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Fitting Cox's Regression Model to Survival Data using GLIM

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SUMMARY

The proportional hazard regression model is reviewed, and its analysis using GLIM is described. Methods of estimating the underlying survivor functions are discussed. The Poisson model which allows the use of GLIM is introduced and interpreted. Two different treatments of tied observations are mentioned, and their properties are compared in the context of a specific example.

Keywords: AGE-SPECIFIC FAILURE RATE; GLIM; HAZARD FUNCTION; LEHMANN ALTERNATIVES; PRODUCT LIMIT ESTIMATE; PROPORTIONAL HAZARDS; SURVIVAL DATA; TIED SURVIVAL TIMES

1. INTRODUCTION

IN many practical contexts investigators are faced with the analysis of positively skewed data, some of which are right-censored. Medical examples include cases in which the individual observations are the survival times of patients, times until progression of a disease for different patients, or more optimistically, times until the disappearance of symptoms. Censoring occurs because some patients may still be alive, or may not have reached the specified end-point of the investigation, at the time at which the data were collected. Other patients may lose contact with the investigation, and thus contribute further censoring. The testing of industrial components provides further examples of this kind of observations.

Recently, a number of regression-type models have been suggested for the analysis of such data. Fully parametric models, making use of exponential and Weibull distributions, have been proposed by Prentice (1973), and their practical implementation by means of GLIM (Baker and Nelder, 1978) has been described by Aitkin and Clayton (1980).

A more adaptable model which is only partially parametric was introduced by Cox (1972). Special programs have been developed in order to fit Cox's model, and the next version of the GLIM program, GLIM4, is being adapted to cope with it (see Baker and Clarke, 1979). The purpose of this paper is to show that Cox's model can be fitted using the existing versions of GLIM, and that tied observations and time-dependent covariates can be accommodated. Furthermore, estimates of the underlying survivor function can easily be derived from the program output. The fitting is achieved using Poisson errors, and the equivalent Poisson model gives some insight into the survival data problem.

The regression models mentioned above have been reviewed by Kay (1977) and are introduced at length in the book of Kalbfleisch and Prentice (1980). The "Man-years in view" model of Case and Lea (1955) has been fitted with GLIM by Mr G. Berry of the MRC Pneumoconiosis Unit, Penarth, using an approach similar to that adopted here.

2. THE PROPORTIONAL HAZARD REGRESSION MODEL

In order to simplify terminology, the exposition will be presented in terms of the survival times of patients in a medical investigation. The author hopes that readers will remain aware of the wider range of possible applications. A vector $\mathbf{z} = (z_1, ..., z_p)$ of explanatory variables is

available for each patient, and could include such information as age on admission to the study, sex, social class, and so on. These covariates could change with time. The survival time of each patient has a distribution, depending on $\mathbf{z}$, which can be characterized in terms of either its survivor function $\mathscr{F}$, where $\mathscr{F}(t; \mathbf{z})$ is the probability that the patient survives a time greater than t, or its hazard function λ, which is the ratio of density to survivor function. In Cox's (1972) model the hazard functions of different patients are proportional and satisfy

$$\lambda(t; \mathbf{z}) = \exp(\mathbf{z}\boldsymbol{\beta})\,\lambda_0(t), \tag{2.1}$$

where $\boldsymbol{\beta}$ is a $p \times 1$ vector of unknown parameters, and $\lambda_0(t)$ is an unknown function representing the hazard for the standard set of conditions $\mathbf{z} = \mathbf{0}$. Often, when the covariates $\mathbf{z}$ consist of a small number of categorical variables, the patients fall into groups sharing certain values of $\mathbf{z}$.

The data consist of survival times, some censored, and others corresponding to deaths. Suppose that there are q deaths, occurring after survival times $t_1, \ldots, t_q$, and suppose to begin with that all of these death times are distinct. Now consider the death occurring after survival time t_h. Let N_h be the number of survival times, censored or uncensored, which are greater than or equal to t_h. Suppose that the N_h corresponding patients fall into $k(h)$ groups, the jth group consisting of $N_{h,j}$ patients all with explanatory vector $\mathbf{z}_{h,j} = \mathbf{z}_{h,j}(t_h)$ $(j = 1, \ldots, k(h);$ $N_{h,1} + \ldots + N_{h,k(h)} = N_h;\ h = 1, \ldots, q)$. Suppose that the death at time t_h, which befell one of these N_h patients, involved one in the $j^*(h)$th group.

In his 1972 paper, and at greater length in a 1975 paper, Cox explains why the model (2.1) can be fitted by maximizing a "partial likelihood" of the form

$$\prod_{h=1}^{q} \frac{\exp(\mathbf{z}_{h,j^*(h)}\boldsymbol{\beta})}{\Sigma_j N_{h,j} \exp(\mathbf{z}_{h,j}\boldsymbol{\beta})}. \tag{2.2}$$

In the next section it will be shown how current versions of GLIM can be used to maximize the expression in (2.2).

3. A Poisson Model

In order to fit the survival model of Section 2 by use of GLIM an auxiliary Poisson model must be considered. A particular realization of this model produces a likelihood which, at its maximum, is proportional to expression (2.2). The model can be fitted with GLIM, using the Poisson error, and thus the maximum likelihood estimate of the parameter $\boldsymbol{\beta}$ and likelihood ratios, valid for both the Poisson model and the survival model, can be found. Under the assumptions that the explanatory vectors $\mathbf{z}$ are not time dependent and that all survivor functions are continuous, the Poisson model can be interpreted in terms of survivals as will be made clear in Section 5. However, these stronger assumptions are not necessary for the technique to work and for the next two sections the equivalence of the Poisson and survival models will be treated as a happy coincidence.

The auxiliary Poisson model can be described as follows. For each value of h, from 1 to q, let $X_{h,1}, \ldots, X_{h,k(h)}$ be independent Poisson random variables, where $X_{h,j}$ has parameter $\mu_{h,j}$ with

$$\mu_{h,j} = N_{h,j} \exp(\alpha_h + \mathbf{z}_{h,j}\boldsymbol{\beta}) \quad (j = 1, \ldots, k(h)).$$

The α_h are constant factors whose interpretation will be clarified in Section 5. If $X_{h,j^*(h)}$ takes the value 1, and the others take the value 0, then the likelihood of α_h and $\boldsymbol{\beta}$ based on $X_{h,1}, \ldots, X_{h,k(h)}$ is

$$\mu_{h,j^*(h)} \exp(-\Sigma_j \mu_{h,j}) = \frac{N_{h,j^*(h)} \exp(\alpha_h + \mathbf{z}_{h,j^*(h)}\boldsymbol{\beta})}{\exp\{\Sigma_j N_{h,j} \exp(\alpha_h + \mathbf{z}_{h,j}\boldsymbol{\beta})\}}.$$

As the sum of these Poisson random variables takes the value 1, and follows the Poisson distribution with parameter $\Sigma_j \mu_{h,j}$, the maximum likelihood estimates will satisfy $\Sigma_j \hat{\mu}_{h,j} = 1$, so that

$$\exp \hat{\alpha}_h = \{\Sigma_j N_{h,j} \exp(\mathbf{z}_{h,j}\hat{\boldsymbol{\beta}})\}^{-1}.$$

At its maximum, therefore, the likelihood of the α and $\boldsymbol{\beta}$ based on all the $X_{h,j}$ $(j = 1,...,k(h);\ h = 1,...,q)$ is

$$\prod_{h=1}^{q} \frac{N_{h,j^*(h)}\, e^{-1} \exp(\mathbf{z}_{h,j^*(h)}\hat{\boldsymbol{\beta}})}{\Sigma_j N_{h,j} \exp(\mathbf{z}_{h,j}\hat{\boldsymbol{\beta}})}.$$

This is proportional to the maximum of the likelihood in (2.2). Thus the Poisson model and the survival model will have identical estimates of $\boldsymbol{\beta}$ and identical likelihood ratios.

This Poisson model can be fitted using GLIM, but before giving an example I shall discuss the problem of tied observations, and give an interpretation of the Poisson model.

4. The Treatment of Tied Observations

The data being analysed may be in a form in which deaths occur after distinct survival times $t_1,...,t_q$ but a multiplicity of deaths m_h $(\geqslant 1)$ occur after each time t_h $(h = 1,...,q)$. There are $m_1 + ... + m_q$ deaths in all. Generalizations of the proportional-hazards regression model which incorporate ties have been given by Kalbfleisch and Prentice (1973), by Cox (1972) and by Peto (1972). The first is an exact treatment, and the other two are approximations, Peto's being rougher than Cox's. These last two can be fitted using GLIM.

Suppose that $m_{h,j}$ of the deaths occurring at time t_h befall patients in the jth group, that is patients with explanatory vector

$$\mathbf{z}_{h,j} \quad (j = 1,...,k(h);\ m_{h,1} + ... + m_{h,k(h)} = m_h;\ h = 1,...,q).$$

In Peto's generalization the likelihood of $\boldsymbol{\beta}$ is given by

$$\prod_{h=1}^{q} \binom{N_h}{m_h} \frac{\exp(\Sigma_j m_{h,j}\mathbf{z}_{h,j}\boldsymbol{\beta})}{\{\Sigma_j N_{h,j}\exp(\mathbf{z}_{h,j}\boldsymbol{\beta})/N_h\}^{m_h}}. \tag{4.1}$$

If in the Poisson model of Section 3, we put $X_{h,j} = m_{h,j}$ $(j = 1,...,k(h);\ h = 1,...,q)$, then the likelihood of the α_h and $\boldsymbol{\beta}$ is

$$\prod_{h=1}^{q} \left[\frac{\{\Pi_j N_{h,j}^{\,m_{h,j}}\} \exp(m_h\alpha_h + \Sigma_j m_{h,j}\mathbf{z}_{h,j}\boldsymbol{\beta})}{\exp\{\Sigma_j N_{h,j}\exp(\alpha_h + \mathbf{z}_{h,j}\boldsymbol{\beta})\}} \right].$$

As the maximum likelihood estimates satisfy

$$\Sigma_j N_{h,j}\exp(\hat{\alpha}_h + \mathbf{z}_{h,j}\hat{\boldsymbol{\beta}}) = m_h,$$

at its maximum this likelihood becomes

$$\prod_{h=1}^{q} \left[\frac{\{\Pi_j N_{h,j}^{\,m_{h,j}}\}\, e^{-m_h} \exp(\Sigma_j m_{h,j}\mathbf{z}_{h,j}\hat{\boldsymbol{\beta}})}{\{\Sigma_j N_{h,j}\exp(\mathbf{z}_{h,j}\hat{\boldsymbol{\beta}})/m_h\}^{m_h}} \right]$$

which is proportional to (4.1). Both Peto's survival model and the equivalent Poisson model will yield the same value for $\hat{\boldsymbol{\beta}}$ and the same likelihood ratios.

To fit Cox's generalization we must consider the $M_h = \binom{N_h}{m_h}$ *combinations* of m_h individuals which can be chosen from the N_h with survival time $\geqslant t_h$. Define the explanatory vector $\mathbf{s}$ for such a combination as the sum of the $\mathbf{z}$ values for the individuals concerned. Suppose that $M_{h,l}$ of the M_h possible combinations form a group with common explanatory vector

$$\mathbf{s}_{h,l} \quad (l = 1,...,k(h);\ M_{h,1} + ... + M_{h,k(h)} = M_h;\ h = 1,...,q).$$

Let the combination corresponding to the m_h deaths be in the $l^*(h)$th group, having explanatory vector $\mathbf{s}_{h,l^*(h)}$. In Section 6 of his 1972 paper, Cox explains that $\boldsymbol{\beta}$ should be estimated by

maximizing the "partial likelihood" given by

$$\prod_{h=1}^{q}\left[\frac{\exp(\mathbf{s}_{h,l^*(h)}\boldsymbol{\beta})}{\Sigma_l M_{h,l}\exp(\mathbf{s}_{h,l}\boldsymbol{\beta})}\right]. \tag{4.2}$$

The equivalent Poisson model has, for $h = 1,...,q$, independent random variables $X_{h,1},...,X_{h,k(h)}$, where $X_{h,l}$ has parameter

$$\mu_{h,l} = M_{h,l}\exp(\alpha_h + \mathbf{s}_{h,l}\boldsymbol{\beta}) \quad (l = 1,...,k(h)).$$

If $X_{h,l^*(h)} = 1$, and all of the other $X_{h,l}$ equal zero, then, as in Section 3, Cox's survival model and the Poisson model will have proportional maximum likelihoods and the same estimate of $\boldsymbol{\beta}$.

5. An Interpretation of the Poisson Model

The following argument gives an interpretation of the Poisson model, and shows how the estimates of the α_h can be used to calculate estimates of the survivor functions of the patients. The explanatory vectors $\mathbf{z}$ will not be allowed to vary with time, and the underlying hazard $\lambda_o(t)$ of (2.1) will be assumed to be continuous in t. Ties are, thus, theoretically impossible, but any occurring in the data will be assumed to correspond to survival times which are arbitrarily close to one another, rather than being treated as the result of data grouping. This is a rather rough approach to the problem of ties, and will give results corresponding to Peto's treatment.

As all survival times are independent, there is no loss of generality in assuming that they are measured from the same starting point. Thus we can imagine that at time $t_h - \delta t_h$, N_h patients are at risk, and m_h are about to die. These patients consist of $N_{h,j}$ with explanatory vector $\mathbf{z}_{h,j}$ of whom $m_{h,j}$ are about to die ($j = 1,...,k(h)$). Suppose that all these patients remain at risk during the short time $(t_h - \delta t_h, t_h)$, and that $\lambda_0(t)$ is constant with value $\lambda_0(t_h)$ over this interval. During this interval, the excess life of a patient beyond $t_h - \delta t_h$ behaves like an exponential random variable with parameter $\exp(\mathbf{z}\boldsymbol{\beta})\lambda_0(t_h)$. The number of failures in each group is thus a Poisson random variable, taking the value $m_{h,j}$, with parameter $N_{h,j}\exp(\mathbf{z}_{h,j}\boldsymbol{\beta})\lambda_0(t_h)\delta t_h$. If we interpret $\exp\alpha_h$ as $\lambda_0(t_h)\delta t_h$, this means that $m_{h,j}$ is just a realization of the Poisson random variable $X_{h,j}$ mentioned in Section 3 and in the account of Peto's method in Section 4.

The survivor function $\mathscr{F}(t;\mathbf{z})$ of a patient is related to the hazard $\lambda(t;\mathbf{z})$ according to

$$\mathscr{F}(t;\mathbf{z}) = \exp\left\{-\int_{-\infty}^{t}\lambda(u;\mathbf{z})\,du\right\},$$

and so

$$\mathscr{F}(t;\mathbf{z}) = \{\mathscr{F}_0(t)\}^{\exp(\mathbf{z}\boldsymbol{\beta})}, \tag{5.1}$$

where

$$\mathscr{F}_0(t) = \exp\left\{-\int_{-\infty}^{t}\lambda_0(u)\,du\right\}.$$

Under the stronger assumptions of this section, the fitting of the model can be completed by estimating the $\mathscr{F}(t;\mathbf{z})$. As $\boldsymbol{\beta}$ has already been dealt with, (5.1) shows that it only remains to estimate $\mathscr{F}_0(t)$.

The time scale can be divided into small intervals $(t-\delta t, t)$, including the interval $(t_h - \delta t_h, t_h)$ referred to above. Poisson models in which all $X_{h,j} = 0$ can be constructed for the time intervals during which no deaths occur. They will involve parameters α where $\exp\alpha = \lambda_0(t)\delta t$ has estimate 0. Thus, $\mathscr{F}_0(t)$ can be estimated by

$$\hat{\mathscr{F}}_0(t) = \exp\{-\sum_{t_h \le t}\exp\hat{\alpha}_h\}, \tag{5.2}$$

where the sum is over all death times less than t. The estimates $\hat{\alpha}_h$ are given in the GLIM output.

This approach was outlined by Breslow (1972) under the assumption that λ_0 was a step-function. He gave the estimate (5.2) which is a generalization of an estimate considered by Nelson (1969).

6. An Example

So far, a Poisson model has been developed which is equivalent to the survival model of Cox, but its fitting via GLIM has not been discussed. An example is more informative than a general account, and for such an example we turn to data of Freireich *et al.*, which were used in Section 10 of the paper by Cox (1972), and are shown in Table 1. They concern the remission of

Table 1
Times of remission (weeks) of leukaemia patients

Sample 0	6*	6	6	6	7	9	10*
	10	11*	13	16	17*	19*	20*
	22	23	25*	32*	32*	34*	35*
Sample 1	1	1	2	2	3	4	4
	5	5	8	8	8	8	11
	11	12	12	15	17	22	23

* Censored.

leukaemia patients in terms of weeks after commencement of treatment. Patients formed two samples; Sample 0 had been treated with the drug 6-MP, and Sample 1 with a placebo. Some of the observations are right-censored, and these are denoted with asterisks.

The uncensored survivals covered 17 distinct values, $t_1, \ldots, t_{17}$. In Table 2 these values t_h are listed, together with $N_{h,j}$ and $m_{h,j}$, where $N_{h,j}$ is the number of survival times in Sample j which are greater than or equal to t_h, and $m_{h,j}$ is the number of survival times which are exactly equal to t_h ($j = 0, 1$; $h = 1, \ldots, 17$). Survival times censored at time t_h are included as being greater than or equal to t_h. In general, the detailed circumstances of collection of such observations, for example whether the censored time was the last appointment that a patient kept or the first that he missed, would govern their treatment.

Table 2
Details of each uncensored survival time

t_h	$N_{h,0}$	$N_{h,1}$	$m_{h,0}$	$m_{h,1}$
1	21	21	0	2
2	21	19	0	2
3	21	17	0	1
4	21	16	0	2
5	21	14	0	2
6	21	12	3	0
7	17	12	1	0
8	16	12	0	4
10	15	8	1	0
11	13	8	0	2
12	12	6	0	2
13	12	4	1	0
15	11	4	0	1
16	11	3	1	0
17	10	3	0	1
22	7	2	1	1
23	6	1	1	1

The model fitted by Cox assigned the explanatory vector $(0,0)$ to patients in Sample 0 and $(1, t-10)$ for those in Sample 1, where t is the time from commencement of treatment. Hence, patients in the two samples will have hazards $\lambda_0(t)$ and $\exp\{\beta_1+(t-10)\beta_2\}\lambda_0(t)$ respectively. The parameter β_1 measures the difference in failure rates between the two groups, and β_2 measures the dependence of this difference on time.

First of all the Poisson model which is equivalent to Peto's treatment of ties will be considered. For each death time t_h, this model concerns two Poisson observations $X_{h,0}$ and $X_{h,1}$, with parameters $\mu_{h,0} = N_{h,0}\exp(\alpha_h)$ and $\mu_{h,1} = N_{h,1}\exp\{\alpha_h+\beta_1+\beta_2(t_h-10)\}$ and realized values $m_{h,0}$ and $m_{h,1}$. The parameters α_h can be fitted as a factor with 17 levels, one for each death time, and β_1 as a factor with 2 levels, one for each sample. The parameter β_2 is fitted as a regression coefficient, and $\log N_{h,j}$ must be used as an "offset".

Cox's treatment of ties is more difficult to accomplish. Consider the two failures at time $t_4 = 4$. There were then $N_4 = 37$ patients "at risk": $N_{4,0} = 21$ in Sample 0, and $N_{4,1} = 16$ in Sample 1. There are $M_4 = \binom{37}{2} = 666$ possible pairs of patients at risk, forming 3 distinct groups. The first group consists of $M_{4,0} = \binom{21}{2} = 210$ pairs of patients, both from Sample 0. The explanatory vector of these pairs is the sum of the explanatory vectors of two individuals from Sample 0 and is thus $\mathbf{s}_{4,0} = (0,0)$. Then there are $M_{4,1} = 21\times 16 = 336$ pairs of patients consisting of one from each sample, and having explanatory vector $(1, t-10)$. Finally there are $M_{4,2} = \binom{16}{2} = 120$ pairs of patients, both from Sample 1 and having explanatory vector $(2, 2t-20)$. Three Poisson variables, $X_{4,0}$, $X_{4,1}$ and $X_{4,2}$ correspond to this death time. They have parameters $M_{4,0}\exp(\alpha_4)$, $M_{4,1}\exp\{\alpha_4+\beta_1+\beta_2(t_4-10)\}$ and $M_{4,2}\exp\{\alpha_4+2\beta_1+2\beta_2(t_4-10)$ respectively, and realized values of 0, 0 and 1, as both deaths at $t = 4$ befell patients in Sample 1. Similar groups of Poisson random variables can be formed for each death time. The last death time is represented by only two Poisson random variables as no pairs of patients both from Sample 1 were then "at risk". This gives 46 Poisson observations in all. Again the α_h can be fitted as a factor with 17 levels, β_1 as a factor with 2, and β_2 as a regression coefficient. The $\log M_{h,j}$ are used as "offsets".

In GLIM the death-time factor was denoted by A, the sample factor by X, and the time dependence by T. The models $A+X+T$, $A+X$ and A were fitted, and the results are summarized in Table 3. Two separate analyses were performed, using Peto's and Cox's

TABLE 3

Analysis of the data of Freireich et al.

(Standard errors of estimates are given in parentheses)

	Peto's treatment of ties	*Cox's treatment of ties*
$A+X+T$		
Deviance	27·62	30·28
d.f.	15	27
$\hat{\beta}_1$	1·51 (0·42)	1·63 (0·43)
$\hat{\beta}_2$	−0·008 (0·06)	0·007 (0·07)
$A+X$		
Deviance	27·63	30·29
d.f.	16	28
$\hat{\beta}_1$	1·51 (0·41)	1·63 (0·43)
A		
Deviance	42·85	46·54
d.f.	17	29

treatments of ties. The results obtained using the latter are similar to those quoted by Cox (1972, Section 10), and GLIM is likely to give the more accurate results.

Both analyses indicate clearly that β_2 is not significant, but β_1 is. The goodness-of-fit of the model based on Cox's treatment of ties cannot be assessed by reference to χ^2 tables. This is because the number of parameters in the saturated model will increase with the number of observations, thus violating the assumptions underlying the asymptotic justification of the test. The same is true of the model based on Peto's treatment of ties, unless it is assumed that neither the number of groups nor the number of distinct death times grows unboundedly with the number of observations. In both cases comparisons of models are assessed by reference to χ^2 tables in the usual way.

Peto's treatment of ties leads naturally to the survivor function estimate (5.2). I suggest that an estimate of $\mathscr{F}_0$ be derived from the result of Cox's treatment as follows. Equations (4.1) and (4.2) are both approximations to the true likelihood for particular failure times, (4.2) being the closer approximation. Thus,

$$\binom{N_h}{m_h}\{\Sigma_j N_{h,j}\exp(\mathbf{z}_{h,j}\hat{\boldsymbol{\beta}}_{\text{Peto}})/N_h\}^{m_h} \doteqdot \Sigma_l M_{h,l}\exp(\mathbf{s}_{h,l}\hat{\boldsymbol{\beta}}_{\text{Cox}})$$

so that

$$\binom{N_h}{m_h}\{m_h\exp(-\hat{\alpha}_{h,\text{Peto}})/N_h\}^{m_h} \doteqdot \exp(-\hat{\alpha}_{h,\text{Cox}}) \quad (h = 1,\ldots,q).$$

Equation (5.3) can now be replaced by

$$\hat{\mathscr{F}}_{0,\text{Cox}}(t) = \exp\left\{-\sum_{t_h \leqslant t}\frac{m_h}{N_h}\binom{N_h}{m_h}^{1/m_h}\exp\left(\frac{\hat{\alpha}_{h,\text{Cox}}}{m_h}\right)\right\}.$$

The estimates of $\mathscr{F}_0(t)$ found in the two analyses from the model $A+X$ are listed in Table 4. The two sets of results correspond closely.

TABLE 4

Estimates of the survivor function $\mathscr{F}_0(t)$

Time interval	*Peto's treatment of ties*	*Cox's treatment of ties*
[0, 1)	0·98	0·98
[1, 2)	0·96	0·97
[2, 3)	0·95	0·96
[3, 4)	0·93	0·94
[4, 5)	0·90	0·92
[5, 6)	0·87	0·89
[6, 7)	0·86	0·88
[7, 8)	0·81	0·83
[8, 10)	0·79	0·82
[10, 11)	0·76	0·79
[11, 12)	0·72	0·75
[12, 13)	0·70	0·73
[13, 15)	0·68	0·70
[15, 16)	0·65	0·68
[16, 17)	0·62	0·65
[17, 22)	0·55	0·58
[22, 23)	0·45	0·47

When this method is used with larger or more complicated data sets an auxiliary program can be written, in any suitable language, in order to transform the raw observations into input for the GLIM program.

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