



## Mathematical Model for the Molecular Dynamics of Hemophilia in A Population Incorporating Gene Screening and Mutation

Safiyanu Adamu<sup>1</sup>, Ibrahim Isa Adamu<sup>1</sup>, Usman Alani Solomon<sup>2</sup>, Hanifa Umar Yusuf<sup>1</sup>,  
John Samuel Zira<sup>1</sup> & Mohammed Manga<sup>1</sup>

<sup>1</sup>Department of Mathematics, Modibbo Adama University of Technology, Yola, Nigeria

<sup>2</sup>Department of Land Information, National Center for Remote Sensing, Jos, Nigeria

Corresponding Author's E-mail: [safiyanadam56@gmail.com](mailto:safiyanadam56@gmail.com)

### Abstract

Genetic diseases constitute a spreading threat to healthy life in a population. Population epidemiological studies are required to learn the prevalence of disease causing environmental exposure in genetically susceptible individuals. In this paper, the population partitioned into seven compartments and modeled the interaction dynamics. An ordinary Linear system of differential equations was developed to monitor the size of populations of hemophilia. We analyzed the model where the existence of the solution of the system was confirmed and the validity of the model was proven by establishing the positivity of solutions. We solved the system to obtain an analytical solution. We established the Hemophilia Free Equilibrium (HFE) and computed the local equilibriums. The results show that the HFE was stable.

**Keywords:** Hemophilia, Chromosomes, Gene, Equilibrium Points

### Introduction

Hemophilia (Royal or bleeding) is an inheritable genetic disorder that impairs the body's ability to make blood clots, a process needed to stop bleeding. There are two basic classes of hemophilia; hemophilia A which occurs due to insufficient clotting factor VIII and hemophilia B which occurs due to insufficient clotting factor IX. Hemophilia is one of the X-linked (sex-linked) genetic recessive disorders at the X – chromosomes. X – linked recessive disorder is that which requires the gene to be 'a recessive gene' and the gene is at the X – chromosomes. There are studies carried out to analyze the inheritance dynamics of any gene not necessarily a gene responsible for a genetic disease placed on the X – Chromosomes (Carmen, Francesca, Luigi & Martin 2017). The abnormal gene responsible for hemophilia is carried on the X chromosome. Females have two X chromosomes. A female with the hemophilia gene on one of her two X chromosomes is called a hemophilia carrier. But the presence of the hemophilia gene on one X may not cause her to have hemophilia if the normal gene on the other X chromosome compensates. Males have only one X chromosome, so the presence of the hemophilia gene on a male's X chromosome results in the deficiency or absence of FVIII or FIX. Affected men do not transmit the disorder to their sons, but all of their daughters are obligate carriers (Regina, 2012)

### Complications, Disabilities due to Hemophilia and Treatment

The exact costs of hemophilia are not easy to pin down. Before the 1980s factor concentrates were prepared from thousands of donors and pooled. The contamination with the virus of pooled preparations was common (Bree & Leonard, 2013). Mayo clinic report (Dec. 20,2018) highlighted complications caused by hemophilia as; *Deep internal bleeding, Damage to joints, Infection, Adverse reaction to clotting factor treatment, etc.* Hemophilia disease complications lead to disabilities when not managed properly. According to Mayo Clinic, a debilitating inhibitor knows what it is like to experience disability in some shape or form. A person with less than 1 percent clotting factor without an inhibitor who treats two or three times a week can experience life with few if any joint bleeding. It cannot simply be said that hemophilia is not a disability or say it is a disability. The unfortunate truth is that in 2018 despite new treatments, hemophilia is a disability. The complications in hemophilia disease lead to the search for medication to relieve patients from the severe pain caused by the disease. A bleeding disorder is treated by factor replacement in hemophilia. The standard cure is an early factor replacement. Factor can be administered during an episode of bleeding (on-therapy) or in a prophylactic manner in the absence of bleeding (Bree and Leonard, 2013). There is currently no cure for hemophilia. It can be treated or managed by factor replacement infusions, which medically add the blood factors that aid in clotting and coagulation (Nabila, 2017)

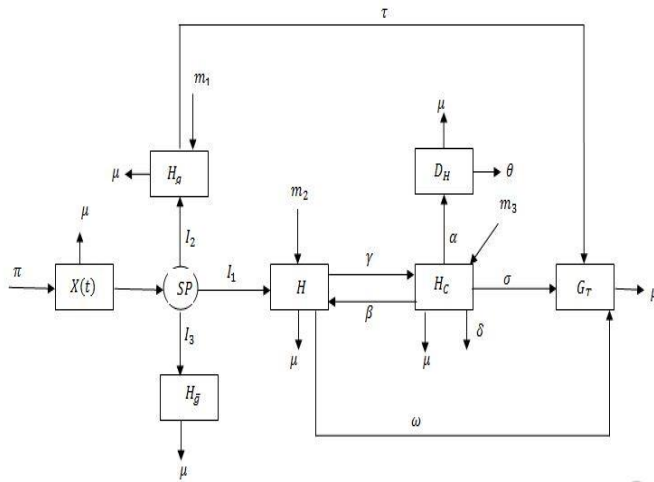


Figure 1. Flow diagram of the Hemophilia dynamics model

**Model formulation**

The model is formulated based on the following assumptions:

- i. Recruitment by birth is strictly into the unscreened compartment and at a constant rate
- ii. Genetic screening is instituted at the population level
- iii. Gene therapy is instituted at the population level of diseased individuals ( $H(t)$ ), individuals with hemophilia complications ( $H_c(t)$ ), and the individual who are hemophilia gene carriers ( $H_g(t)$ ).
- iv. The incidences of developing Hemophilia is constant
- v. Immigration rate of hemophiliacs without complications, hemophiliacs with complications and disabilities into  $H(t)$ ,  $H_c(t)$  and  $H_g(t)$  respectively are constant
- vi. Individuals develops the disease without complications first and progress to the state of complications and can recover from complications if properly managed
- vii. Individuals with complications develops disability and cannot recover from the disability

viii. Diseased individuals may die as a result of complications, disability, or naturally

**Table 1:** Definitions of Variables and Parameters of the Extended Model

Variable /parameters	Description
$X(t)$	Unscreened individuals at time, t
$H_g(t)$	Individual with hemophilia gene carriers at time, t
$H_g(t)$	Individual without hemophilia gene at time, t
$H(t)$	Individuals with mild hemophilia at time, t
$H_c(t)$	Hemophilia with complication individuals at time, t
$D_H(t)$	Disability due to hemophilia complications at time, t
$G_T(t)$	Individuals that undergo genetic therapy at time, t
$\pi$	Birth rate into the total population
$\gamma$	Rate of developing complications
$\beta$	Rate of recovery from complications
$\alpha$	Rate of becoming disabled
$\mu$	Natural mortality rate
$\delta$	Death rate due to hemophilia complications
$\theta$	Death rate as a result of disabilities
$I_i$	Incidence rate of developing hemophilia, $i=1,2,3$ .
$\tau$	Rate at which Hemophilia carriers undergo genetic therapy
$\omega$	Rate at which Hemophiliacs without complications undergo therapy
$\sigma$	Rate at which Hemophiliacs with complications undergoes genetic therapy
$m_i$	Rate of immigration of hemophiliacs into $H_g$ , $H$ and $H_c$ respectively, $i=1,2,3$

By considering the model assumptions, state variables and parameters, the ordinary linear system of differential equations which describes the dynamics of hemophilia in a population is as follows:

$$\frac{dX}{dt} = \pi - \mu X - (I_1 + I_2 + I_3)X \tag{2.1}$$



$$\frac{dH}{dt} = I_1X - (\mu + \omega + \gamma)H + \beta H_c + m_2 \tag{2.2}$$

$$\frac{dH_g}{dt} = I_2X - (\mu + \tau)H_g + m_1 \tag{2.3}$$

$$\frac{dH_{\bar{g}}}{dt} = I_3X - \mu H_{\bar{g}} \tag{2.4}$$

$$\frac{dH_c}{dt} = \gamma H - (\beta + \alpha + \delta + \mu + \sigma)H_c + m_3 \tag{2.5}$$

$$\frac{dD_H}{dt} = \alpha H_c - (\theta + \mu)D_H \tag{2.6}$$

$$\frac{dG_T}{dt} = \tau H_g + \omega H + \sigma H_c - \mu G_T \tag{2.7}$$

With the following initial conditions

$$X(0) = X_0 \geq 0, H(0) = H_0 \geq 0, H_g(0) = H_{0g} \geq 0, H_{\bar{g}}(0) = H_{0\bar{g}} \geq 0, H_c(0) = H_{0c} \geq 0,$$

$$D_H(0) = D_{0H} \geq 0, G_T(0) = G_{0T} \geq 0$$

(2.8)

**Analysis of the Model**

In this section we shall analyze the system of model equations (2.1) – (2.8). these involves existence and uniqueness, positivity, Analytical solution, local stability.

**Uniqueness and Existence**

**Theorem 1.**

If  $f_i$  and  $\frac{\partial f_i}{\partial y_i}$  are continuous functions of  $x, y$  in some interval rectangle;  $\{ (x, y) : \alpha < x < \beta; \gamma < y < \delta \}$  containing the point  $(x_0, y_0)$ , then in some interval  $x_0 - \delta < x < x_0 + \delta$  such that  $\delta > 0$ , then there exist a unique solution.

**Proof**

From equation (2.1) - (2.7), we let:

$$f_1 = \pi - \mu X - (I_1 + I_2 + I_3)X$$

$$f_2 = I_1X - (\mu + \omega + \gamma)H + \beta H_c + m_2$$

$$f_3 = I_2X - (\mu + \tau)H_g + m_1$$

$$f_4 = I_3X - \mu H_{\bar{g}}$$

$$f_5 = \gamma H - (\beta + \alpha + \delta + \mu + \sigma)H_c + m_3$$

$$f_6 = \alpha H_c - (\theta + \mu)D_H$$

$$f_7 = \tau H_g + \omega H + \sigma H_c - \mu G_T$$

Clearly  $f_i; i = 1, 2, 3, 4, 5, 6, 7$  are continuous, hence the solution for the system exist

Now the partial derivative with respect to the dependent variables are presented as follows

$$\frac{\partial f_1}{\partial X} = -(\mu + I_1 + I_2 + I_3)$$

$$\frac{\partial f_2}{\partial H} = -(\mu + \omega + \gamma)$$

$$\frac{\partial f_3}{\partial H_g} = -(\mu + \tau)$$

$$\frac{\partial f_4}{\partial H_{\bar{g}}} = -\mu$$

$$\frac{\partial f_5}{\partial H_c} = -(\beta + \alpha + \delta + \mu + \sigma)$$

$$\frac{\partial f_6}{\partial D_H} = -(\theta + \mu)$$

$$\frac{\partial f_7}{\partial G_T} = -\mu$$

We can observe here that all the partial derivatives

$$\frac{\partial f_i}{\partial y_i}, i(1)7 \text{ exist and are continuous.}$$

Since both  $f_i$  and  $\frac{\partial f_i}{\partial y_i}$  are continuous, then the system has a unique solution with the initial conditions.

**Solution to the Linear System**

We solve the system of the ode (2.1-2.7) as follows



$$\begin{aligned} \frac{dX}{dt} + AX &= \pi \\ \frac{dH}{dt} - I_1X + BH - \beta H_C &= m_2 \\ \frac{dH_g}{dt} - I_2X + CH_g &= m_1 \\ \frac{dH_g^-}{dt} - I_3X + \mu H_g^- &= 0 \\ \frac{dH_C}{dt} - \gamma H + EH_C &= m_3 \\ \frac{dD_H}{dt} - \alpha H_C + FD_H &= 0 \\ \frac{dG_T}{dt} - \omega H - \tau H_g - \sigma H_C + \mu G_T & \end{aligned}$$

To obtain the following results

$$\begin{aligned} X(t) &= \frac{\pi}{A} + Ce^{-At} \\ H(t) &= A_1e^{-t} + A_2 \cos t + A_3 \sin t + \frac{\pi I_1 + A\beta m_3 + AEm_2}{P_3} \\ H_g(t) &= e^{-\frac{1}{2}t} (B_1 \cos \frac{3}{2}t + B_2 \sin \frac{3}{2}t) + \frac{C\pi I_2 + ACm_1}{Q_3} \\ H_g^-(t) &= e^{-\frac{1}{2}t} (C_1 \cos \frac{3}{2}t + C_2 \sin \frac{3}{2}t) + \frac{\pi I_3}{Q_2} \\ H_C(t) &= E_1e^{-t} + E_2 \cos t + E_3 \sin t + \frac{\pi I_3}{S_3} \\ D_H(t) &= e^{-\frac{\sqrt{5}-1}{4}t} \left( F_1 \cos \sqrt{\frac{\sqrt{5}-5}{8}}t + F_2 \sin \sqrt{\frac{\sqrt{5}-5}{8}}t \right) + e^{\frac{(\sqrt{5}-1)}{4}t} \left( F_3 \cos \left( \frac{1}{2} \sqrt{\frac{\sqrt{5}+5}{2}}t \right) + F_4 \sin \left( \frac{1}{2} \sqrt{\frac{\sqrt{5}+5}{2}}t \right) \right) + \frac{\pi\gamma I_1 + ABm_3\alpha + Am_2\alpha\gamma}{T_4} \\ G_T(t) &= G_1e^{-t} + e^{-\frac{1}{2}t} (G_2 \cos \frac{3}{2}t + G_3 \sin \frac{3}{2}t) + \frac{C^2\pi\gamma\delta I_1 + C^2\pi\omega I_1 - C\pi\beta\gamma I_2 + ABE\tau m_1 - ABC\delta m_3 + AC\gamma\delta m_2 + AC\beta\omega m_3 + ACE\omega m_2}{U_5} \end{aligned}$$

where

$C, A_i, B_i, C_i, E_i, F_i, U_i, G_i; i(1)5$

are arbitrary constants

where

$$A = \mu + I_1 + I_2 + I_3$$

$$B = \mu + \omega + \gamma$$

$$C = \mu + \tau$$

$$E = \beta + \alpha + \delta + \sigma + \mu$$

$$F = \theta + \mu$$

$$P_3 = ABE - A\beta\gamma$$

$$Q_2 = A^2 + 2AC + C^2$$

$$Q_3 = A^2C + AC^2$$

$$S_3 = ABE - A\beta\gamma$$

$$T_4 = ABEF - AF\beta\gamma$$

$$U_5 = ABCE\mu - AC\beta\gamma\mu$$

### Hemophilia Gene Free Equilibrium

At hemophilia gene free

$$H = H_g = H_c = D_H = G_T = m_1 = m_2 = m_3 = I_1 = I_2 = 0$$

So that

$$\frac{dX}{dt} = \pi - (I_3 + \mu)X$$

$$\frac{dH_g}{dt} = I_3X - \mu H_g$$

Now to obtain the Hemophilia gene free equilibrium states

$$\frac{dX}{dt} = \frac{dH_g}{dt} = 0$$

In a matrix form we have

$$\begin{pmatrix} -P & 0 \\ I_3 & -\mu \end{pmatrix} \begin{pmatrix} X \\ H_g \end{pmatrix} = \begin{pmatrix} -\pi \\ 0 \end{pmatrix}$$

where  $P = \mu + I_3$

Computing  $|A - \lambda I| = 0$

$$\text{where } A = \begin{pmatrix} -P & 0 \\ I_3 & -\mu \end{pmatrix}$$

$$\begin{vmatrix} -P - \lambda & 0 \\ I_3 & -\mu - \lambda \end{vmatrix} = 0$$

$$(-P - \lambda)(-\mu - \lambda) = 0$$



$$\lambda = -P$$

$$\lambda = -\mu$$

Hence the free equilibrium is stable.

So that the hemophilia gene free equilibrium point is;

$$\left( X, H, H_g, H_g^-, H_c, D_H, G_T \right) = \left( \frac{\pi}{P}, 0, 0, \frac{\pi I_3}{\mu P}, 0, 0, 0 \right)$$

### Local Stability Analysis of the Linear System

A solution  $\phi(t)$  to a system of the ordinary differential equation is said to be stable if every solution  $\varphi(t)$  at the initial time  $t=0$  remains close for all future time. The physical stability of a system say  $\bar{z} = Az; t \geq 0, z(0) = 0$  is determined completely by the eigenvalues of the coefficient matrix  $A$  which are the roots of the polynomial  $P(\lambda) = \det(A - \lambda I) = 0$  where  $I$  is the identity matrix (David and Redmond, 2008). The eigenvalues can be real or complex-valued. So that;

- i. Every solution is stable if all the eigenvalues of  $A$  have a negative real part.
- ii. Every solution is unstable if at least one eigenvalue of  $A$  has a positive real part.

Now the system of ode 2.1-2.7 can be expressed in matrix form as

$$\begin{bmatrix} -A & 0 & 0 & 0 & 0 & 0 & 0 \\ I_1 & -B & 0 & 0 & \beta & 0 & 0 \\ I_2 & 0 & -C & 0 & 0 & 0 & 0 \\ I_3 & 0 & 0 & -\mu & 0 & 0 & 0 \\ 0 & \gamma & 0 & 0 & -E & 0 & 0 \\ 0 & 0 & 0 & 0 & \alpha & -F & 0 \\ 0 & \omega & \tau & 0 & \delta & 0 & -\mu \end{bmatrix} \begin{bmatrix} X \\ H \\ H_g \\ H_g^- \\ H_c \\ D_H \\ G_T \end{bmatrix} = \begin{bmatrix} -\pi \\ -m_2 \\ -m_1 \\ 0 \\ -m_3 \\ 0 \\ 0 \end{bmatrix}$$



This system of the form  $Mg = b$

where

$$A = \mu + I_1 + I_2 + I_3$$

$$B = \mu + \omega + \gamma$$

$$C = \mu + \tau$$

$$E = \beta + \alpha + \delta + \sigma + \mu$$

$$F = \theta + \mu$$

Where

$$M = \begin{bmatrix} -A & 0 & 0 & 0 & 0 & 0 & 0 \\ I_1 & -B & 0 & 0 & \beta & 0 & 0 \\ I_2 & 0 & -C & 0 & 0 & 0 & 0 \\ I_3 & 0 & 0 & -\mu & 0 & 0 & 0 \\ 0 & \gamma & 0 & 0 & -E & 0 & 0 \\ 0 & 0 & 0 & 0 & \alpha & -F & 0 \\ 0 & \omega & \tau & 0 & \delta & 0 & -\mu \end{bmatrix}, g = \begin{bmatrix} X \\ H \\ H_g \\ H_g \\ H_c \\ D_H \\ G_T \end{bmatrix}, b = \begin{bmatrix} -\pi \\ -m_2 \\ -m_1 \\ 0 \\ -m_3 \\ 0 \\ 0 \end{bmatrix}$$

To determine the stability of the above system we obtain the characteristics equation  $|M - \lambda I| = 0$  as follows;

$$\begin{vmatrix} -A & 0 & 0 & 0 & 0 & 0 & 0 \\ I_1 & -B & 0 & 0 & \beta & 0 & 0 \\ I_2 & 0 & -C & 0 & 0 & 0 & 0 \\ I_3 & 0 & 0 & -\mu & 0 & 0 & 0 \\ 0 & \gamma & 0 & 0 & -E & 0 & 0 \\ 0 & 0 & 0 & 0 & \alpha & -F & 0 \\ 0 & \omega & \tau & 0 & \sigma & 0 & -\mu \end{vmatrix} - \begin{vmatrix} \lambda & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \lambda & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \lambda & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \lambda & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \lambda & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \lambda & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \lambda \end{vmatrix} = 0$$

$$\begin{vmatrix} -A-\lambda & 0 & 0 & 0 & 0 & 0 & 0 \\ I_1 & -B-\lambda & 0 & 0 & \beta & 0 & 0 \\ I_2 & 0 & -C-\lambda & 0 & 0 & 0 & 0 \\ I_3 & 0 & 0 & -\mu-\lambda & 0 & 0 & 0 \\ 0 & \gamma & 0 & 0 & -E-\lambda & 0 & 0 \\ 0 & 0 & 0 & 0 & \alpha & -F-\lambda & 0 \\ 0 & \omega & \tau & 0 & \sigma & 0 & -\mu-\lambda \end{vmatrix} = 0$$

Evaluating the determinant, we have

$$-(A + \lambda)(C + \lambda)(F + \lambda)(\lambda + \mu)^2[\lambda^2 + (B + E)\lambda - (\beta\gamma - BE)] = 0$$

$$(A + \lambda)(C + \lambda)(F + \lambda)(\lambda + \mu)^2[\lambda^2 + (B + E)\lambda - (\beta\gamma - BE)] = 0$$

Solving the equation gives

$$\lambda_1 = -A$$

$$\lambda_2 = -C$$

$$\lambda_3 = -F$$

$$\lambda_{4,5} = -\mu \text{ twice}$$

and  $\lambda^2 + (B + E)\lambda - (\beta\gamma - BE) = 0$  it follows that

$$\lambda_{6,7} = \frac{-(B + E) \pm \sqrt{(B + E)^2 + (\beta\gamma - BE)}}{2}$$

$$\text{Let } \Delta = \sqrt{(B + E)^2 + (\beta\gamma - BE)}$$

So that

$$\lambda_{6,7} = \frac{-(B + E) \pm \Delta}{2}$$

$$\lambda_6 \text{ is stable if } \Delta < |B + E|$$

All they  $\lambda$ s are negative.

Therefore, since all the eigenvalues of the polynomial have negative real parts, we conclude that the Hemophilia gene endemic equilibrium state is locally stable.

**Conclusion**

Hemophilia disorder causes a threat to health and financial burdens. We studied the dynamics of the Hemophilia gene in a population, considering seven possible compartments. We developed and solved models for the study, where we considered the spread of the hemophilia gene in the population. We could deduce from the results that the spread of the hemophiliacs in the population can be contained with a control on the incidence rates.

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