How Does Genetic Screening Affect a Closed Community Afflicted with the Tay-Sachs Disease?

by

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Introduction

Tay-Sachs disease is an inherited, genetic disorder that has no cure and kills it's victims within the first six years of life. The gene involved creates an enzyme, hexosaminidase A (Hex A) that eliminates the buildup of fatty deposits in the brain and nervous system. If a mutation occurs in the gene that is responsible for producing this enzyme, the brain is unable to remove these deposits and severe brain damage occurs, causing brain damage and eventually killing the child.

Tay-Sachs is a recessive disease, meaning that in order to be born with the disease, an afflicted child must have defective versions of the gene from both his or her mother and father. If the child has one defective version and one correct version of the gene (a carrier) he or she will live a normal life, but there is a possibility that he can pass the gene on to his or her child. A person with two correct genes (non-afflicted) cannot pass the disease to his or her children, although there is a chance a random mutation can occur causing a normal gene to become defective.

Even carriers show signs of the disease, however, such as variations in the Hex-A enzyme that can be detected by blood tests even though enough normal Hex-A is produced to stop the person from experiencing the effects of Tay-Sachs disease. Many private corporations and non-profit organizations now perform blood tests searching for Hex-A and dozens of other genetic diseases in prospective couples prior to marriage. With new technology, large numbers of samples can be processed at reasonable prices. The main issue with genetic screening is ethical – is it right to break up a marriage to prevent the riskto children? Is that playing God? The main problem in screening community is not to actually screen the people, but to convince people to allow themselves to be screened.

Normally, a single Tay-Sachs gene is defective in about 1 in 3000 people in the general population, but in Ashkenazi Jewish communities the rate is 1 in 25. It is unknown why this is, although it is possible that that region in the genome is unstable for Ashkenazi Jews and mutates easily or the gene mutated once and was simply passed down through the generations. This model assumes that the Ashkenazi Jewish community modeled is a closed community, with no marriages outside of the community. Some Orthodox Jewish communities are like this, and as a result they suffer from higher rates of Tay-Sachs disease in their children.

The purpose of this model is to find how effective a screening program would be to help stop afflicted births. People are screened by taking blood samples and looking for certain proteins caused by a carrier mutation. By changing the rate of screening, the effectiveness of a screening program at different levels of intensity can be found.

The Process of Model Building

Our model originally started as a population model with three different population groups: afflicted, carriers and nonafflicted. The proportion of children born to each population group was set in order to keep the model simple, while getting the population growth and death sections to work well.

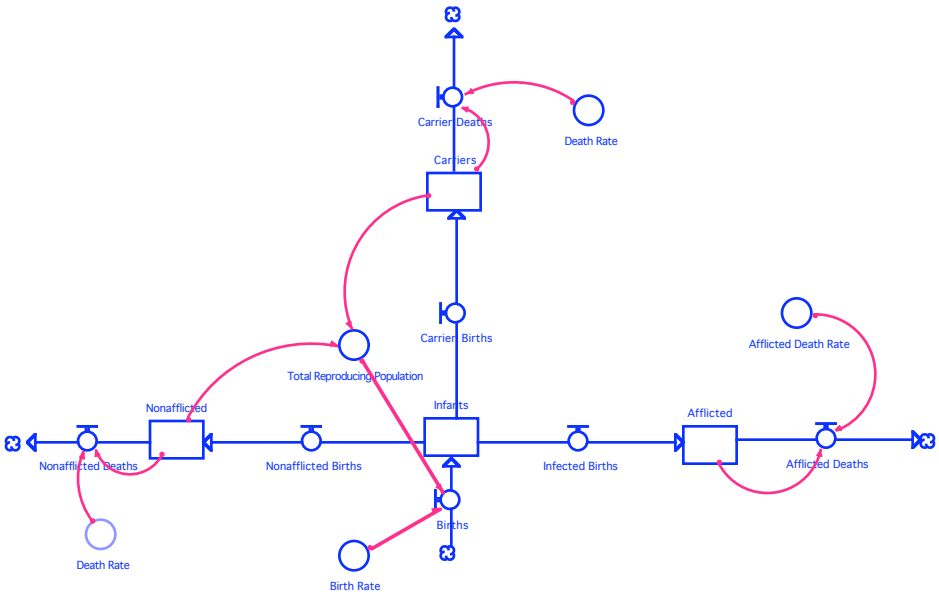


Figure 1: The Basic population model with a centralized newborns stock.

Next we added converters to calculate the exact and changing probabilities of a child being born to each subgroup. Since only carriers and the nonafflicted population live long enough to reproduce, only three possible combinations were considered: carrier-carrier, carrier-nonafflicted and nonafflicted-nonafflicted. In each flow, the total number of births were multiplied with the probability of two people with given genes meeting as well as the

results (the passing of good, defective genes or both) of such a pairing.

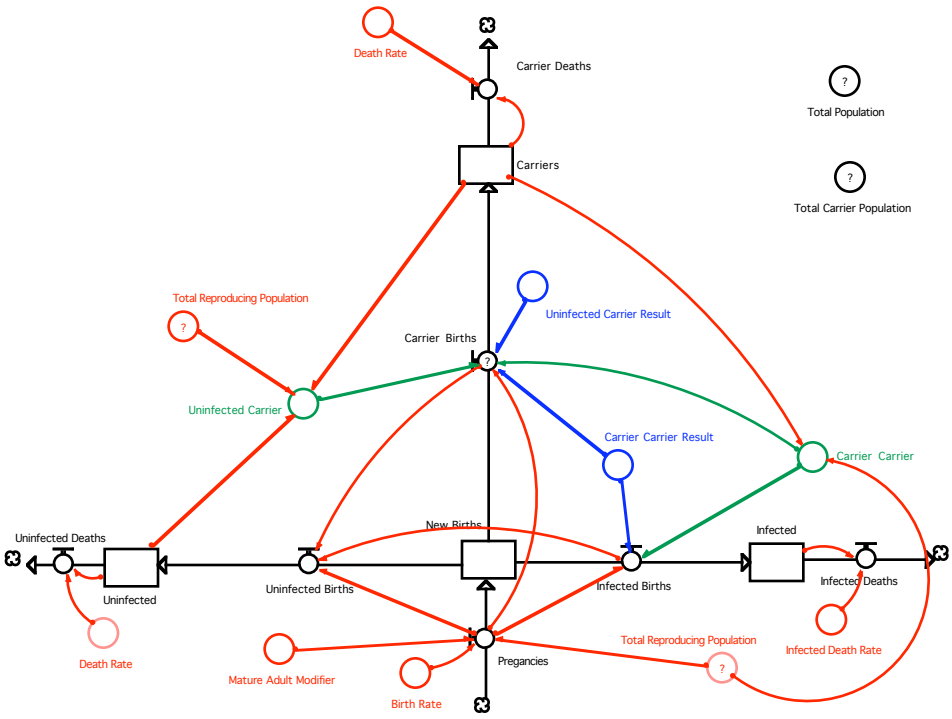


Figure 2: The model with the probability converters for each type of birth.

Finally, the screening component was added. A variable percentage of the population of both carriers and nonafflicted are screened every year. A percentage is used instead of a fixed number because the number of people screened does not reflect the actual capacity that could be screened, but rather the number of people that can be convinced to be screened. There is no effect on nonafflicted people that are screened because everyone assumes they are nonafflicted and proceed with their lives normally when their beliefs are confirmed. Screened carriers, on the other hand, are not allowed to reproduce with other screened carriers and since people screen themselves in pairs before marriage or before having more children, screened carriers are not allowed to reproduce with normal carriers. In addition, new mutations randomly occurring in the human genome can result in Tay-Sachs disease and could cause an nonafflicted baby to be born a carrier (The odds of this are 1/3000). Even more rare is when two mutations occur simultaineously in a nonafflicted baby (1 in 9000000 chance).

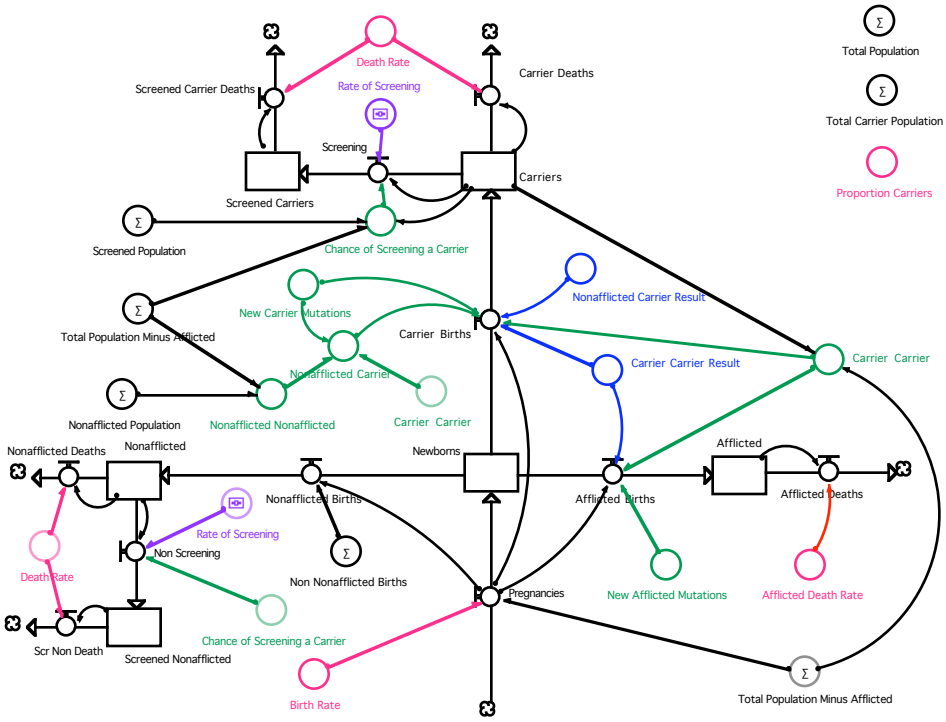


Figure 3: The model with screening components.

The Finished Model and How it Works

The complete model can be found in the Appendix.

In our model, there are three different types of people: those with one Tay-Sachs gene, two Tay-Sachs genes or no Tay-Sachs genes (carriers, afflicted and nonafflicted, respectively). The ratios of the carrier and nonafflicted groups determine what type of reproducing pairs are formed between them, because only carriers and nonafflicteds are allowed to reproduce (people afflicted with the Tay-Sachs disease die by the age of 6, thus they cannot reproduce).

The total carrier and nonafflicted populations are multiplied by the birth rate to find the total number of children born, which is placed into the Newborns stock until each child can be assigned a genotype. The probability of a nonafflicted person reproducing with an nonafflicted person, with a carrier or two carriers reproducing is found by multiplying the probability of any given person being nonafflicted or a carrier by the probability of any other given person being nonafflicted or a carrier divided by two (to represent gender) with the total reproducing population subtracted by one (to represent not reproducing with one's self). An example of this is figure 4. These factors are then multiplied by the total number of births every year and by the outcomes of

each pairing (babies genotype) to find the total numbers of births in each genotype, such as in figure 5.

$$carrier\_carrier = \frac{carriers}{Total\_Population\_Minus\_Afflicted} * \frac{carriers * .5}{Total\_Population\_Minus\_Afflicted - 1}$$

Figure 4: The probability of two carriers reproducing.

$$Carrier\_Births = Carrier\_Carrier * Births * Carrier\_Carrier\_Result$$

Figure 5: Carrier births as a result of carrier-carrier pairs.

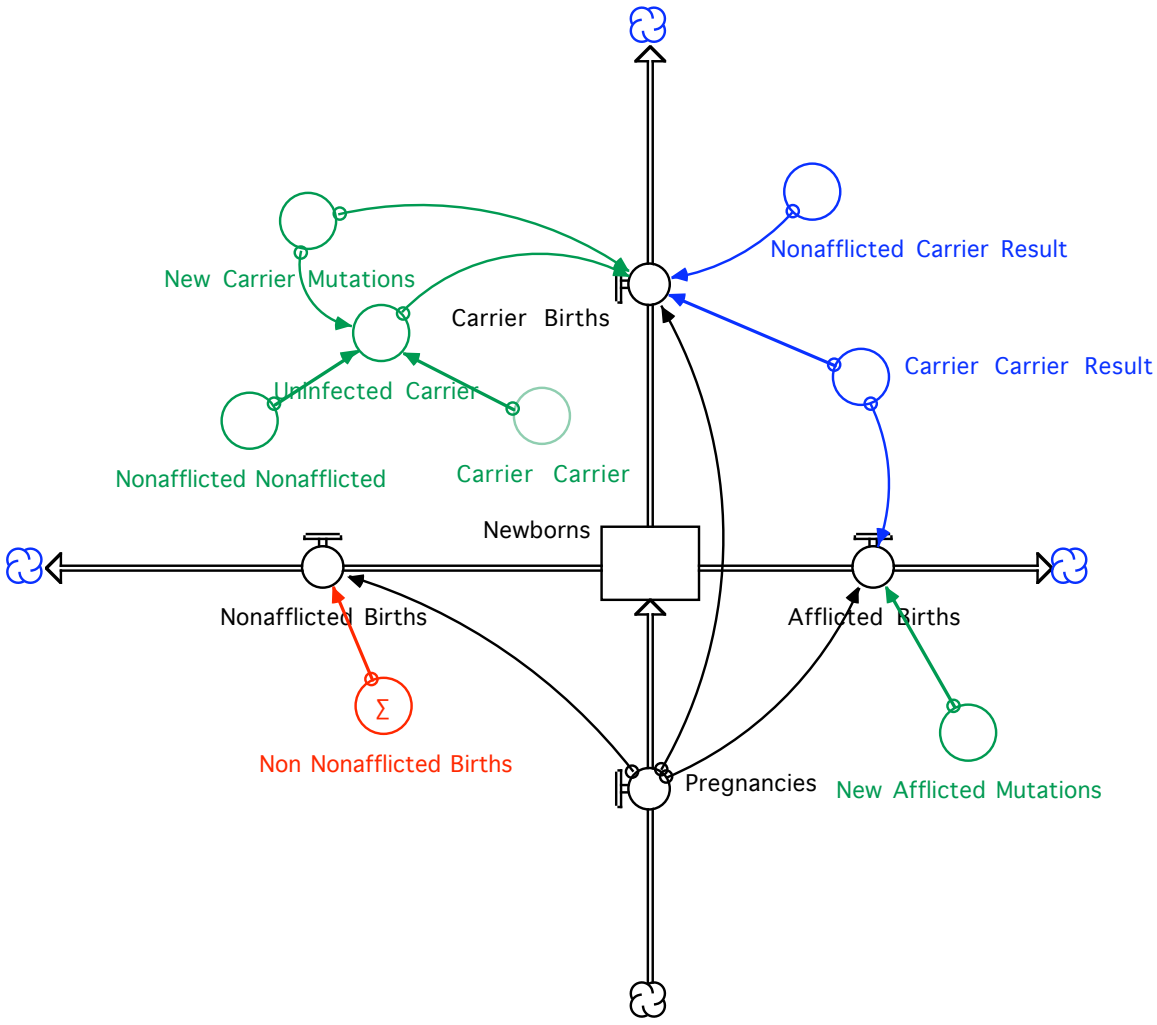


Figure 6: The Births and Pregancies section of the model

After the probability of each pairing is calculated, the probability of different genotypes for the children is determined. The probabilities used are the basis of Mendelian genetics and are confirmed by Dr. Schultz, PhD. The Type of Pair refers to the parents; the Genotype refers to the child. Below are the probabilities used:

Types of Pair/Genotype	Nonafflicted	Carrier	Afflicted
Nonafflicted- Nonafflicted	100%	0%	0%
Nonafflicted -Carrier	50%	50%	0%
Carrier-Carrier	25%	50%	25%

Table 1: The Resulting genes in a baby depending on the genes of the parents.

The total number of pregnancies each year are multiplied by each set of pairing and genotype probabilities to find out how many people are born afflicted, carrier or nonafflicted. Additionally, approximately 1 in 3000 births will have a mutation that will result in Tay-Sachs disease. Because of the way the population of the carriers and nonafflicted affect the probability of each type of birth, a change in any subgrou can affect the future of the entire population.

The screening component simply screens a percentage of the population that has not been screened yet and transfers nonafflicted and carriers from their normal stocks to special screened stocks for each one. In nonafflicted people, this change in stock has no effect other than the fact that screened people will not be screened again. In the carrier portion of the model, screened carriers are not allowed to reproduce with other carriers since one quarter of their children will have Tay-Sachs. This means that screened carriers will only be able to reproduce with nonafflicted people and that the afflicted population will go down as no afflicted people can be born from these pairs. As a result, the percentage of the population screened every year has a major impact on the number of afflicted babies born.

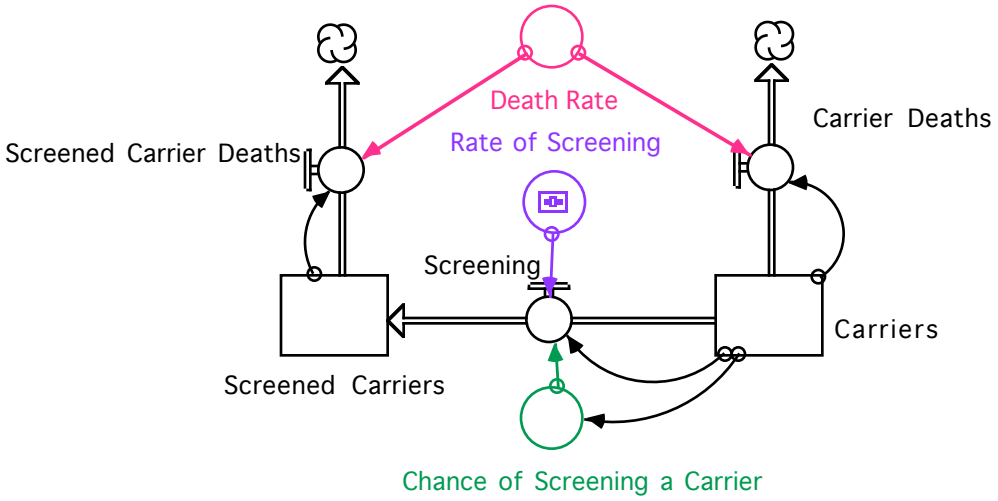


Figure 7: The Carrier screening component

The Model Feedback and Loop Story

The major feedback loop in the model is the proportion of people that are carriers. The more carriers there are the higher the probability that newborns will be born as carriers or afflicted people. This loop is reinforcing, because a high number of carriers means more carrier births, which leads to more carriers. A side effect of this loop is that as the carrier population increases. The afflicted population increases as well. The nonafflicted population has an identical feedback loop, although its side effect is a smaller afflicted population. This loop affects the population of each subgroup and thus affects the entire model by changing the numbers of newborns going into each subgroup. This loop is the basis of the population portion of the model.

Another feedback loop occurs in the screening component. First, the probability of screening a carrier is affected by how many unscreened carriers are in the model. This is a balancing loop because a greater number of unscreened carriers will mean that more are screened every year, decreasing the number of unscreened carriers will mean that more are screened every year, decreasing their numbers. Second is the rate of screening. Because the issue of screening is not technology but ethical, only a certain percentage of the population will have themselves screened each year. This is a balancing loop because fewer people will be screened every year as the proportion of screened people to unscreened people rises. This loop stops the screening program from screening the entire population and affects how effective the

screening program is in terms of carriers screened. This loop is affected by the rate of screening, but this loop is the result is the design of the screening component.

The Model Boundaries

Major Assumptions

This model contains two major assumptions – first that there is not immigration, emigration, war, famine or any other major events occurring in the community. The second is that people in the community will only marry others in the community, that there is absolutely no interbreeding.

The first assumption is made to simplify the population segment of the model. The goal of the model is just to see how screening will affect new afflicted births, not to analyze population trends. Although population-changing events are bound to happen, they would only alter the total population and harm carriers and nonafflicted people equally, thus do not affect the levels of screening.

Second, the community being modeled is an Ashkenazi Orthodox Jewish community, where marriage inside the community is strongly encouraged. Although there are undoubtedly some marriages outside the community, the other variables and population models involved would be a huge undertaking and would not affect the screening program's results significantly due to the fact that most of the community will marry other community members and will face the Tay-Sachs problem.

Another assumption is that two carriers will not reproduce even if they are screened and found to be carriers. It is assumed that a couple will not want to take the risks of having a baby with the disease, but there is no law preventing this or any organization to discourage it, so carriers can, in reality, reproduce with other carriers if they want to.

Choice of Time

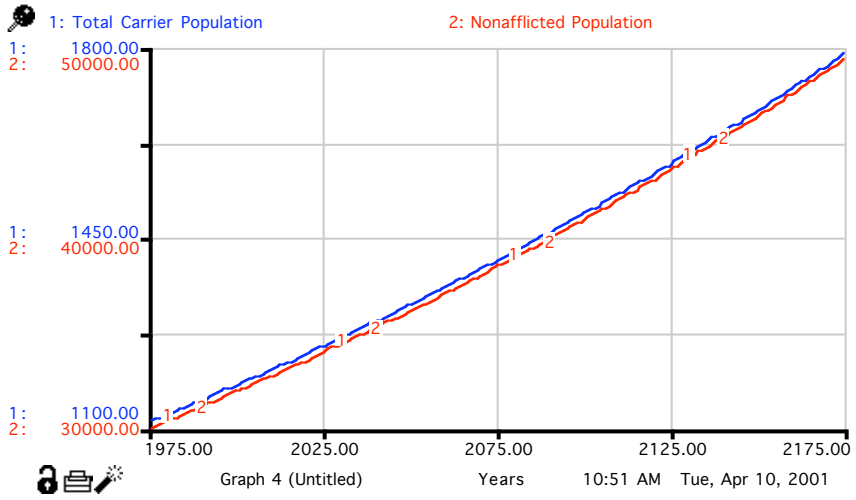
The model runs for 200 years starting from 1975 to 2175. The model runs for this period in order for the screening program to fully take hold and screen the majority of the population. The model starts in 1975 because Tay-Sachs screening programs were started is several Orthodox Jewish in the mid-1970s, although they

are currently screening the populations at different levels of intensity.

Model Testing

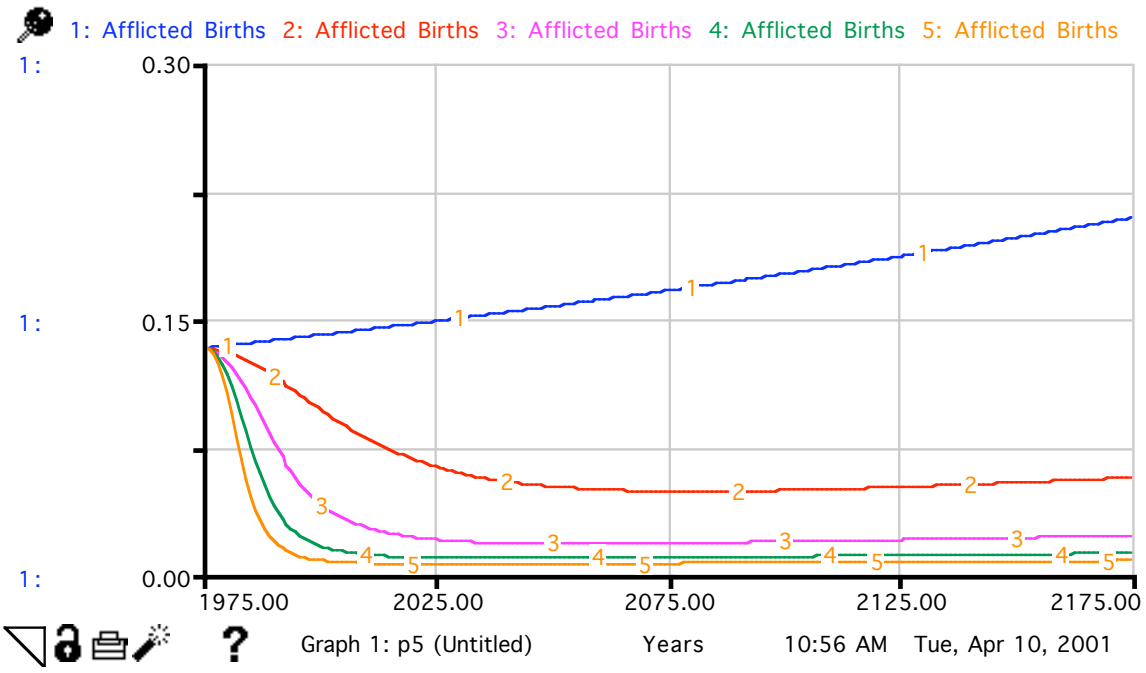
First, the model was tested as a basic population model. In this format, population growth was checked. The growth was large, which was expected because of the relatively high birth rate used. Several different birth and death rates were used, starting with the US Census, then the Israeli Census and finally the birth and death rate of Ashkenazi Jew in Uzbekistan. The goal was to find the rates for only Ashkenazi Jews, and Uzbekistan does have fairly closed communities of Orthodox Ashkenazi Jews, which was the target population.

Secondly, the proportion of each population subgroup and the number of children born to each were tested. The population of carriers must remain proportionally equal to the nonafflicted population due to Hardy-Weinberg equilibrium, which is the principle that a gene that remains in a population for any reasonable amount of time must exist in equilibrium with the rest of the population. In the model the proportion of carriers to nonafflicted people remains constant, as demonstrated in the graph below.



Graph 1: The Total Carrier and Nonafflicted populations.

The last major test was to make sure that the screening components worked correctly. Firstly, people had to be screened every year, which was verified by a simple check of the screened population stocks. Secondly, the goal of screening is to make the number of people born afflicted to decrease. The model was tested at differing rates of screening and the results were always that the number of afflicted children born would decrease in proportion to the population growth and at higher levels of screening the number of afflicted children born every year would actually decrease in number as well. See the graph below.



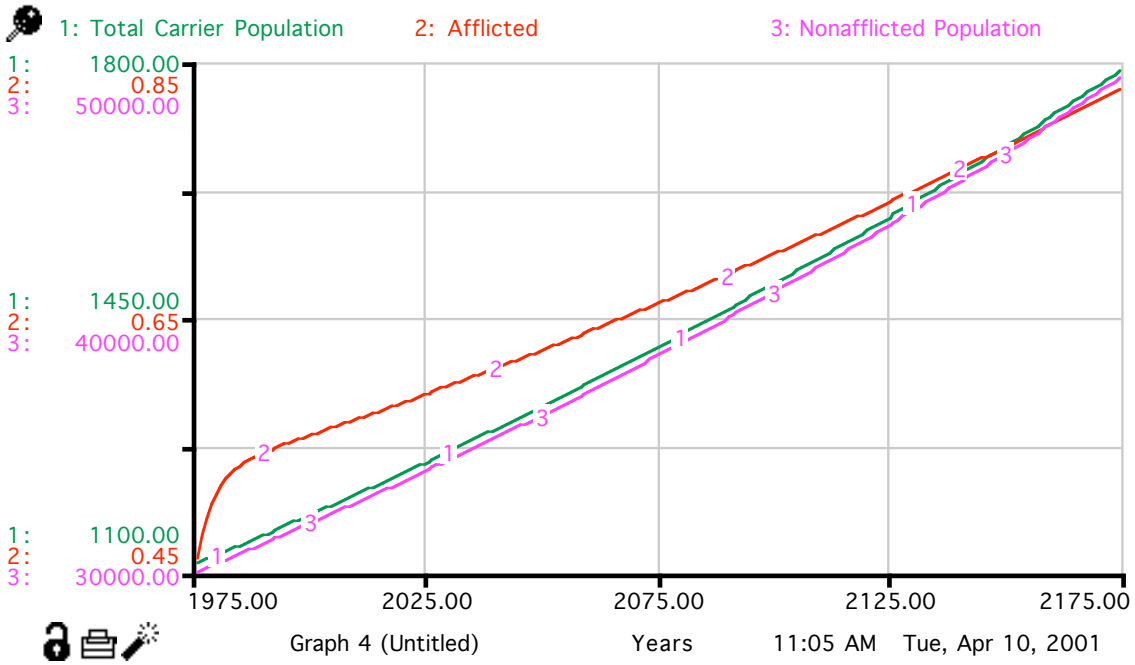
Graph 2: The number of afflicted births each year with screening rates ranging from 0 to 40% of the unscreened population each year.

The Results of Modeling and Thinking

The Result

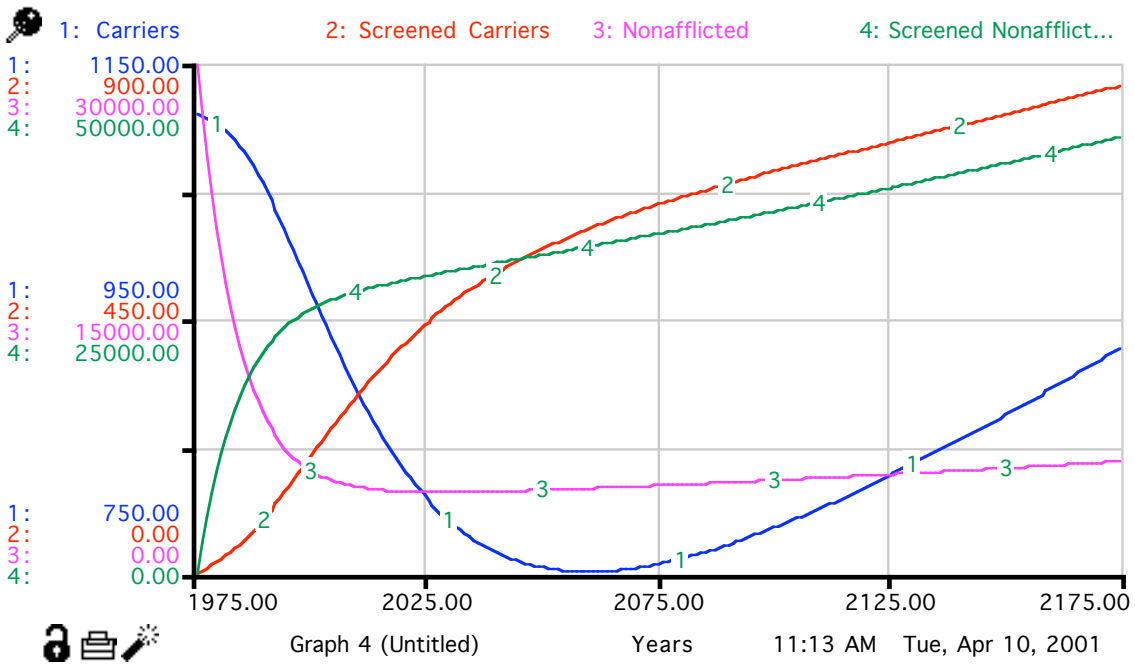
The model shows that, if left alone, the disease will continue to kill newborn in higher numbers as the population grows (see graph 2 above). It also shows that screening for the Tay-Sachs mutation has a definite impact on the number of afflicted children born. The model also shows what levels of screening are necessary to reduce the number of Tay-Sachs deaths to almost zero.

Final Graphs and Tables



Graph 3: A graph showing the total carrier, afflicted and nonafflicted populations.

Graph 1 shows both the nonafflicted and carrier populations increasing at a similar rate, corresponding to Hardy-Weinberg equilibrium. The afflicted population increases at a high rate at first, but this is because there are assumed to be no afflicted people at the beginning of the simolation.



Graph 4: A graph showing the screened and unscreened populations.

Graph 4 shows the number of the screened and unscreened carrier and unafflicted populations over two hundred years with a yearly-screening rate of 10%. This shows that, while many people are screened at first, there are still a large number of unscreened people in the model.

The Final Table

11:13 AM Tue, Apr 10, 2001 Table 2 (Untitled Table)

Years	Carriers	Afflicted	Screened Carriers	Screened Nonafflict	Nonafflicted
2163	900.87	0.22	837.99	41,624.59	6,369.19
2164	903.00	0.22	840.02	41,728.87	6,385.02
2165	905.13	0 Table 2	842.05	41,833.42	6,400.90
2166	907.28	0.22	844.08	41,938.22	6,416.82
2167	909.42	0.22	846.12	42,043.29	6,432.78
2168	911.58	0.22	848.16	42,148.62	6,448.78
2169	913.74	0.22	850.21	42,254.21	6,464.82
2170	915.91	0.22	852.26	42,360.06	6,480.90
2171	918.08	0.22	854.31	42,466.18	6,497.03
2172	920.26	0.22	856.36	42,572.56	6,513.19
2173	922.45	0.22	858.42	42,679.20	6,529.40
2174	924.65	0.22	860.48	42,786.11	6,545.65
Final	926.85	0.22	862.55	42,893.29	6,561.94

Table 2: A table showing the end population results.

Table 2 uses a screening rate of ten percent per year. The total carrier and nonafflicted populations are proportionally correct and the afflicted people remain about the same, despite the tremendous population growth, showing that the screening program is having an effect.

The Key Learning from the Modeling Process

- Understanding of the propagation of a genetic mutation in a community.
- Understanding the difficulty in combating a genetic disease.
- Learning how to model a population divided into interbreeding subgroups.
- Working with complex, interacting genetic probabilities.

- Learning that screening does have a large impact on a genetic disease.

- Realizing that this is a simple genetic disease, involving only one gene.

How does genetic screening affect a closed community afflicted with Tay-Sachs disease?

Screening dramatically reduces the number of afflicted people born every year in a high-risk, closed community. Screening is the only way to fight Tay-Sachs disease, and even a screening rate of 10% vastly cuts down in the afflicted population.

This model is a genetic model that can be easily modified into a generic model. As it is, the model can be used to examine any autosomal recessive genetic disorder or genetic pattern where the afflicted population cannot reproduce either by disability or death. Additionally, the model can be modified so that afflicted people can reproduce, but more converters and connectors would have to be added.

Bibliography

CIA World Factfile Online. Internet. March 25, 2001. www.cia.gov/publications/factfile.com

Dr. Dennis W. Shultz, PhD, Assistant Research Professor of Molecular Biology, Principal Invesigator for ARMD mutations, Casey Eye Institute, Oregon Health Sciences University, Portland, Oregon, USA.

Edlin, Gordon. Genetic Principles: Human and Social Consequences. Boston: Jones and Bartlett Publishers, Inc. 1984.

Judith E. Tsipis, Professor of Biology, Brandeis University Director, Genetic Counseling Program, Brandeis University, Waltham, Massachusetts, USA

Israeli Census Bureau Online. Internet. March 20, 2001. www.cbs.gov.il

Suzuki, David T. An Introduction to Genetic Analysis. New York: W.H. Freeman and Company. 1976.

Wintergreen, Lois. Unnatural Selection. New York:Bantam/Doubleday, 1999.