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COLLEGE ON NEUROPHYSICS

"Neural correlates of behaviour, development, plasticity and memory"

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A synopsis of neural Darwinism

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Trieste, Italy

A synopsis of

NEURAL DARWINISM

Life maintain itself through:

- renewal (birth & death)
- development
- competion

showing both stability and variability

Both play a role in evolution, that, since Darwin, is mostly advancing by random variations, stabilized by the natural selection.

Information, registered and expressed at the molecular level, guarantees, in the renewal process, both the required stability and variability.

But the genetic pool is not sufficient to determine all the fine structures of the new organism and other informational pools are formed :

- the immunological pool
- the nervous system

Mechanisms of formation and time of operation are on different scales and, together with the genetic pool, they characterize the specificity of the new organism.

Completion of development and residual plasticity, including repair and memory mechanism, justify what is called neo (- and neo-neo-...) darwinism

as it manifests itself at the cellular or cell-groups levels. *

Aspects of this are:

- cell competition
- matching
- cell death

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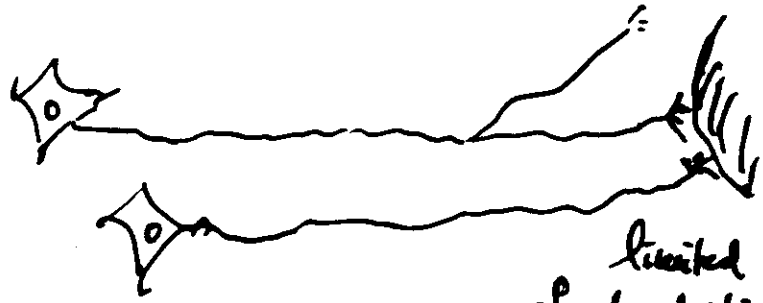
* The cell-groups or cell-collectives, as the "population level" at which the darwinian "driving forces" are operating, has been underlined by G. Edelman in: "Neural Darwinism"

Competition

Neurons compete for dendritic "fields"



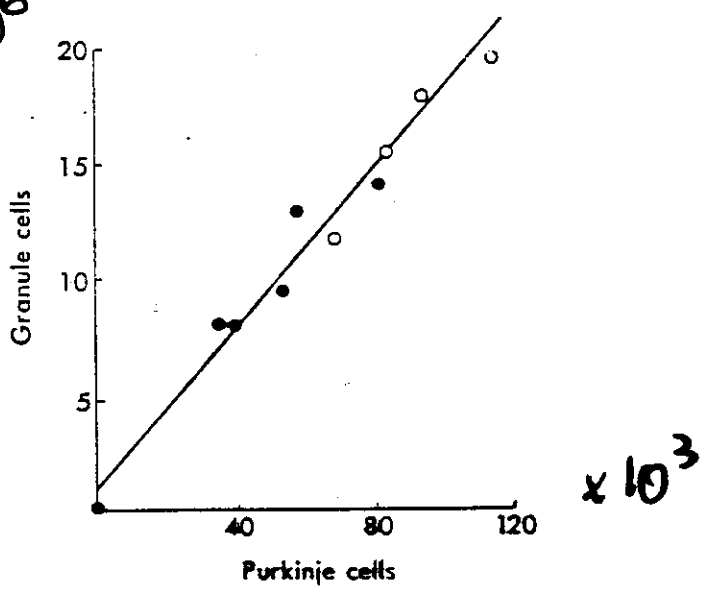
Success is determined by:

- retrograde signals (NGF, --)
- occupation of dendritic "niches"
- stabilization of synaptic contacts
- ---

Unsuccessful neurons are bound to die.

Neuronal death shapes the structures as we observe them in the final matching in number of neurons of different types

An example of



Matching
granule / Purkinje
in cerebellum

Fig. 2. The relationship of granule cell number to Purkinje cell number in cerebellar cortex. The filled circles represent data from counts of Purkinje and granule cells in half cerebella of C57BL/6-*sg*/*sg*⟷+/+chimeras. The Purkinje cell counts (X-axis) are expressed $\times 10^{-3}$; the granule cell counts (Y-axis) are expressed $\times 10^{-6}$. The open symbols represent similar counts in four different non-chimeric inbred strains of mouse and their F_1 hybrids. The solid line is the least-squares-fit of the wild-type counts only. Note how well this fits the staggerer data. Thus, both types of animals support, the conclusion that the granule cell population in cerebellum has a strict numerical matching relationship with the Purkinje cells.

About 200 granule cells per Purkinje cell

(200 g/P)

Taken from:

4

A GENETIC APPROACH TO DEVELOPMENT OF THE MAMMALIAN CNS: STUDIES OF CELL LINEAGE AND CELL:CELL INTERACTION IN THE REGULATION OF CELL NUMBER

KARL HERRUP

Taniguchi Symposia on Brain Sciences No. 9

MOLECULAR GENETICS IN DEVELOPMENTAL NEUROBIOLOGY

Edited by
Yasuzo Tsukada

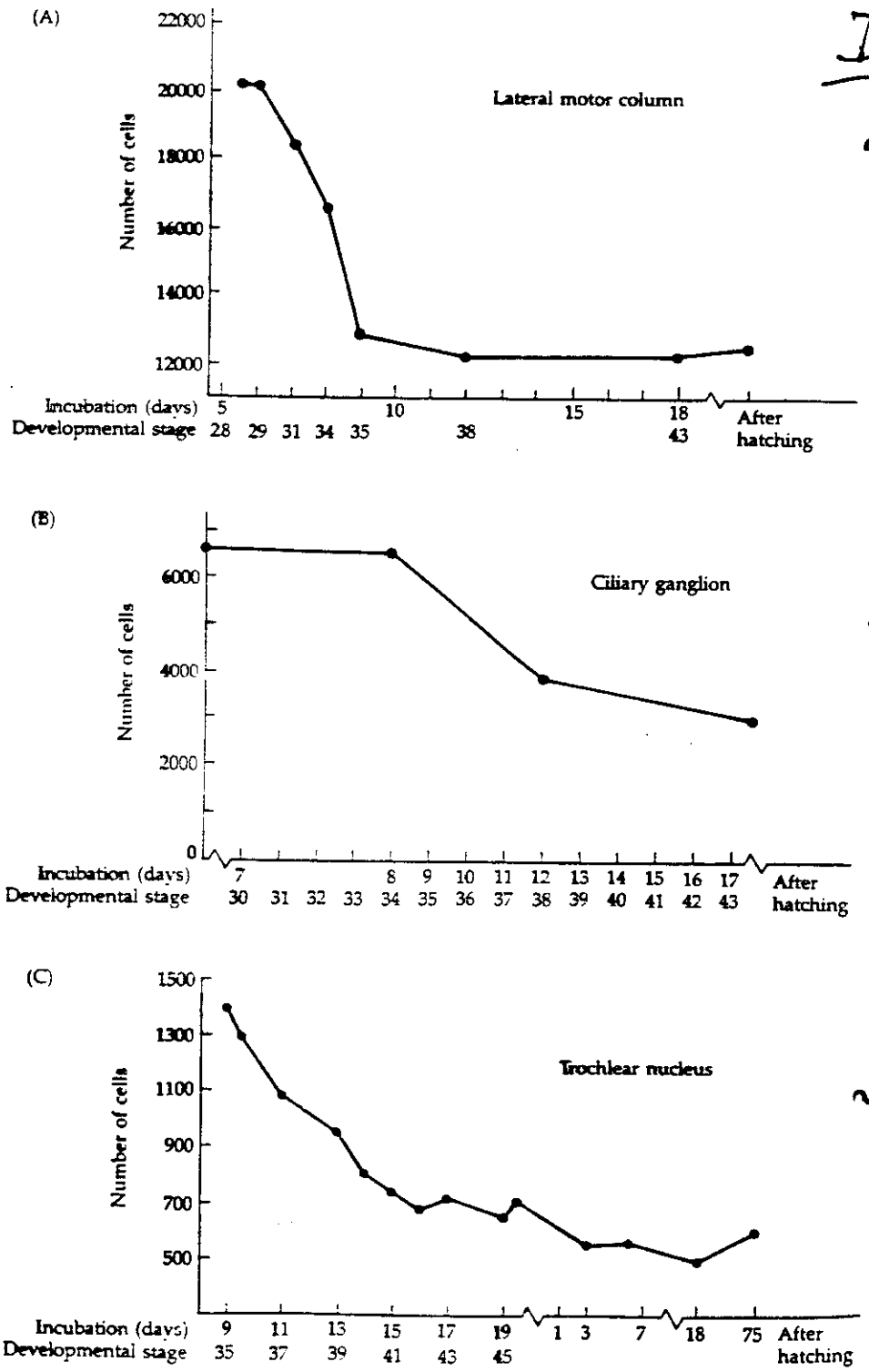
Note: the chimeras are obtained varying the contributions of two different embryos to a whole mouse. The distribution of genotype ratio is visible in all tissues (coat, etc) including the CNS.

Examples of neuronal death

PRINCIPLES OF NEURAL DEVELOPMENT

Dale Purves and Jeff W. Lichtman
WASHINGTON UNIVERSITY SCHOOL OF MEDICINE ST. LOUIS

Death rate:



~ 50%

~ 50%

~ 70%

FIGURE 4. *Normally occurring neuronal death in different parts of the embryonic nervous system in the chick. (A) Lateral motor column of the spinal cord; (B) ciliary ganglion; (C) trochlear nucleus in the brain stem. Hamilton–Hamburger stages and days of incubation are indicated below each graph. In each system a massive loss of neurons occurs in early embryonic life. (A after Hamburger, 1975; B after Landmesser and Pilar, 1974b; C after Cowan and Wenger, 1967.)*

We can ask:

Why a programmed cell death ?

- It has a precise timing, following the proliferation phase.
  - It is substantial, ranging from 50% to 90%.
  - Is not an intrinsic (genetic = the death gene) property of the involved neurons: the neurons can be "saved" if the competion is relaxed, as by allowing more space for synaptic trees.

One possible explanation could follow from the consideration that the surviving neurons will be final in the N.S., they will not be renewed in the life-time of the organism.

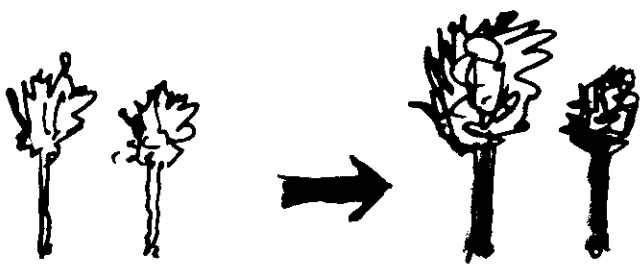
So the competition can give an additional safety margin to the well-functioning of the N.S. since it has been built up of components that have survived through a competition.

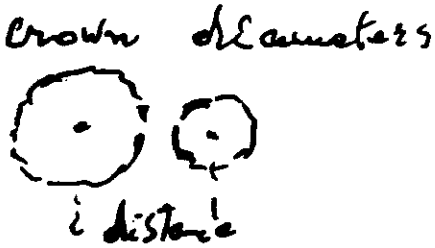
(SELECTED COMPONENTS)

"I would like to buy it"

A curious similarity of high mortality rate (50% or more), with similar precise timing, has been found in the raising of

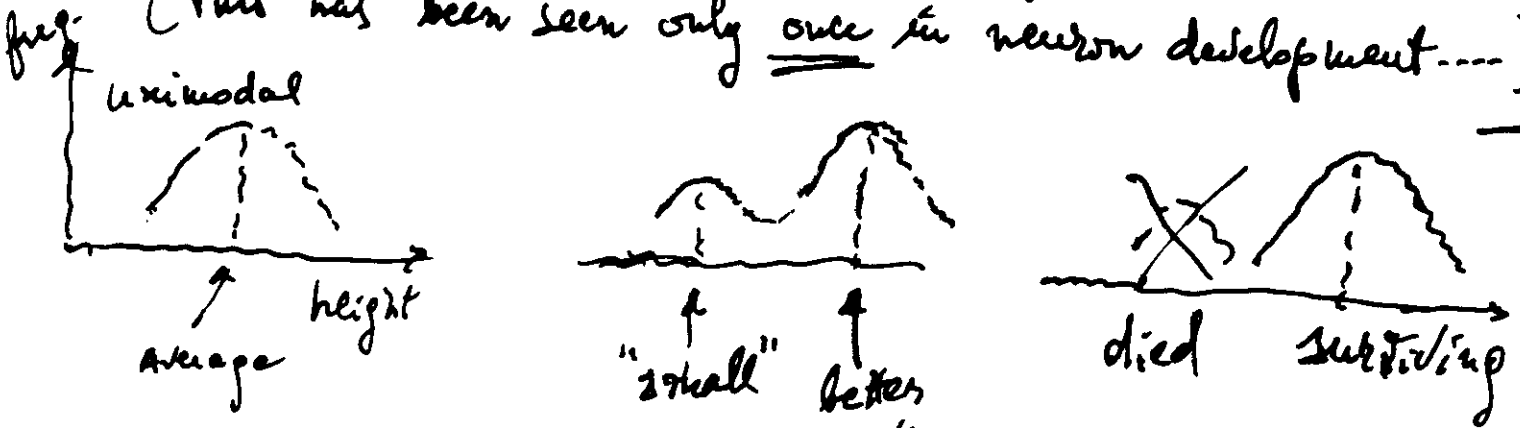
even-aged plant monocultures





An initial small difference in the crown or roots development makes one plant "dominant" on its "nearest neighbour", bringing it finally to die.

[On second thought the analogies appear to have many reasons. The trees population changes from unimodal to bimodal, to return unimodal after the tree-death. (This has been seen only once in neuron development....)]



Could be looked in neuronal development?

Note:

- Neural death in insects, is programmed, following the metamorphosis and is under the control of hormones

K.i. Kimura, J. W. Truman
J. NeuroSc. 10 (1990) 403

- In the nematode Caenorhabdites elegans cell death is under direct gene control ("ced 3, ced 4")
Ellis, Horvitz, Cell 44 (1986) 817

NO "darwinian" COMPETITION!

Multidisciplinary Approach to Brain Development
C. Di Benedetta et al., editors

NEURONAL DEATH IN EMBRYONIC DEVELOPMENT: A MODEL FOR SELECTIVE CELL COMPETITION AND DOMINANCE

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INTRODUCTION

Cell death during neural development is a widespread phenomenon of such a magnitude that mortality can reach peaks as high as 50%, and up to 80-90%. It appears to be a "naturally-occurring"[1] phenomenon, with a well defined timing[2], so that it should be considered not a fortuitous accident of development but as having a definite role in the making of the nervous system.

The explanations so far advanced make appeal either to an error correcting[3] or to a system-matching[4] mechanism. The former, while taking in consideration various type of errors (in cell migration, in axon growth, in synaptic field formation), leaves unsatisfied for the very large errors it implies. The second one is in part equivalent to the model discussed here. In fact it assumes that cells compete for a limited number of available synaptic fields (the finite carrying capacity of the "environment"), but it does not attempt to explain why the proliferation phase is wrongly programmed and why some cells succeed and other degenerate.

We discuss here a model based on an analogy with similar high mortality rates found in even-aged monoculture of plants[5]. The analogy can be viewed as not purely formal: in fact the plants, growing together in the monoculture, interfere with one another by competing for nutrients, moisture and light. Growing embryonic cells can be assimilated to an even-aged monoculture and quite similarly compete both on the input side (nutrients, trophic factors) and on the target side (synaptic field, retrograde signals).

The model suggests that the cells surviving the neurothanasia[6] period are those successful in the competition, the dominant ones. The resulting mechanism of ontogenetic selection[7] can be considered as a way to ensure an additional safety margin for the not renewable components of the final nervous network.

Possible tests of the model, such as a transient bimodality in the cell population, are briefly discussed, together with relations with other models.

GROWTH AND DEATH IN EVEN-AGED MONOCULTURES

Even-aged plant monocultures include forest crops or annual plants, well managed and studied for their economic value, for example for the needs of the newspapers industry. Extensive measurements of plant parameters (height, girth, weight, etc) are quite easy to obtain, together with their frequency distribution. A striking result, recently evidenced by Ford[5], is the development of bimodal frequency distributions of the plant parameters; the appearance of the bimodality is then followed by a high mortality of the plants (of the order of 50%), the distribution becoming finally again unimodal.

The phenomenon is explained as a consequence of interaction between the plants and has been quantitatively described by empirical equations fitted to data or through models of interactions simulated on computers. We will follow the more analytical approach developed by Gates[8].

Assuming a random distribution of vigour in the population, an initial phase of the growth will not be much affected by mutual interference and the frequency distribution of height or weight will be unimodal. Later the interference will become important and for a pair of adjacent members of the population the more vigourous one will damage the less vigourous in increasing way. In the plant case, the dominant member of the pair will overtop the other, shadowing it with its crown and reducing in this way its share of light; analogous effects can come from interroot competition. In this phase the growth of the dominated members will be reduced, contributing to the secondary peak of the frequency distribution. When the difference of growth reaches a critical value (complete "overtopping"), the dominated member "degenerate" and, following a phase of sudden high mortality, the population returns unimodal. It will be finally composed only by the dominating members, that after surviving the competition, will complete their growth.

It is quite easy to translate the previous description to the case of cell competition. One can for example take in consideration axonal growth or/and synaptic field expansion.

THE RANDOM DISTRIBUTION OF GROWTH IN THE POPULATION

We present now the quantitative aspects of the model. We assume that the growth of the members of the even-aged monoculture can be described by the time dependence of an important parameter, say r(t). In the case of plants it is assumed to be the radius of the crown; for the cells it can be the soma radius or the axon lenght or the lateral dimension of the synaptic field. It could be also a non morphological parameter.

For semplicity it is assumed that the vigour v will affect the growth as a multiplicative factor, so that different members of the population will grow with the different time dependence:

$$r(t)=vR(t) \tag{1}$$

The v values are assumed to have a random distribution with density f(v). Gates takes for f(v) a rectangular distribution and this, together with the sharp boundaries of the interference domains, makes the calculations in some way cumbersome. We prefer, for analytical advantages, to assume a gaussian distribution:

$$f(v)=\frac{1}{\sqrt{2\pi}\sigma}\, e^{-(v-1)^2/2\sigma^2} \qquad , v > 0 \tag{2}$$

that is possibly also a more realistic assumption. Taking the mean value $\bar{v}=1$ it means that R(t) is the average low of growth of the population (without interference). The variance σ^2 should be quite small, for example in the range 0.01 to 0.05.

THE INTERFERENCE MECHANISM

The next point to discuss is the mechanism of interference. If two members, say 1 and 2, have their centersat the distance a(see Fig. 1), it is assumed that if $r_1+r_2 < a$ they will grow unaffected, without interference. When $r_1+r_2 \geq a$, the two elements start to interfere, the more vigourous member of the pair damaging the less vigourous one. Furthermore, when the difference in growth reaches the final value a or is larger:

$$r_1-r_2 \geq a \tag{3}$$

the second member is completely dominated and degenerates.

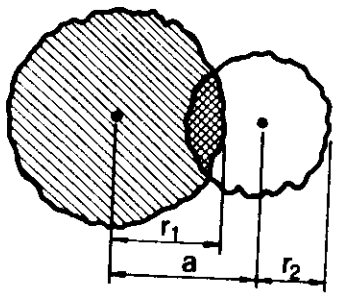

Fig. I. Partial dominance of a larger member over a smaller one. The interference area is damaging only the weaker competitor.

(In the plant case the smaller one will be completely overtopped and shadowed). In the intermediate phase of partial dominance the population shows a bimodality in the distribution, the secondary peak contributed by the partially dominated members[9]. We point out that the "vigour" v needs not to be a real genetically determined factor. It can be a factor expressing the result of many small independent advantages or disadvantages that the members of the population find in the microenvironment in which they grow. This observation is valid already for some cases of plant monocultures and certainly more so for the cell case. The two possibilities can be viewed to arise as a special case of the dispute nature-nurture.

THE MORTALITY RATE.

Without discussing here the bimodality, we limit ourselves to evaluate the mortality rate for the population in the schematic form previously indicated. From (I) and (3) one derives that cell 2 degenerates when

$$v_I R(t) - v_2 R(t) \geq a$$

or when

$$v_I \geq v_2 + \frac{a}{R(t)} \tag{4}$$

Assuming that v_I and v_2 are values taken independently, the joint probability density is simply the product $f(v_I).f(v_2)$. For a cell present at time t=0, the probability that it will be dead at time t will be indicated by P_m . From (4) one obtains that:

$$P_m(t) = \int_0^\infty dv_2 \int_{v_2+\frac{a}{R}}^\infty dv_I \; f(v_I) f(v_2) \tag{5}$$

Introducing in (5) the gaussian distribution (2) one can derive, for the case of relatively small variance (see Appendix):

$$P_m(t) = \frac{I}{2} - \frac{I}{2} \operatorname{erf} \frac{a}{2\sigma R(t)} \tag{6}$$

where erf x is the error function. The survival probability is then given by

$$P_s(t) = I - P_m(t) = \frac{I}{2} + \frac{I}{2} \operatorname{erf} \frac{a}{2\sigma R} \tag{7}$$

To obtain the explicit dependence of the survival probability on time, one must specify the average law of growth R(t). For the competition phase we take an exponential law:

$$R(t) = b\, e^{t/\tau} \tag{8}$$

The mortality rate reaches a peak at time t_{max}. From (6) and (8) we obtain:

$$t_{max} = \tau \ln \frac{a}{\sqrt{2}\, b \sigma} \tag{9}$$

and the mortality peak is

$$\left(\frac{dP_m}{dt}\right)_{max} = \frac{1}{\sqrt{2\pi e}} \frac{1}{\tau} = \frac{.242}{\tau} \tag{10}$$

In Fig. 2 is represented the survival probability $P_s(t)$ for different values of the parameters $a/b\sigma$. For comparison we give together the results in the case of a rectangular distribution of v. One can see that the two distributions give results essentially not different.

COMPARISON WITH OBSERVATIONAL DATA

The highest value of the mortality rate for the isthmo-optic nucleus, as estimated from the Cowan and Clarke data[10] (counting time from the IIth day of incubation) is:

$$\left(\frac{dP_m}{dt}\right)_{max} = I/7 \text{ day}^{-I} = .I4 \text{ day}^{-I}$$

therefore from (IO) we get $\tau = I.7$ day.
The peak is reached the I4th day, therefore from (9) we obtain:

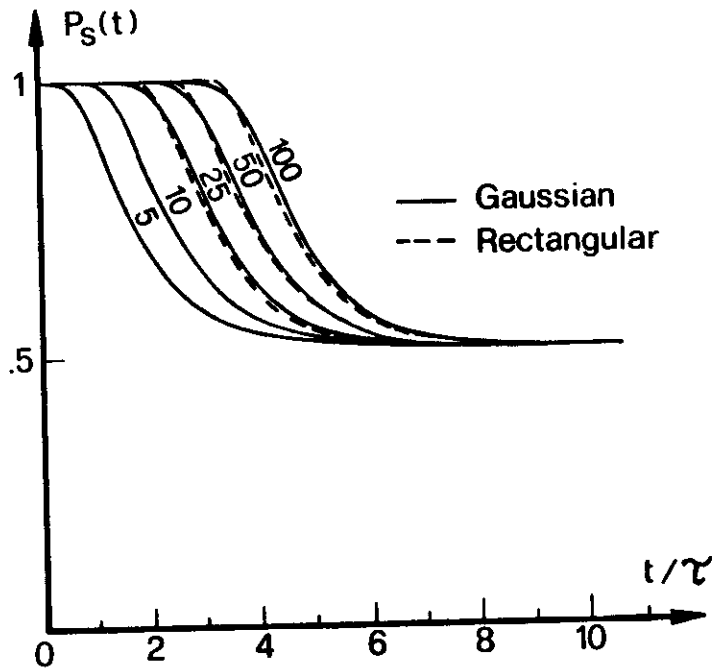

Fig. 2. Survival probability as function of time. Unit time is the time constantτ of exponential growth. Numbers on the curves are values of the parameter $a/b\sigma$. Solid lines for the gaussian distribution of vigour, dashed lines for the rectangular distribution.

$$\frac{a}{b\sigma} = \sqrt{2}\, e^{3/1.7} = 8.3$$

With a value of σ between .2 and .3, we arrive at the value $a/b \simeq 2$, that should be considered of the right order of magnitude. Using the observations of G. Rager et al.[11] on the degeneration of retinal ganglion cells in the chicken, one obtains the peak of mortality rate on incubation day 13th. From the values listed in their Table I, one obtains the value .08 day^{-1} for $(dP_m/dt)_{max}$, therefore $\tau \simeq 3$ days. Since degeneration starts at day 9th, one obtains $a/b\sigma \simeq 5.4$, an estimate of the same order as that obtained for isthmotic nucleus, using the Cowan/Clarke data.

DISCUSSION

From Fig. 3 one can see that the computed curve (solid line) does not agree well with the experimental data in the final part of the curve. This must be expected, since the

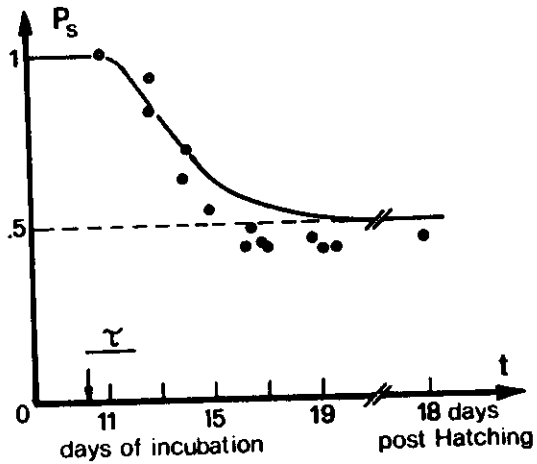

Fig. 3. Survival probability. The solid line is for $a/b\sigma$ =8 and time constant τ=I.7 days. The empty circles are from Cowan/Clarke counts of cells on the isthmo-optic nucleus of the chicken. The fit is obtained taking the initial time t=0 not at incubation day 11th but $\tau/2$ earlier (arrow).

model has been confined only to pairwise competition and therefore the surviving fraction cannot fall below I/2. In the case studied by Cowan/Clarke the final mortality reaches 60%. The model can be extended to include interference in triplets or quadruplets. In this way one can explain the values of mortality larger than I/2.

We point out that a bimodality in size, followed by degeneration of the smaller cells, has been noted by Sohal[12] in the trochlear nucleus of the duck embryo. One may observe however that bimodality is not necessarily a morphological property.

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APPENDIX

To evaluate the mortality as obtained from (5) with (2), we change the origin of the axis to the center (1,1) and rotate them 45° with the transformation:

$$\xi = (v_1 - v_2)/\sqrt{2} \qquad ; \qquad \eta = (v_1 + v_2 - 2)/\sqrt{2}$$

and we obtain:

$$P_m(t) = \frac{I}{2\pi\sigma^2} \int_{-(\sqrt{2}+\frac{a}{\sqrt{2}R})}^{\infty} d\eta \int_{\frac{a}{\sqrt{2}R}}^{\sqrt{2}(1+\frac{a}{R})+\eta} d\xi \; e^{-(\xi^2+\eta^2)/2\sigma^2}$$

For values of the variance σ^2 small compared to 1 the integral can be substituted by:

$$P_m = \frac{1}{2\pi\sigma^2} \int_{-\infty}^{\infty} d\eta \int_{\frac{a}{\sqrt{2}R}}^{\infty} d\xi \; e^{-(\xi^2+\eta^2)/2\sigma^2} = \frac{I}{2}\left(1 - \operatorname{erf}\frac{a}{2\sigma R}\right)$$

where $\operatorname{erf} x = \frac{2}{\sqrt{\pi}} \int_0^x e^{-\xi^2} d\xi$.