

## **Amoebiasis Transmission And Life Cycle: A Continuous State Description by Virtue of Existence and Uniqueness**

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### **Abstract**

Amoebiasis is a contagious disease, triggered by the unicellular microorganism *Entamoeba histolytica* (in form of infective cysts), excreted at the end of its life cycle within human faecal of the infectious host. It is an endemic disease prevalent among the population living under critical hygienic conditions in developing countries. Recent progress made to characterize and distinguish *Entamoeba histolytica* and its homologous non pathogenic *Entamoeba dispar*, has motivated the desire to lay the foundations of a mathematical model for the transmission of amoebiasis on modeling underlying assumptions from the literature of amoebiasis and on the instantaneous rates of change in size of the five population epidemiological classes: susceptible (S), exposed (E), infective (I), carrier (C) and recovered (R) defining amoebiasis states. The variations of the size of each class are implicitly time dependent and they are initiated in accordance with the law of mass action by the transfer of a proportion of individuals of the same disease status from one class to another. The model is novel in this class of infectious disease and is built on a system of nonlinear differential equations embodied on the flowchart thoroughly commented. For the sake of the configuration of the dynamics of amoebiasis at any time during its course, the existence and uniqueness theory raises an issue about the solution to the Initial Value Problem (IVP) associated with the model. Indeed, under some conditions on the parameters of the IVP, the existence and uniqueness of the solution to

amoebiasis transmission mathematical model are restricted to the minimum but extendable interval of time.

**Keywords:** Amoebiasis, *Entamoeba histolytica*, amoebiasis transmission mathematical model.

**AMS classification:** 34C

## Introduction

### Background of the study:

The microorganism unicellular amoeba has been discovered very early in the past and it is dated about more than one century. The first case of amoebic dysentery was noticed in St. Petersburg, Russia by Lösch, F. et al. in 1875. Later, in 1903 Fritz Schaudinn has named Lösch's microorganism causal of the dysentery, *Entamoeba histolytica*. From that time till now the research on this microorganism discovers new facts for understanding this nature better. Significant progress has been made through the classification of *Entamoeba* by which the existence of two identical strains: pathogenic *Entamoeba histolytica* and non-pathogenic *Entamoeba dispar* [1, 2] has been confirmed. These two species exist either in vegetative resistant form cysts in water and in soil fertilized with human faeces or in a parasitic microorganism form of the human and animal intestine [3].

Amoebiasis accounted for 40000 to 100000 cases of death each year [2, 4, 9, 22]. Only 10 to 20% of the persons infected by *Entamoeba histolytica* develop the symptoms and finally diagnosed ill of amoebiasis. According to the report released by The Institut Pasteur in 2012, in some Tropical regions, the prevalence in *Entamoeba histolytica* may even reach 20% of the population. 1% of world population are also infected by *E. histolytica*; this is why *E. histolytica* is the second leading cause of mortality [5] among the human parasites.

Amoebiasis is genuinely a major handicap to the health of the people under fairly poor hygienic conditions and primarily living under the poverty line, mostly in the developing countries like India, Bangladesh, Mexico, Japan [2, 12]. In Africa some surveys and research have been conducted in Soudan, Ivory Coast, Ethiopia, Nigeria, Egypt and South Africa revealing the fact that in some local regions the prevalence of amoebiasis is high [7, 8, 24]. On the contrary, rare cases are reported in developed countries like USA and Western European countries [8].

### Biology and Life Cycle of *Entamoeba histolytica*:

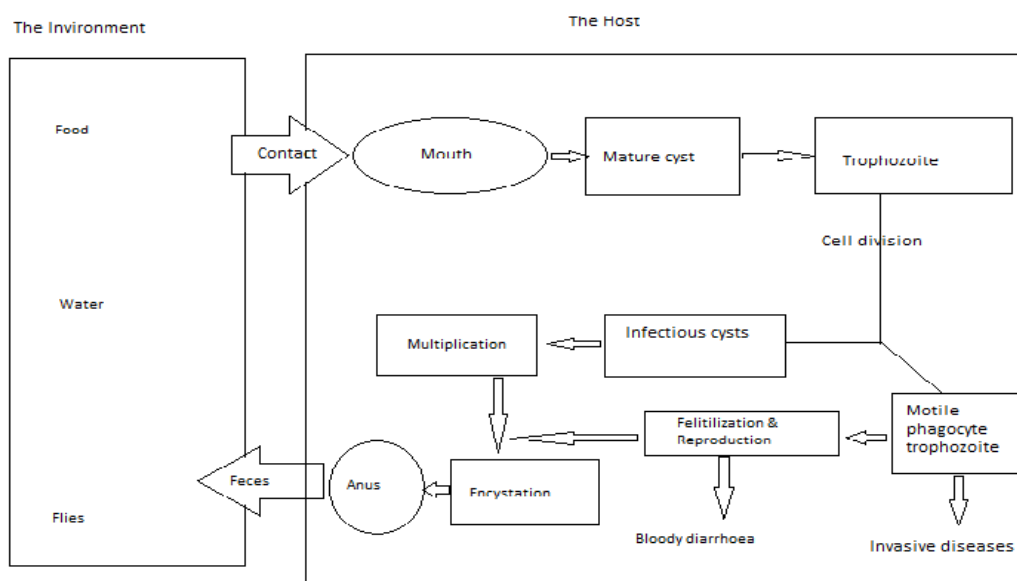
The life cycle of *Entamoeba histolytica* revolves around two stages: *infectious cysts* and *motile phagocyte trophozoites* (10 to 60  $\mu\text{m}$ ) [2, 17]. *Entamoeba histolytica* in infective forms, called cysts, of radial dimension in the range of 10 to 15  $\mu\text{m}$ , are shed within the faeces of the infected host and later infect food and beverage by flies or other means of direct or indirect contact with contaminated faeces. Human and some non-human primates are the only medium through which *Entamoeba histolytica* or

amoeba in general spreads and multiplies. However, dogs and cats can host *Entamoeba histolytica* although none of them shed cysts with their faeces.

Life development of *Entamoeba histolytica* involves many microscopic phases. Initially cysts are ingested and very soon become mature and experience a run of indefinitely mitosis stages resulting in the reproduction of trophozoites or sporozoites, *Entamoeba histolytica* in the trophozoite form locate the large intestine and feed on ingested nutrients, mucous production and live a life of symbiosis or competition with other microorganisms (bacteria and viruses) of the host gut. Trophozoites secrete a biochemical substance (Gal/GalNAc lectin) enabling them to stick to epithelial cells of the intestinal tract of the host [9], invade and feed from them. As the trophozoites grow up inside of the cells, they cause the cells to die and the last are eliminated from the intestine with a bloody stool in faeces. The destruction of intestinal cells is referred to amoebiasis dysenteric. In some cases, the trophozoites invade the mucous and pass through epithelial cells and end up entering blood vessels by which they reach the liver, lungs, brain or skin and trigger invasive extra-intestinal amoebiasis and the liver abscess.

Also, by the time the trophozoite feeds, it matures and becomes schizont undergoing cellular division to form eight merozoites. The merozoites in oval shape have a key role in the cycle of *Entamoeba histolytica*: On the one hand, they perpetuate the reproduction by organizing themselves in male and female reproductive cells; by eggs fertilized by sperm from male merozoite will mature and bring forth an immature cyst while, on the other hand they are degrading the epithelial cells to initiate amoebic dysentery. The immature cysts once have developed and acquired outer protective wall, they are released into the small intestine in a wet, bloody fecal waste and then exit the body through anus.

The following diagram illustrates the life cycle of *Entamoeba histolytica*:



**Figure 1:** Cycle of *E. histolytica*

### **Characterization of Amoebiasis:**

#### ***Levels of amoebiasis Infection:***

Online medical dictionary [10] classifies amoebiasis into three levels: asymptomatic infection, chronic non-dysenteric infection and amebic dysentery.

1. ***Asymptomatic infection:*** A patient at this level of infection has no noticeable symptoms and he/she is apparently feeling well with no trace of illness, but still capable to spread the infection by contaminating food, water with cysts shed in his faeces.
2. ***Chronicle non-dysenteric infection:*** A patient with chronicle non-dysenteric infection develops symptoms of chronic amoebiasis for a long duration characterized by intermittent episodes of diarrhea whose duration is probably equivalent to the incubation period of amoebiasis (one week to four weeks), and this may happen recursively over a period of years. He/she may also suffer from abdominal cramps, fatigue and weight loss.
3. ***Amebic dysentery:*** It is an acute intestinal amoebiasis detected at the time when *Entamoeba histolytica* invades the epithelial cells of the intestine and destroys them culminating in episodes of bloody diarrhea followed by inflammation of both the appendix and the colon and perforation of the intestinal wall as well. Severe abdominal cramps, vomiting, chills and high fever (40 to 40.6°C) are prevalent symptoms in this case of illness.

The onset of amoebiasis takes place within the life cycle of *Entamoeba histolytica* by the time a biochemical substance secreted by the trophozoites oxidize the layer of the mucus protector of the intestine wall, allowing them to penetrate epithelial cells and kill them, causing the inflammation culminating in dysentery [14]. After an episode of amoebic dysentery, 5% of the hosts may develop, within 1 to 3 months, an extra-intestinal amoebiasis; especially Amoebic Liver Abscess (ALA). Statistically, the prevalence of *Entamoeba histolytica* infection raises an issue of about 90% of asymptomatic cases (i.e. Carriers) and 10% of acute infections [11]. Thibeax et al. confirmed the predominant characteristics of asymptomatic infection and 20% of intestinal amoebiasis among which rare extra-intestinal invasive [14].

Carrier individuals excrete intermittently very few numbers of cysts in their stools. But in acute infectious state, patients experience severe colitis; a large number of trophozoites and cysts are excreted with soft mixture bloody stools.

### **Mathematical Formulation of the Model**

The interaction between immune system of the host and *E. histolytica* and the general behavior of both hosts and individuals susceptible to the infections are the cornerstone of the dynamics of amoebiasis. The dynamism of the amoebiasis through the population might be represented by a system of nonlinear differential equations derived considering the characteristics of the disease as it has been developed in the introduction of this paper. Without loss of generality, the model to derive is the IVP expressed in the following general form:

$$\frac{dx}{dt} = f(t, x; \eta), \quad x(t_0) = x_0 \quad (2.1)$$

where  $x \in \mathbb{R}^n$ ,  $x = x(t)$  is a vector function whose components are explicitly time dependent that define the composition in size of different epidemiological compartments (or the amoebiasis status levels of an individual in the population under study).  $\eta \in \mathbb{R}^m$  is the vector of the parameters of the model.

### Underlying Model Assumptions:

The derivation of the epidemiological dynamics of amoebiasis through the population is based on the following premise. The population under consideration is grouped [21, 22] into five epidemiological classifications where at any time  $t$  of the period of the disease outbreak, the individual in the population should be classified in one of the following classes:

1. **Susceptible:** Class of  $s(t)$  individuals in the population who are not yet infected by *E. histolytica* but still susceptible to the infections.
2. **Exposed:** Class of  $e(t)$  individuals already infected, but the level of infection is much smaller to trigger off amoebiasis.
3. **Infective:** Class of  $i(t)$ , individuals who are infected, suffer from the disease. They excrete a considerable amount of infective forms of *E. histolytica* (cysts and trophozoites) in their stools. These individuals experience some symptoms ranging from abdominal cramps to colitis, bloody diarrhea and amoebiasis liver abscess.
4. **Carrier:** This is a category of  $c(t)$  persons who host *E. histolytica* and can spread the infection by excretion of few numbers of cysts in their stools. In general, this stage of illness occurs after a period of acute infection degenerating in a state at which the individual remains infected without any complaint.
5. **Removed:** Class of  $r(t)$  individuals who their immunity has fought infection and recover from illness. Some literature reviews classify individuals who die of amoebiasis in this class.

We express the size of the above classes in terms of proportions of the population under study as follows:

$$S = \frac{s(t)}{N}, E = \frac{e(t)}{N}, I = \frac{i(t)}{N}, C = \frac{c(t)}{N} \text{ and, } R = \frac{r(t)}{N} \quad (2.2)$$

where  $N$  is the total size of the population under study. Let  $\frac{1}{\lambda}$ ,  $\frac{1}{\sigma}$ ,  $\frac{1}{\gamma}$ ,  $\frac{1}{\tau}$  and  $\frac{1}{\omega}$  be

the mean periods of time an individual remains in susceptible, exposed, infective, carrier and removable classes respectively. Assume  $\lambda$  to be the force of infection or the per capita rate at which the susceptible individuals acquire the infection i.e.,

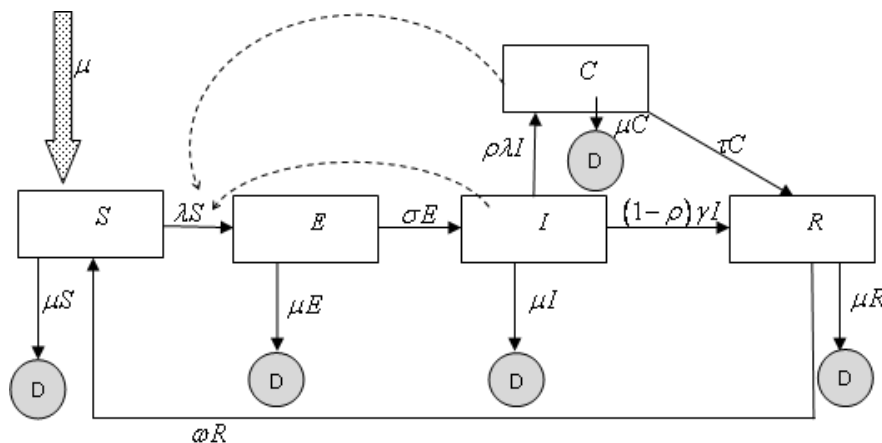
$\lambda = \beta \left[ \frac{i(t)}{N} + \varepsilon \frac{c(t)}{N} \right]$  or  $\lambda = \beta(I + \varepsilon C)$ . Here  $\beta$  is a parameter resulting from the

product of the mean rate of adequate number of contacts to pass on the infection to the susceptible and the probability of being infected given the contact with infectious people, and  $\varepsilon\beta$  is the reduced transmission due to the carrier component [19]. Then  $\lambda, \sigma, \gamma, \tau$  and  $\omega$  are different values assumed to the parameter  $m$ , The waiting duration for the probability distribution defined by  $f(t) = e^{-mt}$  for all  $t \geq 0$  [19, 20, 22] and the literature on modeling infectious diseases argues that a number of individuals leaving one class to another during the period of waiting time  $\frac{1}{m}$  is directly proportional to  $m$  [19, 22].

Suppose also that the mean life expectancy time is  $\frac{1}{\mu}$  and there is a probability  $\rho$  for a random individual in the infectious class  $I$  to become a carrier individual over infectious period of time  $\frac{1}{\gamma}$ , while  $1 - \rho$  is a probability for the remaining individual in the same class to recover over the same period of time. For the sake of simplicity, we assume the population to be uniform and homogeneously mixed. Furthermore, as the survey is conducted over a short time scale, the total size of the population does not vary much and therefore the rates of death and birth balance each other. It is assumed to be represented by  $\mu$ , the per capita natural mortality rate or population's crude rate. The transmission of amoebiasis being horizontal rather than vertical, i.e., that all the newborn are susceptible and individual in each class should at any moment suffer the natural mortality at the rate proportional to  $\mu$ .

**2.2. Compartmental Flow diagram of the model:**

The following diagram, named as SEICRS model, results from the modification of the SIRC endemic model from [19] and helps to describe the dynamics transmission of amoebiasis.



**Figure 2:** Flowchart of the dynamics of amoebiasis

The flowchart paired with the model is essentially composed of rectangles, black arrows, dotted black arrow, plain shadowed circles and one down plain dots arrow. The rectangles represent different partitions of the populations describing the states of the disease; arrows indicate the direction of the transfer of the people from one compartment to another. Dead proportion of the population is symbolically represented by plain circles D. Apart from identifying the direct contact between members of the susceptible and infective classes, the dotted arrows indicate the degree at which these infectious classes may play to amplify the spread of amoebiasis. New recruitment in susceptible people by newborn is indicated by down directed plain arrow.

The mechanism of the dynamics of amoebiasis paired with the flowchart is explained through the following four assertions:

1. During the course of amoebiasis, a proportion of the susceptible population who has been in direct contact with infective faeces from the members of the classes I or C, leaves their status of being susceptible for the simple reason of being contaminated and then becomes exposed at the rate of  $\lambda$  while the remaining may experience the natural death at the rate proportional to  $\mu$ . In other words, the proportions equivalent to  $\lambda S$  and  $\mu S$  leave this class of susceptibility to amoebiasis, while at the same time, the susceptible people increase by the recruitment  $\mu$  from the newborn and from people recovered at the rate of recovery  $\omega$  i.e.,  $\omega R$ . These two processes describe the net balance equivalent to an instantaneous rate  $\frac{dS}{dt}$  of change in size of the susceptible class S. By the principle of the law of mass action [26], This rate of change in size, can be expressed in terms of the following differential equation:

$$\frac{dS}{dt} = \mu(1-S) - (\beta I + \varepsilon \beta C)S + \omega R \quad (2.2.1)$$

2. The susceptible portion of people infected move to the class of exposed, they will remain in this class for the whole latent period of the duration  $\frac{1}{\sigma}$ . But during this period of stay, there are two possible issues to this proportion of the exposed individuals in this class  $E$ : either they become infective at a rate proportional to  $\sigma$  or some of them may experience natural death at a rate equivalent to the per capital birth rate of the population  $\mu$ . Mathematically, the net change of the total exposed hosts in this population at any time during the course of amoebiasis, is denoted  $\frac{dE}{dt}$  and it is equivalent to the balance between the proportion entering and that leaving this stage of the development of the disease amoebiasis. It follows that the equation expressing the rate of change in size of the exposed proportion of the population is

$$\frac{dE}{dt} = (\beta I + \varepsilon \beta C)S - (\sigma + \mu)E \quad (2.2.2)$$

3. In the middle age of the dynamics of amoebiasis, there are two indistinguishable categories of the people who are already infective namely  $I$  and  $C$ . Most of the time, the proportion of exposed population by becoming infective, their infective state may be either acute or latent and they are able to spread out the infection in proportions of respective probabilities  $\beta$  and  $\varepsilon\beta$ , where  $0 < \varepsilon < 1$ . The literature on amoebiasis confirms the two coexistence of these two states in approximate proportions of 20% and 80% respectively for this reason, the model suggests there is a probability  $\rho$  that an infective person is carrier. During the period of infectivity  $\frac{1}{\gamma}$ , the acute infective people leave this stage at rates proportional to  $\gamma$  but taking account of the probability  $\rho$ . i.e.,  $\rho\gamma$  to become carriers while the remaining proportion  $(1-\rho)\gamma$  recovers and enters the class  $R$ . Note that infective carriers will not remain forever, they will decrease as they recover from illness at the rate  $\tau$ . Note that the death of infective people will also decrease the size of the populations in both compartments  $I$  and  $C$  at the rate equivalent to  $\mu$ . Mathematically, the dynamics of amoebiasis over these two classes is expressed in terms of the following ordinary differential equations:

$$\frac{dI}{dt} = \sigma E - (\gamma + \mu)I \quad (2.2.3)$$

$$\frac{dC}{dt} = \rho\gamma I - (\tau + \mu)C \quad (2.2.4)$$

4. As far as the dynamics of amoebiasis on the recovered class  $R$  is concerned, the ordinary differential equation (2.2.5) sums up different transfers taking place as the immune system of infective people has cleared the infection. This equation summarizes how the size of  $R$  changes continuously during the period of the decay of immunity induced by amoebiasis. During the recovery period of length  $\frac{1}{\omega}$ , a recover proportional to the size of  $R$  is removed from the proportion of the population admitted in the recovered class  $(1-\rho)\gamma I + \tau C$ , at the rate  $\omega$  and then turns back to the state of susceptibility. At the same moment, some of the individuals in this class may suffer death and yield an additional proportional of hosts to be removed from the class of recovery  $R$  proportionally to its size at a rate of  $\mu$ .

$$\frac{dR}{dt} = (1-\rho)\gamma I + \tau C - (\omega + \mu)R \quad (2.2.5)$$

that governs the dynamics transmission of amoebiasis and they satisfy the following relation:

$$\frac{dS}{dt} + \frac{dE}{dt} + \frac{dI}{dt} + \frac{dC}{dt} + \frac{dR}{dt} = 0 \quad (2.2.6)$$



The overall sum of variation in size at each class is zero. In other words, there is net compensation between variations in size on overall components at any time of the dynamics of amoebiasis.

Integrating (2.2.6) with respect to the time, the integral yield the following result

$$S(t) + E(t) + I(t) + C(t) + R(t) = k \quad (2.2.7)$$

At any time of the outbreak of amoebiasis, the size of the population doesn't change. i.e.,  $k = 1$  and hence.

$$S(t) + E(t) + I(t) + C(t) + R(t) = 1, \quad \forall t \geq t_0 \quad (2.2.8)$$

As the consequence of the equation (2.2.8), it is clear that one variable of the system of the initial value problem (IVP) coupled with the flowchart reduces to:

$$\frac{dS}{dt} = (\mu + \omega) - (\beta I + \varepsilon \beta C + \mu + \omega)S - \omega E - \omega I - \omega C \quad (2.2.a)$$

$$\frac{dE}{dt} = (\beta I + \varepsilon \beta C)S - (\sigma + \mu)E \quad (2.2.b)$$

$$\frac{dI}{dt} = \sigma E - (\gamma + \mu)I \quad (2.2.c)$$

$$\frac{dC}{dt} = \rho \gamma I - (\tau + \mu)C \quad (2.2.d)$$

Subject to the initial condition:

$$S(t_0) = S_0 \geq 0, E(t_0) = E_0 \geq 0, I(t_0) = I_0 \geq 0, C(t_0) = C_0 \geq 0 \quad (2.2.e)$$

Where the vector state function  $x$  introduced in the general form of the initial value problem (2.1) is characterized by its components which are the proportions of the individuals in each class. i.e.,  $x = (S, E, I, C) \in \Omega$ , with  $\Omega \subset C[0, a]$  the domain of the IVP.

Note that at any time  $t \in [0, a]$ ,  $\Omega(t) = \{(S(t), E(t), I(t), C(t)) : S(t) + E(t) + I(t) + C(t) \leq 1\}$  is closed and bounded subset of  $IR^4$  [27, ];  $[0, a]$  is the period of the disease.  $\Omega$  is a compact subset of  $C[0, a]$  and for this reason,  $\Omega$  is a Banach space [30, 32, 33]

## Wellposedness of Amoebiasis Transmission Mathematical Model

### Existence of the Solution to the Model:

Consider the function the vector function  $f(t, x)$  defined on the compact Banach space  $\Omega$ .

$f(t, x) = (f_1(x), f_2(x), f_3(x), f_4(x))$ , where the components are real valued functions in the right hand side of the differential equations (2.2.a) to (2.2.d) respectively. i.e.,

$$f_1(x) = (\mu + \omega) - (\beta I + \varepsilon \beta C + \mu + \omega)S - \omega E - \omega I - \omega C,$$

$$f_2(x) = (\beta I + \varepsilon \beta C)S - (\sigma + \mu)E, \quad f_3(x) = \sigma E - (\gamma + \mu)I \quad \text{and} \quad f_4(x) = \rho \gamma I - (\tau + \mu)C.$$

Each real valued function  $f_i$ ,  $i=1, 2, 3, 4$  is continuous and differentiable with respect to the variables  $S, E, I$  and  $C$ , as well as to respect to each parameter on  $\Omega$ .

For this reason, the function  $f(t, y)$  is continuous on  $\Omega$ , a compact subset of  $C[0, a]$  [25] and it follows that  $f(t, y)$  is uniformly continuous on  $\Omega$ . This completes the condition for the existence of the solution.

By Weierstrass extreme value theorem, the function  $f(t, y)$  attains its maximum, say  $L$ , on this domain. i.e.,  $\text{Max}_{y \in \Omega} |f(t, y)| = L$  or  $L = \|f\|$  and it depends only on the coefficients of the model.

### Lipschitz Condition on $\Omega$ :

Given that the domain  $\Omega$  of interest of the IVP is compact and connected, for  $x, y \in \Omega$ ,  $y - x \in \Omega$ . Furthermore,  $\lambda y - (1 - \lambda)x \in \Omega$  for all  $x, y \in \Omega$ ,  $0 \leq \lambda \leq 1$ . In other words,  $\Omega$  is convex. Now, let  $v = y - x$  and define the function

$$\psi : [0, 1] \rightarrow \mathbb{R}^4 \quad \text{by} \quad \psi(\lambda) = f(t, x + \lambda v) \quad [24] \quad (3.2.1)$$

and differentiating  $\psi$  with respect to  $\lambda$  we obtain:

$$\frac{d\psi(\lambda)}{d\lambda} = \frac{df(t, u)}{du} \frac{du}{d\lambda}, \quad \text{where} \quad u = x + \lambda v$$

$$\frac{d\psi(\lambda)}{d\lambda} = \frac{df(t, u)}{du} v$$

$$d\psi(\lambda) = \frac{df(t, u)}{du} v d\lambda$$

$$\int_0^1 d\psi(\lambda) = \int_0^1 \frac{df(t, u)}{du} v d\lambda$$

$$|\psi(1) - \psi(0)| \leq \int_0^1 \left\| \frac{df(t, u)}{du} \right\| |v| d\lambda \quad (3.2.2)$$

Since  $\frac{df(t, u)}{du}$  being continuous on the compact set  $\Omega$ , by Weierstrass Extreme value

Theorem, there exists a positive number  $M$  such that  $\left\| \frac{df(t, u)}{du} \right\| \leq M$ . Further,

$\psi(1) = f(t, x + 1*(y - x)) = f(t, y)$  and  $\psi(0) = f(t, x + 0*(y - x)) = f(t, x)$ . From (3.2.1), it follows that

$$|f(t, y) - f(t, x)| \leq M |y - x| \quad \text{for all} \quad x, y \in \Omega. \quad (3.2.3)$$

It follows from this inequality that the function  $f$  is Lipschitz on  $\Omega$ .

Define the matrix  $A$  by  $A = \frac{df(t,u)}{du}$ , then

$$A = \begin{bmatrix} -(\beta I + \varepsilon BC + \mu + \omega) & -\omega & -(\beta S + \omega) & -(\varepsilon \beta S + \omega) \\ \beta I + \varepsilon \beta C & -(\sigma + \mu) & \beta S & \varepsilon \beta S \\ 0 & \sigma & -(\gamma + \mu) & 0 \\ 0 & 0 & \rho \gamma I & -(\tau + \mu) \end{bmatrix}$$

Now, Euclidian norm of  $A$  is given by

$$\|A\|^2 = |\beta I + \varepsilon BC + \mu + \omega|^2 + |\omega|^2 + |\beta S + \omega|^2 + |\varepsilon \beta S + \omega|^2 + |\beta I + \varepsilon \beta C|^2 + |\sigma + \mu|^2 + |\beta S|^2 + |\varepsilon \beta S|^2 + |\sigma|^2 + |\gamma + \mu|^2 + |\rho \gamma I|^2 + |\tau + \mu|^2$$

But  $0 \leq S, E, I, C \leq 1$

$$\|A\|^2 \leq |\beta + \varepsilon B + \mu + \omega|^2 + |\omega|^2 + |\beta + \omega|^2 + |\varepsilon \beta + \omega|^2 + |\beta + \varepsilon \beta|^2 + |\sigma + \mu|^2 + |\beta|^2 + |\varepsilon \beta|^2 + |\sigma|^2 + |\gamma + \mu|^2 + |\rho \gamma|^2 + |\tau + \mu|^2$$

All coefficients are positive and less than 1 except probably  $\beta$  which can take values greater than 1, it follows that

$$\begin{aligned} \|A\|^2 &\leq (\beta + \varepsilon B + \mu + \omega)^2 + \omega^2 + (\beta + \omega)^2 + (\varepsilon \beta + \omega)^2 + (\beta + \varepsilon \beta)^2 + (\sigma + \mu)^2 + \beta^2 \\ &\quad + \varepsilon^2 \beta^2 + \sigma^2 + (\gamma + \mu)^2 + \rho^2 \gamma^2 + (\tau + \mu)^2 \\ \|A\|^2 &\leq 2(\beta + \varepsilon B)^2 + 2(\beta + \varepsilon B)(\mu + \omega) + (\mu + \omega)^2 + \omega^2 + (\beta + \omega)^2 + (\varepsilon \beta + \omega)^2 + (\sigma + \mu)^2 + \beta^2 \\ &\quad + \varepsilon^2 \beta^2 + \sigma^2 + (\gamma + \mu)^2 + \rho^2 \gamma^2 + (\tau + \mu)^2 \\ \|A\|^2 &\leq 2\beta^2(1 + \varepsilon)^2 + 2\beta(1 + \varepsilon)(\mu + \omega) + (\mu + \omega)^2 + \omega^2 + (\beta + \omega)^2 + (\varepsilon \beta + \omega)^2 + (\sigma + \mu)^2 \\ &\quad + \beta^2(1 + \varepsilon^2) + \sigma^2 + (\gamma + \mu)^2 + \rho^2 \gamma^2 + (\tau + \mu)^2 \end{aligned}$$

As  $1 + \varepsilon^2 \leq (1 + \varepsilon)^2$  and  $\varepsilon \beta + \omega \leq \beta + \omega$  the above reduces to

$$\|A\|^2 \leq 3\beta^2(1 + \varepsilon)^2 + 2\beta(1 + \varepsilon)(\omega + \mu) + (\omega + \mu)^2 + 2(\beta + \omega)^2 + (\sigma + \mu)^2 + (\gamma + \mu)^2 + (\tau + \mu)^2 + \rho^2 \gamma^2 + \sigma^2 + \omega^2$$

Letting

$$M = \left[ 3\beta^2(1 + \varepsilon)^2 + 2\beta(1 + \varepsilon)(\omega + \mu) + (\omega + \mu)^2 + 2(\beta + \omega)^2 + (\sigma + \mu)^2 + (\gamma + \mu)^2 + (\tau + \mu)^2 + \rho^2 \gamma^2 + \sigma^2 + \omega^2 \right]^{\frac{1}{2}}$$

The inequality (3.2.3) is satisfied for all  $x, y \in \Omega$ .

**Uniqueness of the solution:**

A  $C[0, a]$  function  $y(t)$  is the solution of the IVP  $\frac{dy}{dt} = f(t, y); y(t_0) = y_0$  if and only if  $y(t)$  is the solution of the integral equation  $y(t) = y_0 + \int_0^t f(s, y) ds$  for all  $t \in [0, a]$ .

Let us approximate the solution to this integral equation by Picard's theorem and thus define the basic iterations as follows:

$$\begin{aligned} y_0(t) &= y_0 \\ y_{k+1}(t) &= y_0 + \int_0^t f(\xi, y_k(\xi)) d\xi \\ k &= 0, 1, 2, \dots \end{aligned} \quad (3.3.1)$$

Let  $\epsilon > 0$  be any enough large positive real number that satisfies  $|f(t, y_k(t)) - f(t, y_0)| < \epsilon$  for all  $k = 1, 2, 3, \dots$  and for any  $t \in [0, a]$ . Then, by the uniform continuity of  $f$  on  $\Omega$ , there exists a positive real number  $\delta > 0$ , depending only on  $\epsilon$ , for which  $|y_k(t) - y_0| < \delta$  for all  $k = 1, 2, 3, \dots$  i.e.,  $y_k(t) \in N_\delta(y_0)$ , for any  $t \in [0, a]$ .

Where  $N_\delta(y_0) = \{y(t) \in \Omega : |y(t) - y_0| < \delta\}$ .

Using (3.3.1) and subtracting the initial iteration from the second one, yield

$$\begin{aligned} |y_{k+1}(t) - y_0| &\leq \int_0^t |f(\xi, y_k(\xi))| d\xi \text{ for all } t \in [0, a] \text{ and for all values of } k = 0, 1, 2, \dots \\ |y_{k+1}(t) - y_0| &\leq \int_0^t \text{Max}_{y \in \Omega} |f(\xi, y(\xi))| d\xi \text{ for all } t \in [0, a] \text{ and for all values of } \\ k &= 0, 1, 2, \dots \\ |y_{k+1}(t) - y_0| &\leq La \text{ for all } t \in [0, a] \text{ and for all values of } k = 0, 1, 2, \dots \end{aligned} \quad (3.3.3)$$

Clearly, from (3.3.2) and (3.3.3) result the inequality:

$$0 < a < \frac{\delta}{L} \quad (3.3.4)$$

By Picard's iterations, we deduce a sequence  $\{y_n(t)\}$  of approximate solutions to IVP which, for some prescribed conditions, would converge uniformly to the solution  $y(t)$  as  $n$  tends to infinity on the Banach space  $\Omega$ . For the sake of the said conditions, establish a functional inductive relation between two consecutive approximate solutions  $y_{k+1}(t)$  and  $y_k(t)$ . Using the iterative defined by (4) and letting  $k = 1$

$$|y_2(t) - y_1(t)| \leq \int_0^t |f(\xi, y_1(\xi)) - f(\xi, y_0(\xi))| d\xi$$

$$|y_2(t) - y_1(t)| \leq M \int_0^t |y_1(\xi) - y_0(\xi)| d\xi$$

Using (3.3.3) we obtain:

$$|y_2(t) - y_1(t)| \leq M \int_0^t L a d\xi$$

$$|y_2(t) - y_1(t)| \leq M L a^2$$

$$|y_2(t) - y_1(t)| \leq \frac{M}{L} \delta^2$$

For  $k = 2$  we have:

$$|y_3(t) - y_2(t)| \leq \int_0^t |f(\xi, y_2(\xi)) - f(\xi, y_1(\xi))| d\xi$$

$$|y_3(t) - y_2(t)| \leq M \int_0^t |y_2(\xi) - y_1(\xi)| d\xi$$

$$|y_3(t) - y_2(t)| \leq M \frac{M}{L} \delta^2 \int_0^t d\xi$$

$$|y_3(t) - y_2(t)| \leq \left(\frac{M}{L}\right)^2 \delta^3$$

In general, for any  $k = j$ ,  $y_{j+1}(t)$  and  $y_j(t)$  satisfy the following formula:

$$|y_{j+1}(t) - y_j(t)| \leq \left(\frac{M}{L}\right)^j \delta^{j+1} \text{ for } t \in [0, a] \quad (3.3.5)$$

The sequence  $\{y_n(t)\}$  defined on the compact subset  $\Omega \subseteq C[0, a]$  converges only if it is a Cauchy sequence. i.e., if for any  $\tilde{\epsilon} > 0$  there exists a positive integer  $N$  such that  $|y_m(t) - y_n(t)| < \tilde{\epsilon}$  for all  $m, n > N$

Now let's consider the following expression,

$$\begin{aligned} |y_n(t) - y_m(t)| &\leq |y_n(t) - y_{n-1}(t) + y_{n-1}(t) - y_{n-2}(t) + \dots + y_{m-1}(t) - y_m(t)| \\ |y_n(t) - y_m(t)| &\leq |y_n(t) - y_{n-1}(t)| + |y_{n-1}(t) - y_{n-2}(t)| + \dots + |y_{m+1}(t) - y_m(t)| \\ |y_n(t) - y_m(t)| &\leq |y_{m+(n-m)}(t) - y_{m+(n-m-1)}(t)| + |y_{m+(n-m-1)}(t) - y_{m+(n-m-2)}(t)| + \dots + |y_{m+1}(t) - y_m(t)| \\ |y_n(t) - y_m(t)| &\leq \sum_{i=m}^{n-m} |y_{m+i}(t) - y_m(t)| \end{aligned} \quad (3.3.6)$$

Using (3.3.5) in (3.3.6) we obtain the inequality

$$|y_n(t) - y_m(t)| \leq \sum_{i=m}^{n-m} \left(\frac{M}{L}\right)^i \delta^{i+1} \quad (3.3.7)$$

Since,  $f(t, y)$  is Lipschitz, uniformly continuous function on  $\Omega$ ,  $\delta$  can be expressed in terms of  $\epsilon$  as follows:

For the said  $\epsilon > 0$ ,  $|f(t, y) - f(t, x)| < \epsilon$  whenever  $|y - x| < \delta$  for all  $x, y \in \Omega$  and considering (3.2.3), It follows;

$$M|y - x| < \epsilon$$

$$|y - x| < \frac{\epsilon}{M}$$

Finally

$$\delta = \frac{\epsilon}{M} \tag{3.3.8}$$

Using (3.3.8) in (3.3.7) results:

$$|y_n(t) - y_m(t)| \leq \sum_{i=m}^{n-m} \left(\frac{M}{L}\right)^i \delta^{i+1}$$

$$|y_n(t) - y_m(t)| \leq \frac{1}{M} \sum_{i=m}^{n-m} \left(\frac{M}{L} \times \frac{\epsilon^{1+\frac{1}{i}}}{M}\right)^i$$

For  $n \rightarrow \infty$  and putting  $h = \frac{\epsilon}{L}$ , the above inequality becomes

$$|y_n(t) - y_m(t)| \leq \frac{\epsilon}{M} \sum_{i=m}^{\infty} h^i \tag{3.3.9}$$

The series in the RHS of (3.3.9) converges to  $\frac{h^m}{1-h}$  as  $m \rightarrow 0$  only if  $|h| < 1$ . Since,  $\epsilon$  can't be made smaller as it is pleased for this reason the sequence of approximate the solution to IVP converges only if  $L > \epsilon$  and then  $|y_n(t) - y_m(t)| \rightarrow 0$  as  $n \rightarrow 0$  and hence the sequence  $(y_n(t))$  converges uniformly to the unique value, say  $y(t)$ , on a Banach space  $\Omega$ .

As  $y_n(t)$  satisfies (3.3.1),

$$y_n(t) = y_0 + \int_0^t f(\xi, y_n(\xi)) d\xi \text{ and taking high values of } n, \text{ we realize that}$$

$$y(t) = y_0 + \int_0^t f(\xi, y(\xi)) d\xi \text{ which is unique on } \Omega .$$

## Conclusion

Without loss of the generality,  $0 < \epsilon \leq 1$  and within this limit of  $\epsilon$ , for the existence and uniqueness of the solution to the amoebiasis transmission model will be conditioned by the value of the Lipschitz constant  $M$  and specifically by the value of  $L$ . As long as  $L$  depends only on the value of the coefficients of the model, these coefficients should satisfy the condition  $L > 1$ . It is only under this condition that the solution to the IVP will exist and be unique over the period of time bounded above by

$\frac{1}{ML}$ . Thus, the minimum interval of time within the outbreak of amoebiasis, over which the configuration of the dynamics transmission of amoebiasis is well defined should be  $\left[0, \frac{1}{ML}\right]$ .

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