RE–EXAMINING THE GOMPERTZIAN MODEL OF AGING

By

Matthew Witten

and

Caleb E. Finch

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MATTHEW WITTEN† AND CALEB E. FINCH‡

Abstract. The Gompertzian survival model is probably the most commonly used analytical model in the experimental biology of aging. Its two parameters lend themselves to apparent ready analogy with biological survival concepts. The purpose of this discussion is to examine the validity of the Gompertzian survival model within the context of the experimental biology of aging. The two Gompertzian parameters are the intrinsic aging rate γ and the age–independent mortality rate h_0 . We will demonstrate that this analogy with biological behavior, for these two parameters, is incorrect and we will demonstrate that it can lead to subsequently incorrect interpretations of the biology/physiology of organisms analyzed using this model.

Key words. /Aging/Life–History Traits/Gompertzian Survival/Biomarkers/

— **Introduction** —. Johnson[1] has pointed out that the study of aging "*has been a complex, often misleading, and largely intractable area for experimental research. Analyses are hampered by the complexity of the aging process in which many molecular, cellular, and organ systems display remarkable changes, many of which are progressive with chronological age.*" Consequently, analytical modeling efforts — in the field of the biology of aging — are equally hampered.

The quantification of the biological aging process has received its primary treatment in the seminal work of George Sacher[2–6]. This series of papers attempted to relate the biology of aging, as seen through survival analysis, to the theoretical mortality rate function of Gompertz[7–9] as given by the equation

$$\lambda(a) = h_0 e^{\gamma a} \tag{1}$$

where $\lambda(a)$ is the mortality rate(the probability of dying in the age interval $(a, a + \Delta a)$ given that you have survived until age a). Plots of $\log \lambda(a)$ versus a give rise to the classical log–linear mortality rate curves often seen in experimental aging research(Figure[1]; Johnson[1]). Further theoretical discussion of survival methods, in general, may be found in Lawless[10]. Theoretical application of survival methods, as applied to the biology of aging, may be found in Witten[11–16]. Sample experimental papers, making use of the Gompertz model, may be found in Cheney et al.[17], Johnson[1] and Yu et al.[19]. The purpose of the current paper is to address the gap between the demographic level of survival analysis and the individual/genetic level of survival analysis.

†HQW 10S, Computational Biology and Medicine, Control Data Corporation, 8100 34th Avenue South, Mailing Address/Box 0, Minneapolis, MN 55440–4700. M. Witten would like to thank the Institute For Mathematics and Its Applications, University of Minnesota, for its support, during his stay as a visitor.

‡Ethel Percy Andrus Gerontology Center, MC019, University of Southern California, Los Angeles, CA 90089–0191

RUNNING HEAD: Gompertzian Survival

— **The Biological Significance of h_0 and γ** —. The relationship between population survival curves and the biological processes of aging remains an enticing one. The hope being the ability to infer knowledge of the individual's biological behavior from demographic level behaviors(Witten[16], Guess and Witten[22]). One of the most commonly used demographic survival models is the Gompertzian survival model(equation(1)). One can show(Witten[12–13,16] and references therein contained), that the Gompertzian survival curve is given by the following equation

$$S(a) = \exp\left[\frac{h_0}{\gamma}\left(1 - e^{\gamma a}\right)\right] \tag{2}$$

Sample illustrations of how $S(a)$ varies with changes in γ and h_0 may be found in Witten[12,15]. In order to apply such a model, to a biological problem, it becomes necessary to give the parameters a reasonable biological meaning or interpretation.

Cutler[20] observes that the Gompertz parameters may be interpreted as a parameter h_0 incorporating "*the intensity of external environmental hazards*" and an aging parameter γ "*incorporating how the processes of aging effectively increase the random probability of death as a function of time.*"

Alternatively, the Gompertzian mortality rate parameters h_0 and γ are often interpreted as follows. As the parameter γ appears in the argument of the exponential function(see equation(1)above), it must have the dimensions of *1/age*; the variable γa being dimensionless for all values of age a. Thus, γ is usually interpreted as the *age–related mortality rate coefficient*, or more simply, the *intrinsic rate of aging.* Johnson[1] calls it the *basal rate of aging.* That is, γ describes the *intensity* with which an organism ages due to its intrinsic biology(the non–environmentally related factors). The h_0 parameter, often termed the *age–independent mortality rate coefficient*, is assumed to account for all of the non–age related(or environmental) factors; the *extrinsic* rate of aging.

While γ may well be related to intrinsic biological aging processes(this is not entirely clear and we shall return to this in a moment; E.J. Masoro, personal communication), it is clear that h_0 cannot be assigned to be the catch–all for everything else that might change the mortality rate function. In fact, we can give h_0 a very concise and rigorous meaning by re–expressing equation(1) as follows

$$\frac{d\lambda(a)}{da} = \gamma\lambda(a); \qquad \lambda(0) = h_0 \tag{3}$$

The function $\lambda(a)$, as given in equation(1), is the solution of equation(3), and it is exactly, as we have previously noted, the probability of dying in the small age interval $(a, a + da)$; given that the organism has survived until age a. That is, $\lambda(a)$ is the conditional rate or probability of death. It then follows that $\lambda(0)$ is the probability that an organism will die, shortly after birth, given that it was born alive. From equation(3), it follows that h_0 is exactly this same probability. It becomes clear that h_0 incorporates

environmental/extrinsic factors, in so far as these factors might be related to the first few moments of life. Sacher[5] was not far off when he suggested that the h_0 parameter controlled the initial vulnerability to disease and to death. However, if h_0 is, in fact, the probability of dying after the first few moments of life(some very short time interval), then it is more than reasonable to assume that it there is a large genetic component involved. It is not hard to envision a scenario in which an organism is killed, after live birth, due to poor environment, bad medical treatment, or sheer maliciousness. Realistically, most neonatal deaths are due to genetic factors; malformed cardiovascular and/or neural systems. Therefore, it becomes difficult to dissect away the genetic component from the environmental component of the h_0 mortality rate coefficient. In fact, one might envision h_0 to be composed of two contributing components or factors h_0^e (the environmental factor) and h_0^g (the genetic factor); these two factors somehow combining to form an overall observed h_0 .

Examining the work of Witten and Finch[21], we see that the Gompertzian curve best fits the survival of a population given that we assume the model is to be fit with a starting time, not at birth, but at the age of onset of puberty(this was also observed by Cutler[20]). The inability of the Gompertz equation to fit the whole lifespan curve is discussed, in detail, in Witten[14](neonatal component) and Witten[15](old age component). Given the preceding assumptions, h_0 represents the probability that given an organism has survived until puberty, it will die in the next small time instant. Again, we see that the Gompertzian model requires that h_0 be the probability of dying shortly after some very small initial time point; for example, birth or puberty. Adjusting the Gompertzian survival model, for a later starting date, is discussed in Cheney et al.[17].

Part of the confusion, of interpretation of these parameters, stems from the variety of experimental results showing that various experimental protocals produce a variety of changes both in the h_0 and in the γ parameters. Even within the various diet restriction experiments, there is a confusing array of results. This is particularly true with respect to the issue of the biological interpretation of the parameter γ . Yu et al.[19] have demonstrated that different diet protocals and different diet formulations can affect the two Gompertzian parameters in different ways. Thus, it is not clear how what is obviously an environmental influence, eating habits and the diet formulation, can be simultaneously affecting both h_0 and γ . One possible explanation for this seeming lack of consistancy is that the γ that is experimentally measured is, in point of fact, a weighted combination of the internal "biological signals(aging rates)" or γ_j 's of the form

$$\gamma = \sum_{j=1}^{m} w_j \gamma_j \tag{4}$$

where γ_j is the aging rate or coefficient of aging associated with some j^{th} internal biological factor or system. And w_j is the weight of importance, of this subsystem, to the overall value of γ . That is, it is a measure of how much that particular factor influences

or induces changes in the overall value of γ. This question of the apparent sensitivity of the survival curve, to external manipulation, is also raised in Cutler[20].

Cutler[20] also questions whether or not γ is related to the biological aging rate of an individual; given the apparent sensitivity of the population level survival curves to external manipulation. In particular, he questions the homogeneity of γ. We may address the homogeneity issue in the following manner and thereby, perhaps, better understand how γ behaves.

Consider the biologically plausible scenario in which a number of idealized biological subsystems(the numbered squares in Figure[2]) are linked together in such a way as to sense various changes in each other's respective behaviors; in much the same sense that physiological systems sense each other's changes. We do not require that every box(physiological system) talk to every other box. Each box outputs an hypothetical γ–signal. The importance of each γ–signal, to the overall value of γ, is weighted by the value in the circle(Figure[2]). For the sake of simplicity, let us consider the overly simplified two box mouse illustrated in Figure[3].

Suppose that the γ_1–signal decreases due to some sort of experimental intervention. The 2 box can, sensing such a change, elect to maintain the level of its own γ_2–signal. If it makes such a choice, the overall level of the γ–signal(in this particular example) would then decrease.

Alternatively, the 2 box can, sensing such a change in the 1 box, elect to compensate for the change by altering the level of the γ_2–signal. Such a response can be completely compensatory; meaning that the value of γ is identical to that of the system before the experimental intervention. Or, it may be partially compensatory; compensating for only part of the change. In this case, we would see a change in the overall value of γ.

Diet restriction experiments(Yu et al.[19]), show that certain dietary interventions change γ and others do not. We conjecture that, in point of fact, all of the experimental interventions induce a change in the value of γ. Rather, certain protocals invoke a complete compensatory response, while others do not invoke a complete response.

If, in fact, γ is controlled in the aforementioned manner, this suggests why γ is fairly homogeneous within a particular population. Rather than γ being distributed in a homogeneous fashion, we conjecture that the subsystem controllers/weights are allowed a certain leeway whose resultant sum γ appears to be homogeneous; thereby suggesting a solution to the questions raised in Cutler[20].

One can also attempt to understand how γ is related to the *individual rate of aging*. One way to address this question is to ask the following alternative question: "What collections or mixtures of survival curves, at the individual level, can give rise to Gompertzian/power law like survival curves?" Guess and Witten[22] have examined this question and were able to demonstrate that it is impossible to obtain a Gompertzian survival curve from any mixture of exponential survival curves. That is, a population exhibiting

Gompertzian-like survival behavior cannot be created by mixing a collection of individuals whose lifespans are drawn from any mixture of exponential survival distributions. This implies that at least one of the individuals, in a Gompertzian population, must have an increasing(non–constant) mortality rate. Hence, we have the result that a population exhibiting Gompertzian–like survival cannot be made up of any mixture of individuals with constant mortality rates.

In summary, we have seen that both γ and h_0 can be affected by extrinsic, as well as intrinsic factors. Therefore, it is not reasonable to assign to γ the biological definition of age–dependent mortality rate and h_0 the biological definition of age–independent mortality rate.

— On The Independence of h_0 and γ —. Multiparameter mathematical models, such as equation(1), tacitly assume that the model parameters behave independently with respect to each other. That is, the behavior of one parameter does not influence the behavior of the other parameter. Thus, in equation(1), we would not expect to see any meaningful relationship between the parameters h_0 and γ . This is particularly true in the sense that the two Gompertzian parameters are assigned supposedly independent biological meaning; the age–dependent and age–independent mortality rate coefficients.

We have examined the estimates for h_0 and γ for 8 species groups: Fish, Birds, Mammals, Rotifers, Arachnida, Nematodes, Molluscs, and Insects. The results are summarized in Table[1](the various estimation procedures and algorithms are discussed in Witten and Finch[21]). Table[1a] contains the results of a linear regression of h_0 versus γ . Table[1b] illustrates the results of a regression of $\ln h_0$ versus $\ln \gamma$. As we can see, from a qualitative examination, in either regression form(particularly the ln–ln form), there was a definite linear (log–linear) relationship between the two Gompertz mortality rate coefficients.

We can then ask for the probability of such an occurence. The probability that we would have exactly four positive and four negative slopes is a binomial and can be computed to be the following

$$B(R = 4, n = 8, p = \frac{1}{2}) = \frac{35}{128} \tag{4}$$

The fact that we have such a mixture of slopes(positive and negative) is not a great surprise to us. This is exactly the expected distribution of slopes. That is, given a 50–50 chance of a positive or negative slope, and given that there are 8 slopes, we would expect to obtain 4 positive and 4 negative slopes. Of interest, as well, is the fact that we could not have gotten a better probability for a hypothesis test in which the null hypothesis is that there is no relationship between h_0 and γ . Hence, with this distribution of slopes, we cannot reject a null hypothesis H_0 : of no relationship between these two parameters.

It is important to realize that there is some statistical confounding in this data analysis. For example, the sexes are lumped together, rather than being treated separately.

Additionally, different species of animal are lumped together into a larger class. Finally, the sample sizes vary greatly amoung the different data sets.

— **Closing Comments** —. The systematic application of the Gompertz mortality model, in the experimental biology of aging, has made the model a commonly used analytical model. However, rigorous analysis of the model, as applied to a large number of species survival datasets, shows that the model has serious inconsistancies which can give rise to false interpretations of the biology of aging within the context of this model. In order to resolve these inconsistancies, we propose that some set of multifactorial survival experiments must be performed. Such experiments would measure the survival of a species as a function of two variables, such as diet and radiation level, which were being manipulated. Using a contrast analysis, it would then be possible to ascertain how various factors influence the two Gompertzian mortality rate coefficients. Until such experiments are performed, it is an error to assign h_0 as the age–independent or basal mortality rate and γ as the age–dependent mortality rate or basal mortality rate.

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— LEGENDS FOR TABLES —

[1a] In this table we illustrate the details of the linear regression between the Gompertzian mortality rate coefficients γ and h_0 . The first column indicates the species of animal, the second gives the number of available data points for the regression, the third gives the slope of the regression, the fourth gives the intercept, the fifth column gives the F value and the last column gives the percent of the data variance accounted for by a linear regression between γ and h_0 .

[1b] In this table we illustrate the equivalent information for a regression between $\ln \gamma$ and $\ln h_0$.

SPECIES	# OF DATA PAIRS	SLOPE	INTERCEPT	F-VALUE	% VARIANCE EXPLAINED BY A LINEAR REGRESSION
Fish	4	648.7	7.76×10^{-3}	3.36	62.7
Birds	12	0.78	1.03×10^{-3}	1.79	15.2
Mammals	95	–4.5	1.17×10^{-2}	0.006	0.006
Rotifers	6	–21.4	0.46	1.17	22.67
Arachnida	3	17.4	-4.83×10^{-3}	0.62	38.4
Nematodes	6	–10.3	0.27	5.88	59.51
Paramecia*	6	–0.31	3.42×10^{-2}	4.7×10^{-4}	0.01
Mollusca	7	–5.8	2.6×10^{-2}	9.2	64.9
Insecta	50	6.03	0.12	3.57	6.93

* Paramecia are not included in any of the regression analyses due to the fact that they are considered to be binary fission organisms rather than organisms reproduce sexually.

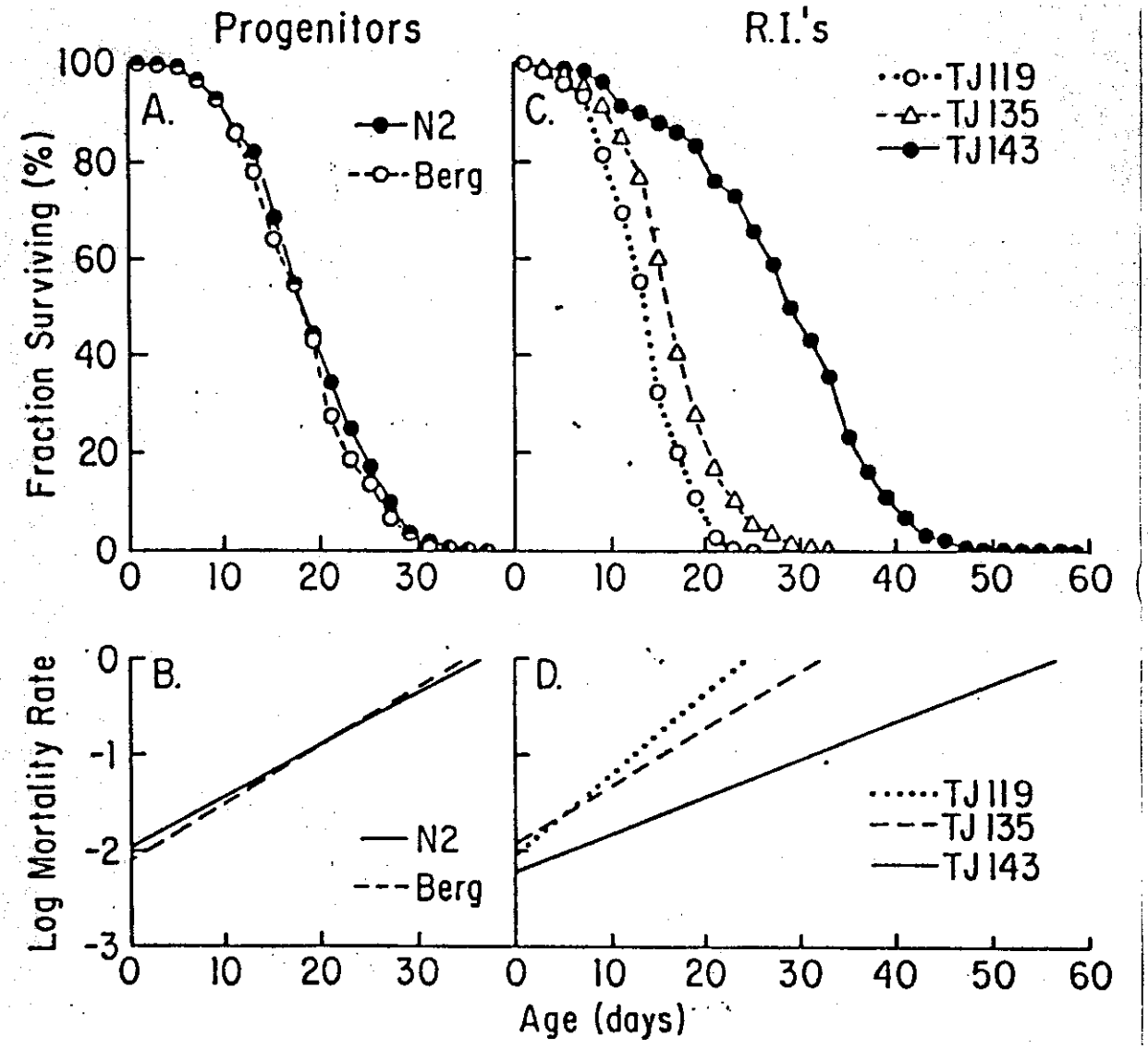
SPECIES	# OF DATA PAIRS	SLOPE	INTERCEPT	F–VALUE	% VARIANCE EXPLAINED BY A LINEAR REGRESSION
Fish	4	0.42	0.66	22.8	91.96
Birds	12	0.27	-4.39	6.96	6.97
Mammals	95	-0.13	6.93	6.04	37.6
Rotifers	6	–0.11	-2.03	0.66	14.15
Arachnida	3	0.87	1.42	0.33	25.59
Nematodes	6	–0.29	–3.23	8.93	69.07
Paramecia*	6	–5.23	–3.84	0.42	9.47
Mollusca	7	–0.27	–6.07	2.94	85.47
Insecta	50	3.535	–2.10	0.29	0.50

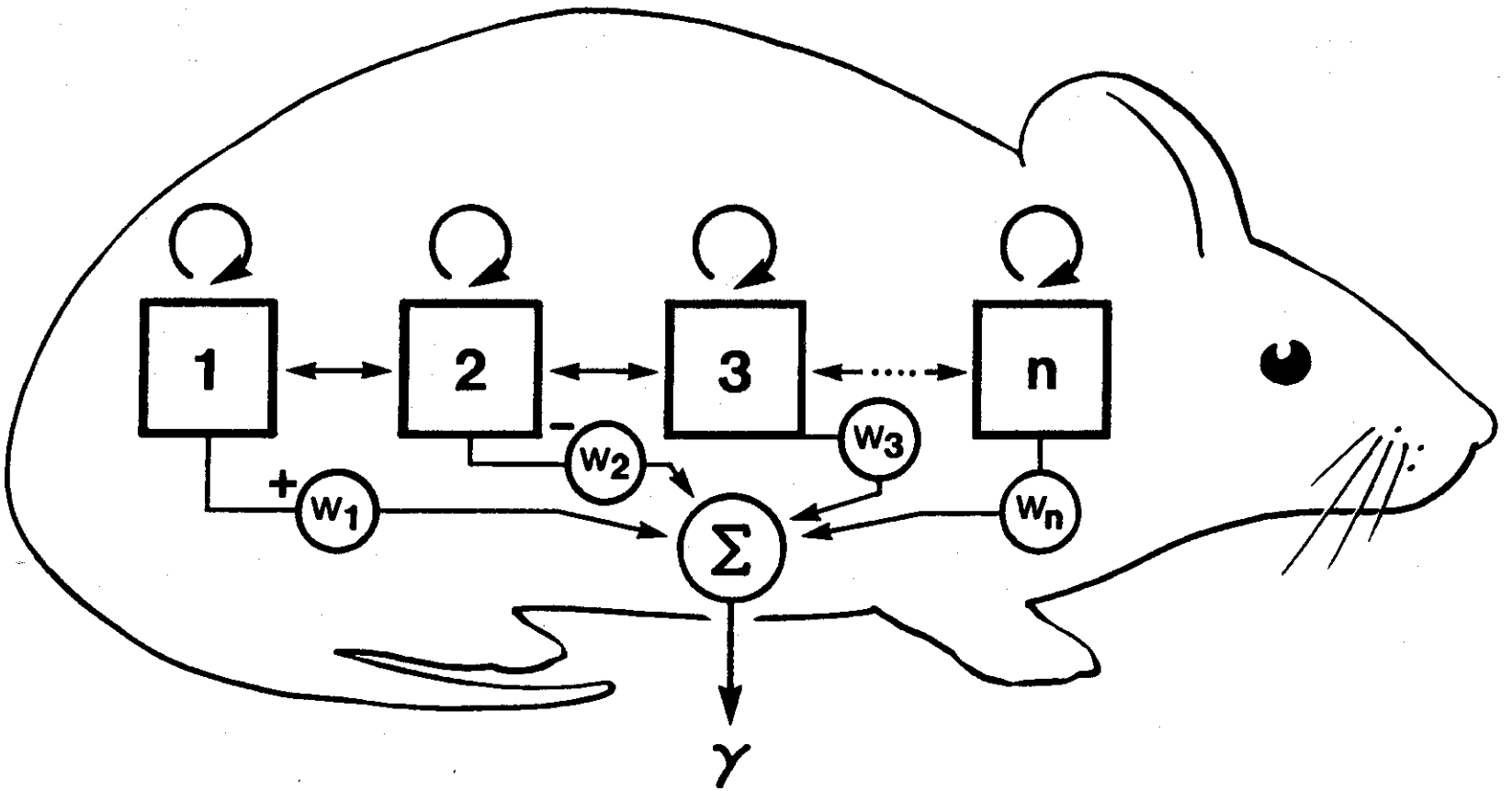
— LEGENDS FOR FIGURES —

[1] Survival data(A and C) and log mortality rates(B and D) for the parental and three RI lines of nematode(Johnson[1], reprinted with permission from the author). Observe the classical Gompertzian–like behavior of the survival curves(A and C) and the clearly log–linear behavior of the log mortality rate curves(B and D).

[2] An illustration of an idealized n–subsystem feedback loop. Each box represents one of the physiological subsystems of an organism under study. The arrows indicate hypothetical connections between the subsystems. The circular node is the hypothetical summation of all of the individual outputs γ_j of each of the subsystems to form the observed value γ .

[3] A simplified illustration of the idealized n–subsystem mouse to a two box mouse. The values of w_1 and w_2 are the weights assigned to each of the physiological signals γ_j . That is, these weights indicate how important each subsystem contribution is to the overall value of γ .


Progenitors
R.I.'s
A.
C.
N2
Berg
TJ119
TJ135
TJ143
Fraction Surviving (%)
100
80
60
40
20
0
0
10
20
30
0
10
20
30
40
50
60
B.
D.
Log Mortality Rate
0
-1
-2
-3
N2
Berg
TJ119
TJ135
TJ143
Age (days)


1
2
3
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+
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w_1
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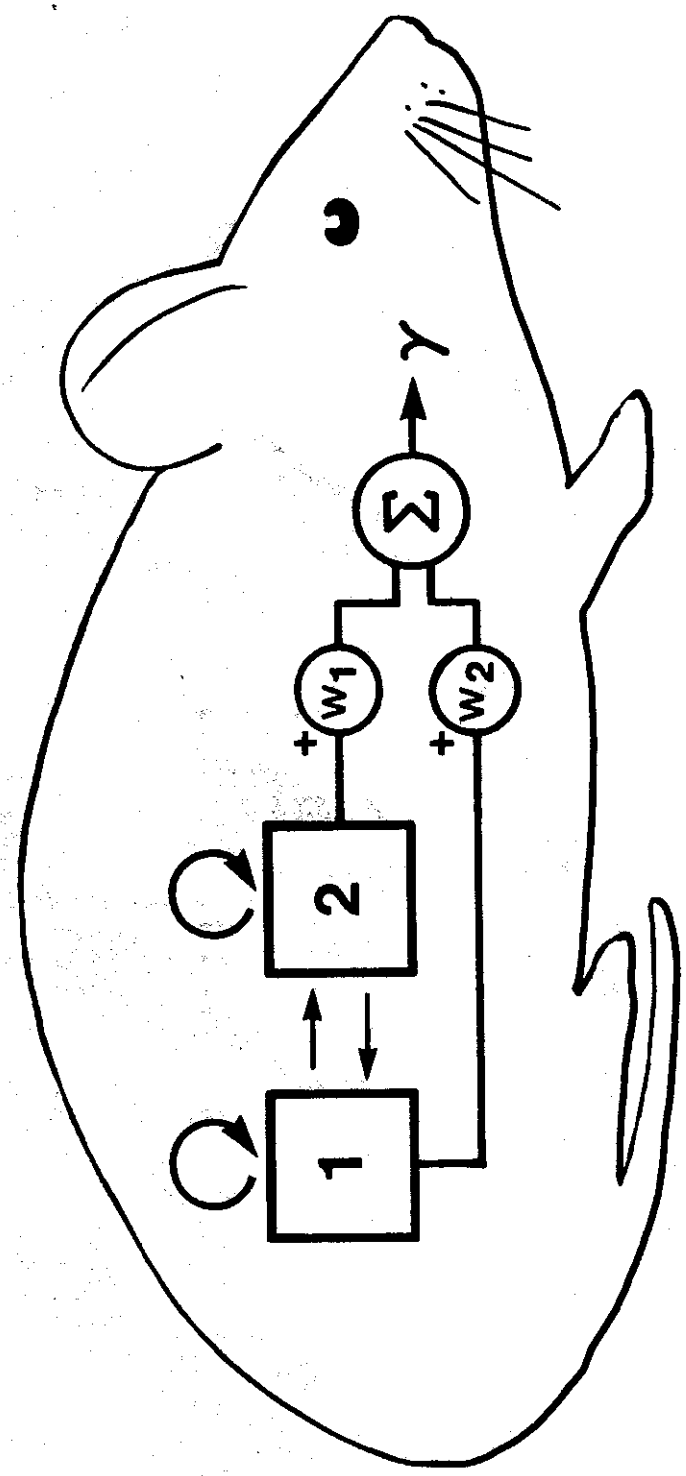
Σ
γ


γ
3
w1
w2
+
+
2
1