

# A comprehensive Hemophilia Interaction Network Model

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## ABSTRACT

Haemophilia is a bleeding disorder in which the clotting mechanism does not work properly and it slows down the blood clotting. Persons with this condition experience prolonged bleeding followed by an injury. There are basically two genes which are mainly responsible for this disease (F8 and F9). This paper focuses on finding out novel interaction between genes as well as proteins involved in the process and constructing the pathway using system biology (Cell Designer <http://celldesigner.org/>). According to the concentration of the molecules, the reaction protocols were defined for simulation type using mass action kinetics equations  $V = k^* \pi * S_i$  or irreversible Michaelis-Menten equations  $V = \frac{V_m * S}{K_m + S}$ . Then the parameter like time span, error tolerance and solver were set and finally the haemophilia pathway was executed for simulation. The following data was generated: simulation graph, Signal Injection: Pulse response graph and Reaction Rate(s) Vs Species graph of Haemophilia pathway. This pathway is useful in identifying novel genes as well as proteins which interact with F8 genes with respect to time.

**Keywords:** F8, F9, System Biology, Kinetics, Simulation.

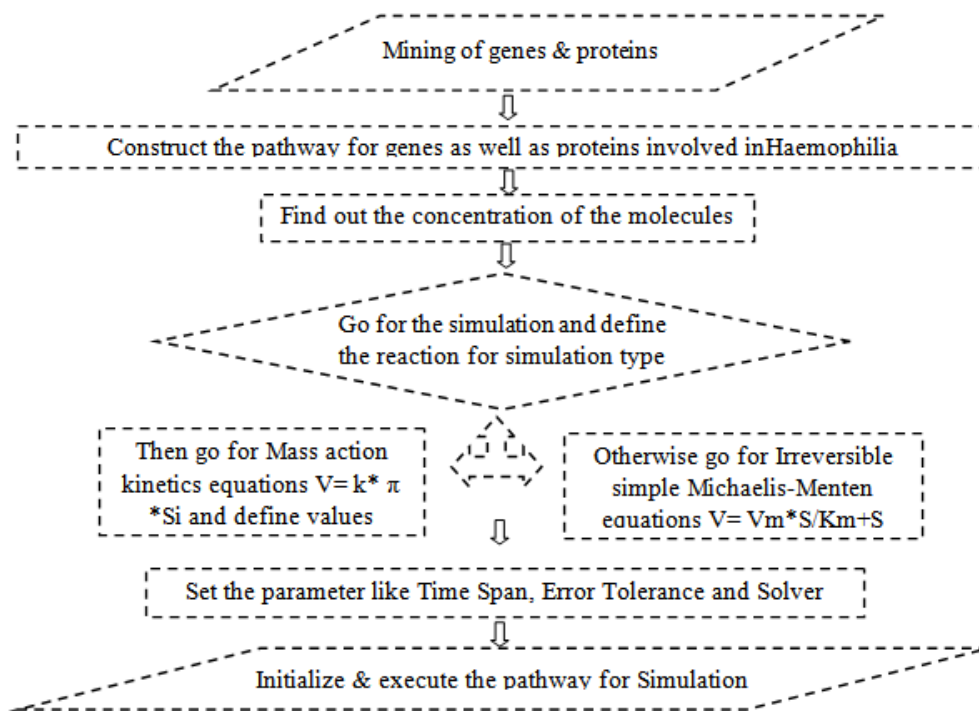
## INTRODUCTION

Haemophilia is a bleeding disorder. Serious complications can result from bleeding. The main types of this condition are haemophilia A (also known as classic haemophilia or F8) and haemophilia B (also known as Christmas disease or F9). Person with an unusual form of haemophilia B, known as haemophilia B Leyden [3-5], experience series of excessive bleeding in childhood but have few bleeding problems after puberty [6-9]. Changes in the *F8* gene are responsible for haemophilia A, while mutations in the *F9* gene cause haemophilia B [10-14]. The *F8* gene provides instructions for making a protein called coagulation factor VIII [15-18]. Associated protein, coagulation factor IX, is produced from the *F9* gene, circulating and binding characteristics of wild-type factor IX [19-22], coagulation factors are proteins that work together in the blood, Blood clots protect the body by sealing off damaged blood vessels and preventing blood loss [23-25]. *F8* or *F9* gene lead to the production of an

abnormal version. These problems with blood clotting lead to continuous bleeding that can be difficult to deal with [26-30]. The mutations that cause severe haemophilia almost completely eliminate the activity of coagulation factor VIII [31, 32]. Haemophilia reduces but does not eliminate the activity of one of these proteins [33]. Coagulation factors circulate in the bloodstream in an inactive form until an injury that damages blood vessels occurs. In response to injury, coagulation factor IX is activated by another coagulation factor called factor X [34-36]. The active protein (sometimes written as coagulation factor IXa) interacts with coagulation factor VIII. A small percentage of mutations delete or insert multiple base pairs or rearrange segments of DNA within the gene. Several mutations near the beginning of the *F9* gene sequence cause haemophilia B Leyden. Several rare mutations in the *F9* gene cause an increased sensitivity (hypersensitivity) to a drug called warfarin which is an anticoagulant.

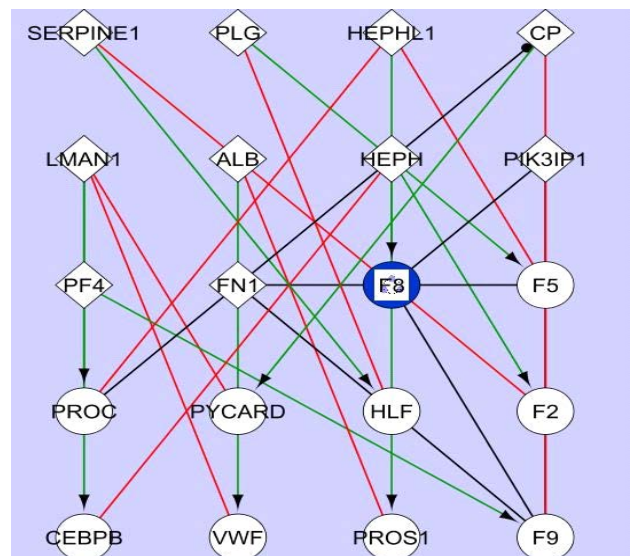
## MATERIALS AND METHODS

The methodology used is depicted in flow chart given below:



1. Data mining of genes & proteins involved in Haemophilia from the literature sources was carried out
2. Constructed the pathway for genes as well as proteins involved in Haemophilia with the help of Cell designer v4.1 <http://celldesigner.org/> [1].
3. The concentration of the molecules was taken from the literature as well as we define some default value for gene and protein concentration.
4. It was followed by simulation. The reaction for simulation type was defined using either Mass action kinetics equations  $V = k * \pi * Si$  or Irreversible simple Michaelis-Menten equation  $V = Vm * S / Km + S$  for all entities (Genes and Proteins).
5. The parameter like Time Span, Error Tolerance of the pathway for the Haemophilia disease for simulation graph were set.
6. Initialized and executed the pathway for Simulation with the help of Simulation Tool (Road Runner) using python script
7. Finally Simulation result graph, Signal Injection: Pulse response graph and Reaction Rate(s) Vs Species graph of Haemophilia pathway were generated.

green colors showed interacting genes and the interacting proteins, diamond shape represents the protein and circle represents the genes, which interact with each other, arrow indicates the relation one to one or one to many or many to many.

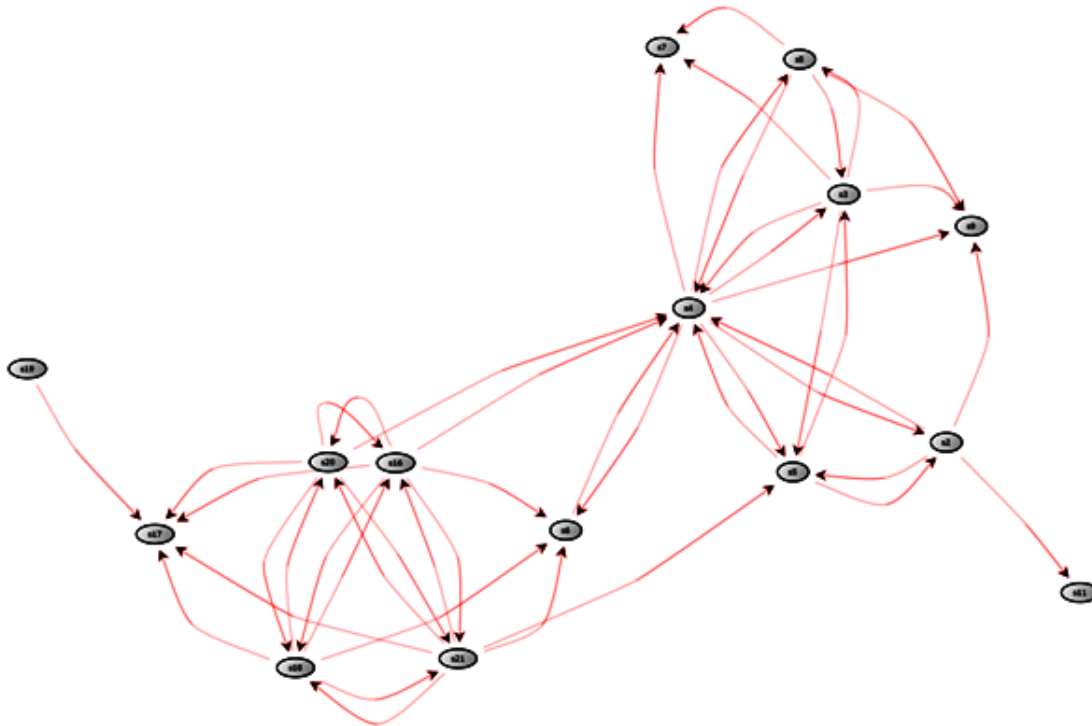


**Figure 1.** Construction of pathway for genes as well as proteins involved in Haemophilia

## RESULTS AND DISCUSSION

Data mining of genes & proteins involved in Haemophilia was carried out from literature sources, then construction of pathway for genes as well as proteins which involved into haemophilia was done with the help of Cell designer v4.1 <http://cytoscape.org/> [2]. In Figure 1 the red, blue,

Orthogonal Layout represents genes and proteins involved in haemophilia with the help of Cytoscape <http://cytoscape.org/> [2], (Figure 2) where red, blue, green colors show interacting genes and the interacting proteins, diamond shape represent the protein and circle represents the genes, which interact with each other.



**Figure 2.** Construction of pathway for genes as well as proteins involved inHaemophilia

According to the concentration of the molecules, we defined the reaction for simulation type using mass action kinetics equations  $V = k \cdot \pi \cdot S_i$  or irreversible simple Michaelis-Menten equations  $V = \frac{V_{max} \cdot S}{K_m + S}$  and set the parameter like time span, error tolerance and solver. Then, the haemophilia pathway for simulation was executed. The parameters of pathway for haemophilia disease where Reaction rate(s) are represented by the s1, s2, s3, s4, s5, s6, s7, s8, s9, s10 and so on and their values in different - different time step units are denoted in Table1.

Mass action kinetics equations dynamic approach to the equilibrium state-

$$\frac{dx}{dt} = k(p - x)^a (q - x)^b$$

Irreversible Michaelis-Menten equations dynamic approach to the equilibrium state-

$$v = \frac{d[p]}{dt} = V_{max} \frac{[S]}{K_m + [S]} = \frac{K_{cat}[E]}{K_m + [S]} \frac{[S]}{K_m + [S]}$$

**Table 1.** Simulation table of pathway for haemophilia disease concentration of the molecules after simulation according to different - different time steps

Time/Name	S1	S2	S3	S4	S5	S6	S7	S8	...
0.0	0.998	0.998	0.942	0.997	0.998	0.0	0.099	0.0	...
1.0	0.998	0.904	0.928	1.223	2.780	3.790	0.773	3.684	...
2.0	0.998	0.946	0.969	1.309	3.237	7.731	0.805	7.552	...
3.0	0.998	0.968	0.992	1.351	3.417	11.78	0.824	11.56	...
4.0	0.998	0.974	1.004	1.372	3.499	15.90	0.824	15.66	...
5.0	0.998	0.987	1.010	1.383	3.538	20.05	0.839	19.79	...
6.0	0.998	0.988	1.013	1.388	3.557	24.21	0.831	23.94	...
7.0	0.998	0.989	1.015	1.390	3.566	28.39	0.833	28.10	...
8.0	0.998	0.989	1.016	1.392	3.570	32.56	0.833	32.27	...
9.0	0.998	0.989	1.016	1.392	3.572	36.92	0.833	36.44	...
10.0	0.998	0.990	1.016	1.392	3.573	40.09	0.834	40.61	...

Figure 3 shows the simulation graph with respect to concentration and time of pathway for haemophilia according to concentration of the molecules. In Figure 3 colored lines represent the entities (Genes and Proteins) which interact with each other with respect to time and Time initialize with 0.0, and time terminal

limit is defined by 10.0. X axis represents the time of pathway and Y axis represents the concentration of pathway, s4 (red), s3 (blue), s9 (green) etc. indicates different type of genes and proteins interacting with each other.

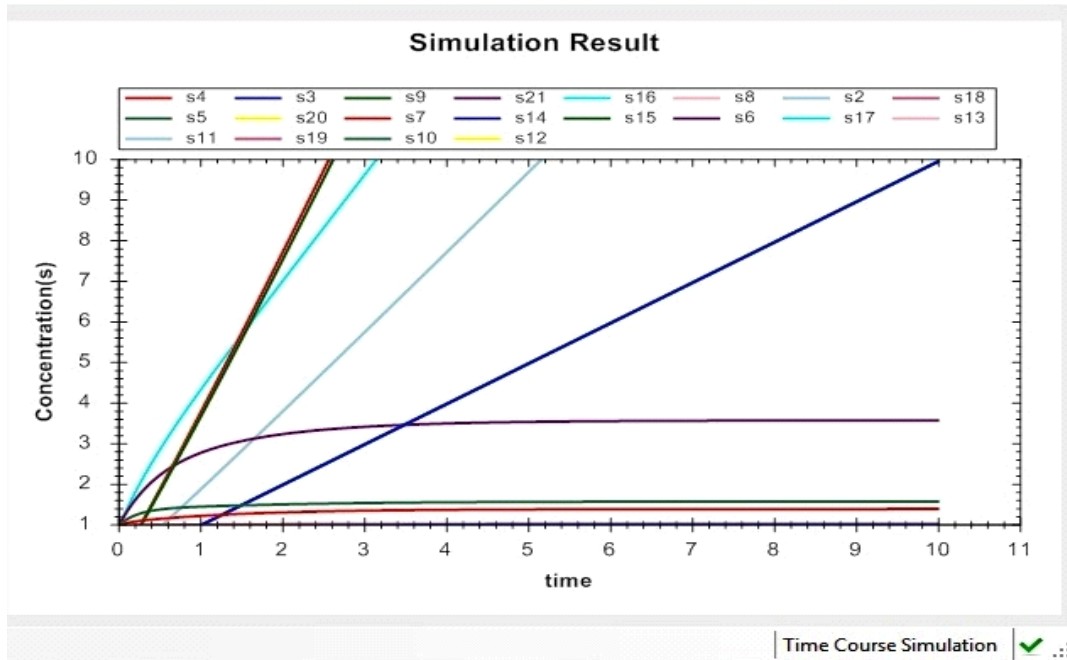


Figure 3.: Simulation graph with respect to concentration and time of pathway for haemophilia.

Pulse Response graph in Figure 4 represents the pulse response with respect to concentration and time of pathway for haemophilia according to concentration of the molecules. The colored lines represent the entities (Genes and Proteins) which interact with each other with respect to End time - 10.0 and Step Size with 0.01.

The X axis represents the time of pathway; Y axis represents the concentration(s) in pathway, and s4 (red), s3 (blue), s9 (green) etc. represents different type of relationship of genes and proteins interacting with each other.

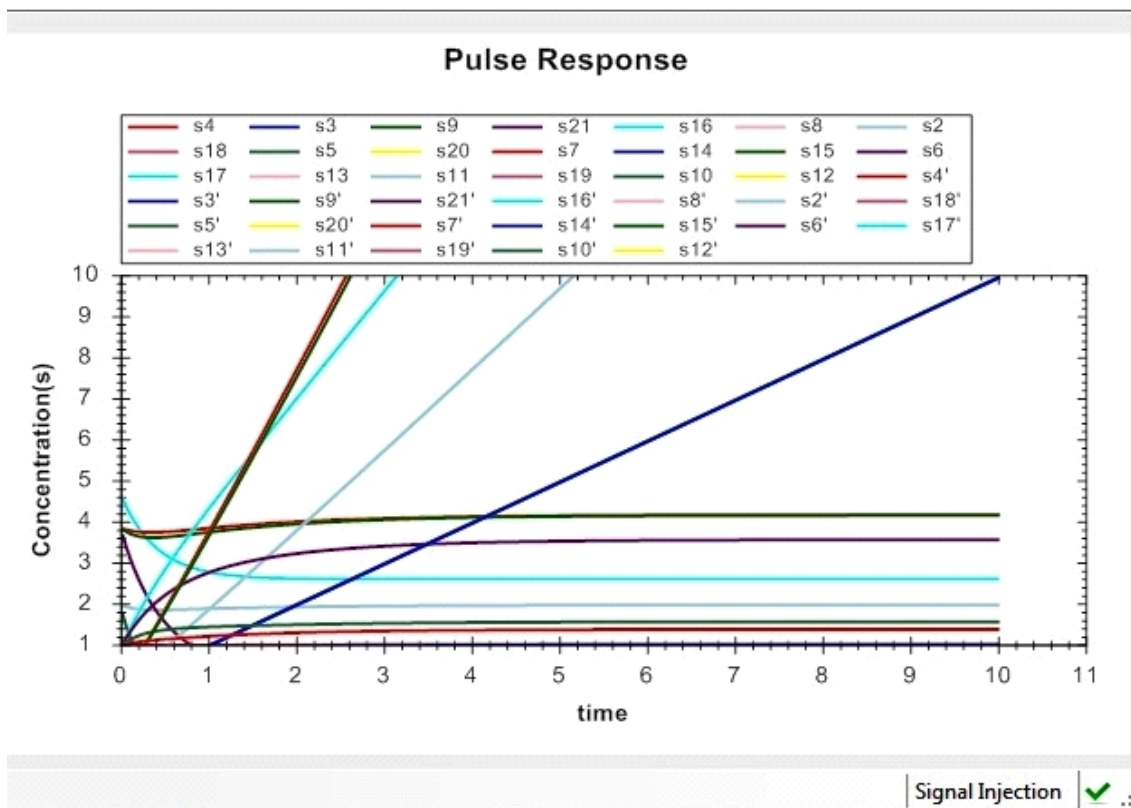


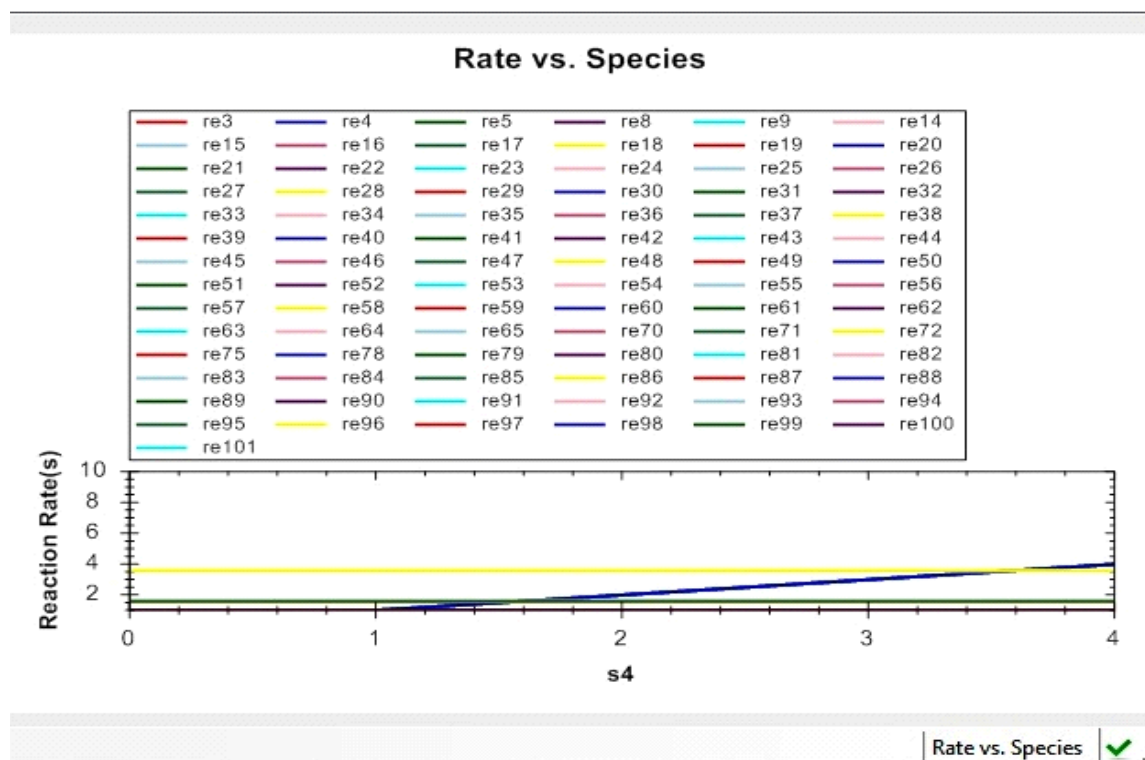
Figure 4. Signal Injection: Pulse response graph with respect to concentration and time of pathway for haemophilia

Rate vs. Species graph represents the relationship between genes and proteins with respect to Reaction Rate(s) and particular species or entities for haemophilia. In Figure 5 colored lines represent the

relationship with Genes as well as Proteins; re3, re4, re5, re8, re9, re14, re15, re16, re17, re18 represents the reaction rate of particular genes as well as proteins which interact with each other. In this graph

parameters are set for the **s4** like MinConcentration (0.0), MaxConcentration(5.0) and StepSize (1.00) as defined by the user. X axis represents the Species (**s4**) of pathway and Y axis represents the Reaction Rate(s)

in pathway, and s3 (red), s4 (blue), s5 (green) etc. represent different type of relationship of genes and proteins interacting with each other.



**Figure 5.** Reaction Rate VS Species graph with respect to reaction rate(s) on Y axis and Species on X axis pathway for haemophilia.

## CONCLUSION

Finding out novel interaction between genes as well as proteins involved in haemophilia disease were carried out, after which pathway was constructed using system biology according to the concentration of molecules. The simulation was carried out and Simulation result graph, Signal Injection: Pulse response graph and Reaction Rate(s) Vs Species graph of Haemophilia pathway were presented. This pathway is useful in identifying which novel genes as well as proteins interact with F8 genes with respect to time(s). The key interacting genes and proteins are F5, HEPH, HLF, PROS1.

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