \gamma_s + \gamma_C \delta_h \delta_s + \gamma_h \delta_s \delta_M + \delta_C \gamma_h \delta_M + \delta_h \delta_s \gamma_M + \delta_C \gamma_s \delta_M + \delta_C \delta_s \gamma_M$$

$$+ \gamma_C \delta_s \delta_M)s + \gamma_C \delta_h \gamma_s \delta_M + \delta_C \delta_h \gamma_s \gamma_M + \gamma_C \delta_h \delta_s \gamma_M + \gamma_C \gamma_h \delta_s \delta_M + \delta_C \gamma_h \gamma_s \delta_M$$

$$+ \delta_C \gamma_h \delta_s \gamma_M, \quad K_4 = (\delta_M + \delta_s + \delta_h + \delta_C)s^3 + (\gamma_h \delta_s + \gamma_C \delta_h + \delta_h \gamma_M + \gamma_C \delta_s + \delta_C \gamma_h$$

$$+ \delta_C \gamma_s + \delta_C \gamma_M + \delta_s \gamma_M + \delta_h \gamma_s + \gamma_s \delta_M + \gamma_h \delta_M + \gamma_C \delta_M)s^2 + (\gamma_h \gamma_s \delta_M + \delta_C \gamma_s \gamma_M$$

$$+ \gamma_h \delta_s \gamma_M + \gamma_C \gamma_h \delta_M + \gamma_C \delta_h \gamma_M + \gamma_C \delta_s \gamma_M + \delta_h \gamma_s \gamma_M + \gamma_C \gamma_s \delta_M + \gamma_C \delta_h \gamma_s + \delta_C \gamma_h \gamma_M$$

$$+ \delta_C \gamma_h \gamma_s + \gamma_C \gamma_h \delta_s)s + \gamma_C \delta_h \gamma_s \gamma_M + \gamma_C \gamma_h \delta_s \gamma_M + \gamma_C \gamma_h \gamma_s \delta_M + \delta_C \gamma_h \gamma_s \gamma_M, \quad K_5 = s^4$$

$$+ (\gamma_M + \gamma_h + \gamma_C + \gamma_s)s^3 + (\gamma_C \gamma_M + \gamma_C \gamma_s + \gamma_h \gamma_s + \gamma_h \gamma_M + \gamma_C \gamma_h + \gamma_s \gamma_M)s^2$$

$$+ (\gamma_C \gamma_s \gamma_M + \gamma_C \gamma_h \gamma_s + \gamma_h \gamma_s \gamma_M + \gamma_C \gamma_h \gamma_M)s - \alpha_s \beta_{M,s} S_{s,0} \alpha_h \beta_{C,h} S_{h,0} + \gamma_C \gamma_h \gamma_s \gamma_M$$

$$A_1 = \left(\frac{\delta_M}{a^2} + \frac{\delta_s}{a^2} + \frac{\delta_h}{a^2} + \frac{\delta_C}{a^2} \right) \alpha_n^2 + \gamma_M + \gamma_h + \gamma_C + \gamma_s, \quad A_2 =$$

$$\left(\frac{\delta_h \delta_M}{a^4} + \frac{\delta_C \delta_M}{a^4} + \frac{\delta_C \delta_s}{a^4} + \frac{\delta_C \delta_h}{a^4} + \frac{\delta_s \delta_M}{a^4} + \frac{\delta_h \delta_s}{a^4} \right) \alpha_n^4 + \left(\frac{\delta_C \gamma_M}{a^2} + \frac{\delta_s \gamma_M}{a^2} + \frac{\delta_h \gamma_s}{a^2} \right.$$

$$\left. + \frac{\gamma_h \delta_M}{a^2} + \frac{\gamma_C \delta_M}{a^2} + \frac{\gamma_C \delta_s}{a^2} + \frac{\gamma_s \delta_M}{a^2} + \frac{\delta_C \gamma_s}{a^2} + \frac{\gamma_C \delta_h}{a^2} + \frac{\delta_h \gamma_M}{a^2} + \frac{\delta_C \gamma_h}{a^2} + \frac{\gamma_h \delta_s}{a^2} \right) \alpha_n^2$$

$$+ \gamma_C \gamma_M + \gamma_C \gamma_s + \gamma_h \gamma_s + \gamma_h \gamma_M + \gamma_C \gamma_h + \gamma_s \gamma_M, \quad A_3 =$$

$$\left(\frac{\delta_C \delta_h \delta_M}{a^6} + \frac{\delta_h \delta_s \delta_M}{a^6} + \frac{\delta_C \delta_s \delta_M}{a^6} + \frac{\delta_C \delta_h \delta_s}{a^6} \right) \alpha_n^6 + \left(\frac{\gamma_h \delta_s \delta_M}{a^4} + \frac{\delta_C \delta_s \gamma_M}{a^4} + \frac{\gamma_C \delta_s \delta_M}{a^4} \right.$$

$$+ \frac{\delta_C \gamma_h \delta_s}{a^4} + \frac{\delta_C \delta_h \gamma_M}{a^4} + \frac{\delta_h \gamma_s \delta_M}{a^4} + \frac{\gamma_C \delta_h \delta_M}{a^4} + \frac{\delta_C \gamma_s \delta_M}{a^4} + \frac{\gamma_C \delta_h \delta_s}{a^4} + \frac{\delta_C \gamma_h \delta_M}{a^4}$$

$$\left. + \frac{\delta_C \delta_h \gamma_s}{a^4} + \frac{\delta_h \delta_s \gamma_M}{a^4} \right) \alpha_n^4 + \left(\frac{\gamma_C \gamma_s \delta_M}{a^2} + \frac{\gamma_C \delta_h \gamma_s}{a^2} + \frac{\delta_C \gamma_h \gamma_M}{a^2} + \frac{\gamma_C \gamma_h \delta_s}{a^2} + \frac{\gamma_h \delta_s \gamma_M}{a^2} \right.$$

$$\left. + \frac{\gamma_C \gamma_h \delta_M}{a^2} + \frac{\gamma_C \delta_s \gamma_M}{a^2} + \frac{\delta_h \gamma_s \gamma_M}{a^2} + \frac{\gamma_C \delta_h \gamma_M}{a^2} + \frac{\delta_C \gamma_h \gamma_s}{a^2} + \frac{\delta_C \gamma_s \gamma_M}{a^2} + \frac{\gamma_h \gamma_s \delta_M}{a^2} \right) \alpha_n^2$$

$$+ \gamma_C \gamma_s \gamma_M + \gamma_C \gamma_h \gamma_s + \gamma_h \gamma_s \gamma_M + \gamma_C \gamma_h \gamma_M, \quad A_4 = - \frac{\delta_C \alpha_n^8 \delta_h \delta_s \delta_M}{a^8}$$

$$+ \left(- \frac{\delta_C \delta_h \delta_s \gamma_M}{a^6} - \frac{\delta_C \delta_h \gamma_s \delta_M}{a^6} - \frac{\gamma_C \delta_h \delta_s \delta_M}{a^6} - \frac{\delta_C \gamma_h \delta_s \delta_M}{a^6} \right) \alpha_n^6 +$$

$$\left(- \frac{\delta_C \gamma_h \gamma_s \delta_M}{a^4} - \frac{\delta_C \gamma_h \delta_s \gamma_M}{a^4} - \frac{\gamma_C \gamma_h \delta_s \delta_M}{a^4} - \frac{\gamma_C \delta_h \gamma_s \delta_M}{a^4} - \frac{\delta_C \delta_h \gamma_s \gamma_M}{a^4} - \frac{\gamma_C \delta_h \delta_s \gamma_M}{a^4} \right)$$

$$\alpha_n^4 + \left(- \frac{\delta_C \gamma_h \gamma_s \gamma_M}{a^2} - \frac{\gamma_C \delta_h \gamma_s \gamma_M}{a^2} - \frac{\gamma_C \gamma_h \delta_s \gamma_M}{a^2} - \frac{\gamma_C \gamma_h \gamma_s \delta_M}{a^2} \right) \alpha_n^2 - \gamma_C \gamma_h \gamma_s \gamma_M$$

$$+ \alpha_s \beta_{M,s} S_{s,0} \alpha_h \beta_{C,h} S_{h,0}$$