

ACUITY RESPONSE CURVES TO MONOCULAR OCCLUSION:  
A COMPUTER SIMULATION

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Abstract

Humans as well as cats and monkeys exhibit a sensitive period in early life during which the visual system is susceptible to monocular deprivation of a normal visual environment resulting in a unilateral loss of visual function. Reverse deprivation causes a reversal of this effect and is the common treatment in young children with amblyopia. Using an objective technique (visual evoked response) of measuring the visual acuity in young children undergoing such reverse deprivation (patching) the changes of acuity can be readily measured. This report examines how data collected in such patients can be used to predict the effects of patching and allow the clinician to simulate the effect of patching therapy before it is begun. An equation describing log change in visual acuity is given as a linear equation including factors of age, period of patching, hours of patching per day, log initial acuity, and the log difference in acutities between the two eyes. A realistic simulation is generated by successive application of the formula, within the limitations of a linear model for an inherently nonlinear system.

1. INTRODUCTION

Visual acuity is the measure of visual function that describes the visual system's ability to see form. Most frequently it is measured as the ability of an individual to resolve and discriminate between letters on an eye chart. Most of us are familiar with the Snellen notation of 20/20, 20/40, etc. The numerator specifies the testing distance and the denominator the size of the test letter. 20/20 means one can read the letters designated for 20 feet from a distance of 20 feet. The actual subtense of the detail in the 20 foot letter is one minute of arc. 20/40 means 2 minutes of arc and so on.

By and large the most common factor associated with less than normal visual acuity is that of refractive error or defocus of the retina. Occasionally, pathology of the eye or visual system affects the acuity. When loss of acuity cannot be accounted for by either refractive error or visible pathology the condition is called amblyopia, commonly identified by the misnomer "lazy eye". This condition is believed to arise in many cases from inappropriate development of vision during early life. Cats and monkeys deprived of clear or single vision during early life develop similar deficits in visual function.(3,6,20) It is suggested that there is a period in early life when the

visual system is still "plastic" and a deprived visual environment prevents the development or maintenance of good visual function.(19) If the individual is still young the treatment for lazy eye will include patching of the good eye to encourage the amblyopic eye to work and to turn off the normal eye which ususally forces the brain to supress the inferior or dissimilar image from the amblyopic eye.(15) Animal experiments demonstrate that this deprivation can be reversed by depriving the non-deprived eye (reverse deprivation), although the newly deprived eye shows very similar effects from deprivation.(6) In humans it has generally been held that patching has little effect on the normal eye (15) although there is recent evidence that this is not the case.(1,7-10,14,16) The difficulty in assessing the effects of patching arises from the fact that most of these subjects are young. In fact the younger they are the more sensitive they are to visual deprivation be it from natural causes such as cataract or from artificial deprivation such as patching.(1,19,22) The younger patients below the age of 3 or 4 years are of most interest, but do not perform well in the usual subjective tests of acuity where some vocal or gesturing response to a target is required. Most clinicians working with this group have had to treat amblyopia in these patients without a good measure of their acuity. Little is known, therefore, of the response to patching in these individuals and the choice of therapy is often left to trial by error and repeated adjustment of therapy as it proceeds. It would be very helpful to the clinician to be able to predict the response of the visual acuity in both eyes to various levels of patching.

It is possible to determine visual acuity objectively in adults, children, infants, and even animals by means of a technique called VER (visual evoked response).(12,13) Small EEG (electroencephalograph) electrodes are attached to the scalp with the active electrode over the occipital portion of the brain nearest the visual cortex. The sudden onset of a patterned visual stimulus such as the appearance of a checkerboard evokes a minute potential change in this region of the scalp. This small voltage change, on the order of several microvolts in amplitude, is about an order of magnitude smaller than the ongoing EEG activity of the brain that is unrelated to the stimulus. Simple amplification does not separate the evoked response

signal from the ongoing EEG noise. Signal averaging is frequently used to improve the signal to noise ratio to the point where the evoked response can be discerned. This is done by time locking the onset of the stimulus with the recording of the EEG. The small response will accumulate with each successive stimulation (N) while the background EEG signal, presumed to show no regular tendency, will increase at a slower rate ( $\sqrt{N}$ ). The amplitude of the evoked response shows a nearly linear relation with the logarithm of the size of the target detail (eg. the size of the checks). By presenting a series of patterned targets of varying size the visual acuity can be extrapolated as the limit of resolution (zero response level). We have used this technique extensively to determine visual acuity in infants and young children with very satisfactory results.(2,5,8-11,17)

This report describes a computer program that incorporates data we have collected from young amblyopes being patched and performs multiple regression on these data to allow prediction of the sort described above. It was already clear from our data that the normal eye is affected by full-time patching in a complementary way to that in which the amblyopic eye is helped. For the most part the effect is symmetric. The normal eye loses in acuity what the amblyopic eye gains. This is not too useful a situation since tradeoff of vision between the two eyes is generally not of sufficient benefit to the patient. This reversal of acuity, although not widely recognized, is not new and clinicians have observed "occlusion amblyopia" and taken steps to prevent it.(15,16) We have observed, however, that part-time patching allows for both eyes to improve in acuity.(10) Analogous animal experiments supports the efficacy of part-time patching.(4) Animal experiments also suggest that monocular deprivation reduces the binocular responsiveness of cells in the visual cortex.(18,20) This implies that patching in young children should be minimized so that binocularity is allowed to develop and flourish. Our program, it is hoped, will serve as a means by which the performance of various patching regimens can be predicted.

## 2. METHOD

The baseline data for generating the regression equations are data we collected at UCSF Children's Eye Clinic

on 6 young amblyopes. Each of these subjects suffered from amblyopia as a consequence of monocular deprivation due to cataract during early life. The cataract was removed and the refractive state of the eye restored with a soft contact lens. The 28 observations included are occasions when initial and final acuities could be obtained for both eyes after a known period of patching or non-patching of the normal eye. The children were seated in their mother's lap and viewed a round translucent screen 20 cm. in diameter from a distance of 1.14 meters. Checkerboard patterns were rear projected onto the screen. Electronic shutters (Uniblitz) controlled projection so that the checkerboard pattern was seen for 40 to 50 milliseconds and then replaced by a blank field of equal luminance until the next checkerboard presentation. The stimulation rate varied from 1 to 1.33 presentations per second, however, the stimulation was discontinued when the child lost interest in the target, moved, or became fussy. The EEG was recorded with active electrode at the midline occiput and reference to the right earlobe with ground at the left earlobe. Two Grass P-15 AC amplifiers were used in cascade to achieve 100,000 times gain with half-amplitude cutoffs of 1 to 30 Hz. The amplified signal was averaged for 64 presentations by a commercial signal averager (Nicolet 527). Hard copy of averaged waveforms was obtained on an Hewlett-Packard X-Y Recorder. Amplitude of the major trough to peak component was measured and regressed with log spatial frequency (30 cycles per degree is equal to one minute of arc or 20/20) of the checkerboard patterns. The acuity was determined as the spatial frequency predicted for zero amplitude response. The acuity is then converted into Snellen notation.

The simulation program is written in Microsoft-80 Disk BASIC and run on an Osborne One computer. The self-contained CRT, dual disk drives and keyboard unit allowed low cost implementation and subsequent use of the program and datafile on most CP/M based business systems complemented with BASIC-80. The output of the simulation is in simple PRINT or LPRINT statements and adjusts for the user's screen or printer width (55 on the Osborne). Print out was obtained via the integral RS232 connector on a Xerox 1720 terminal.

### 3. RESULTS

The program consists of several subroutine modules described below and illustrated in Figure 1. Data entry [1] is based around a random disk file into which are entered the data collected by us at UCSF Children's Eye Clinic. The data file [7] is left open for modification by the user. Each record is available for inspection. Records can be deleted to eliminate suspected outliers. Additional data can be added to allow inclusion of the user's case record, to update the regression equation. Before actual calculation of the regression equation the user is asked to select the regression variables, by editing a small number of program lines that define the regression variables in terms of the data variables. [2] Multiple linear regression [3] is performed twice, once for each eye. This allows for calculation of the expected acuity in both eyes during the simulation. Regression coefficients, coefficient of determination ( $R^2$ ), coefficient of multiple regression (R), and the standard error of estimate ( $S_y$ ) are calculated and output. After the regression equations are determined the user may select either to calculate residuals or to run the simulation.

The residual is the difference between the predicted and actual values of the dependent variable. While the user is free to select the dependent variable, the dependent variable of most interest to a simulation is the change in acuity for a given period of patching. The calculation of the residuals [6] in the case of this variable gives a measure of how closely the regression equation comes to resembling the real world situation. The residual calculation module takes the regression equations and reverts to the data file for calculation of the residuals. The means square of the residuals is also calculated. This is essentially the variance in the dependent variable left over after application of the regression equation.

The simulation [5] consists of successive application of the regression equations calculating the change in visual acuity for each eye. The simulation requires the initial age (months) and acuities (Snellen denominator) and for each patching period the length of the period (weeks) and the amount of patching (hours/day). These are the independent variables of most interest

to the simulation in terms of predicting the effects of various patching regimens. The new age and acuities are calculated for each patching trial and the simulation is continued. Entering a patching period of zero ends the simulation so that the simulation can be started anew. The variables used in the simulation must be transformed from the regression variables.[4] This is done by editing a small number of program lines in the simulation module. The change in acuity is calculated in terms of the regression equation coefficients and dependent variables carried over or entered during the simulation.

Table 1 shows the correlation coefficients for 5 sets of regression equations determined by the program. The dash represents the variable omitted from the regression. The coefficient of determination, correlation coefficient, standard error of estimate and mean residual square are shown for each eye in each run. The closest regression includes all of the factors listed. It is apparent that the inclusion of the amblyopia factor (log acuity difference between the two eyes) substantially adds to the value of the regression equation. Omission of the amblyopia factor dramatically reduces the realism of the simulation using the regression equation as revealed by a marked increase in the residual mean square. Further elimination of the initial acuity factor (log reciprocal acuity) further degrades the simulation. Additional elimination of the patching period factor causes little change in the residuals, but is crucial to a regression that includes initial visual acuity and depth of amblyopia. Figure 2 illustrates a typical simulation printout. The horizontal axis is acuity in a logarithmic scale from 20/1000 to 2/20. A and N represent the acuities of the amblyopic and normal eyes respectively. If the acuities coincide the letter B (both) is used. The age, patching level in hours per day and acuities are also specified for each recalculation.

#### 4. DISCUSSION

The major difficulty with the present analysis is the presumption of a linear relationship between the independent and dependent variables. While transformation of variables is possible at both ends of the regression process, the selection of the transform is left up to the user's intuition and choice of model. The most obvious problem with a linear approximation to a non-linear

situation is illustrated with the following example. Let us suppose 10 hours of patching a day produces a loss of acuity of 2 log units in the patched eye that diminishes with age until age 60 months. Most models of plasticity in the visual system would predict no acuity change after age 60 months, but linear regression would predict a gain of acuity that would now increase with age, an entirely unrealistic prediction. This nonlinearity has not been corrected for in the simulation. A second nonlinearity is that a gain of acuity is limited to 20/20 or perhaps 20/15. This appears to be the limit of the eye's resolution. A model we have proposed for changes in visual acuity in infants suggests that acuity is related to neural connectivity and that acuity in terms of neural connectivity may be better than 20/20.(3,9,11) The subsequent effect of patching may depend not on the observed acuity, but the neural connectivity subserving it. The simulation preserves this model by using the calculated acuity (which can exceed 20/20), but graphically displays only to 20/20. This more accurately represents what the clinician would observe.

A second matter is the selection of variables. The current program provides only for manual selection of variables to be included in the regression. Naturally, variables we felt more significant were entered into the simulation. Stepwise regression was not implemented, but would allow for selection of variables on the basis of the satisfaction of a specified level of significance by the F test. The inclusion of variables that show a spurious high correlation is nonetheless possible. Also, variables that are not easily determined or under the control of the clinician should be excluded. Variables most relevant to the clinical setting were therefore chosen for the regressions shown above. The final test for the regressions' usefulness was the mean residual square. This reflected the "feel of realism" in the simulation.

The regression with the lowest residual mean square includes as independent variables age, length of the patching period, patching level, initial visual acuity, and the depth of the amblyopia. The simulation does render a realistic representation of acuity changes observed with patching. The simulation must be viewed with suspicion, however, in regions where nonlinearities are allowed to penetrate. These are: after the plastic period where the effect

reverses (after age 70 months or so), when acuity exceeds 20/20, and before the age of six months during which normal 20/20 acuity is only beginning to develop.(12) We have observed higher than normal acuities during this early period for the same reason that supernormal acuity may be predicted in older subjects. In these cases superacuity is not limited by the eye's limit of resolution.(11) In order to allow the user full freedom entry of inconsistent acuities for this age group was not restricted.

It should also be made clear that the error of estimate calculated in the regression module becomes less meaningful with each successive recalculation in the simulation module. The accuracy of the simulation could likely be improved with addition of more data. More rigorous statistical analysis may also allow for removing some of the above nonlinearities. Naturally, this rests upon appropriate selection and transformation of data variables. The incorporation of SP-micro a microcomputer oriented version of SPSS (Statistical Package for Social Sciences) would be helpful in improving the scope of the regression module. Our model for acuity changes immediately suggests a nonlinear relationship between patching, age, and acuity change. We suggest that the change in acuity is a function of the patching and an inherent "sensitivity" in the visual system that is an approximately linear function of age, at least for the duration of the sensitive period.

Equation 1:

$\log VA \text{ change} = (k1 * PXGPER + k2 * PXGLVL + k3 * \log VA + k4 * \log AMB) * (\text{Sensitivity})$   
 where: Sensitivity =  $b + k5 * AGE$  for  $b + k5 * AGE > 0$  else 0. and  $k1 - k5$  are coefficients of the regression equation.

PXGPER (# weeks patched)  
 PXGLVL (# hours patched per day)  
 VA (reciprocal initial Snellen acuity)  
 AMB (Ratio of acuities for normal and amblyopic eyes)

Note: The data file uses the Snellen denominator as the acuity measure so the higher the value the lower the acuity.

If the patching level is high the patching coefficient in Equation 1 is also high (positive for the amblyopic eye, negative for the normal eye). If the patching level is low the patching coefficient is again high (now negative for the amblyopic eye and positive for the normal). When the sensitivity runs

out with age the effect no longer reverses as was the case with the linear prediction. A trial regression was performed in a two stage manner by first determining a regression with age alone for the effect with 0 patching and using this regression as the sensitivity factor for a subsequent regression of the remaining factors. This resulted in a very low correlation coefficient. It is presumptuous to regress the sensitivity factor by age alone ignoring other factors and the more appropriate technique would be use of partial correlation coefficients to remove the effects of the remaining factors. It is also presumptuous to suggest that the remaining factors are necessarily in a linear relation.

## 5. CONCLUSIONS

Given the factors age, patching period, patching level, initial acuity and depth of amblyopia the closest regression includes all of these factors in a linear relation. While the regressions presented are performed by omission of these factors and not elimination by means of partial correlations, it is clear that prediction of the effect of patching on acuity will require consideration of acuity factors in addition to age and patching parameters. We plan shortly to test this simulation on new data we have collected on a series of patched infants.

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FACTOR	REGRESSION COEFFICIENTS				
	AMBLYOPIC EYE				
<CONSTANT>	-1.15e0	-1.30e0	-8.6e-1	-5.9e-1	-1.02e0
AGE	-4.7e-3	3.19e-3	-9.1e-3	-4.1e-4	-2.2e-3
PATCHING PERIOD	2.20e-2	2.23e-2	5.65e-2	*****	*****
PATCHING LEVEL	8.68e-2	9.23e-2	1.96e-1	1.68e-1	6.73e-2
INITIAL VIS. AC.	6.40e-1	7.35e-1	*****	*****	1.29e-1
DEPTH OF AMBLYOPIA	1.09e-1	*****	*****	*****	6.67e-1
COEF. DETERM-R <sup>2</sup>	.43	.43	.229	.19	.422
COEF. CORREL-R	.656	.656	.478	.436	.65
STD. ERROR OF Y	1.343e0	1.314e0	1.495e0	1.500e0	1.323e0
MEAN RESIDUAL SQR	5.77e-1	1.971e0	2.297e0	2.067e0	1.582e0
	NORMAL EYE				
<CONSTANT>	-5.0e-1	-1.47e0	8.56e-1	8.59e-1	-3.9e-1
AGE	6.16e-3	1.09e-3	-8.1e-3	-8.0e-3	8.29e-3
PATCHING PERIOD	1.93e-2	2.66e-2	5.27e-2	*****	*****
PATCHING LEVEL	-4.8e-2	1.01e-1	-1.3e-1	-1.3e-1	6.43e-2
INITIAL VIS. AC.	5.55e-1	7.42e-1	*****	*****	-1.8e-1
DEPTH OF AMBLYOPIA	-2.2e-1	*****	*****	*****	5.79e-1
COEF. DETERM-R <sup>2</sup>	.645	.281	.307	.307	.634
COEF. CORREL-R	.803	.53	.554	.554	.796
STD. ERROR OF Y	6.25e-1	1.898e0	8.36e-1	8.19e-1	6.20e-1
MEAN RESIDUAL SQR	4.01e-1	1.088e0	1.152e0	1.154e0	1.290e0

TABLE 1: REGRESSION COEFFICIENTS FOR LOG CHANGE IN VISUAL ACUITY  
 (\*\*\*\* indicate an omitted factor)

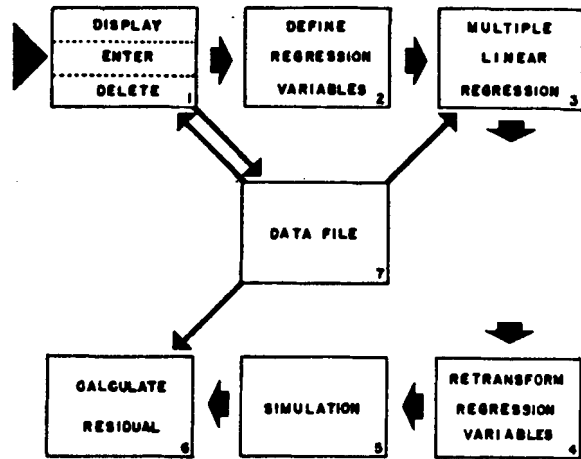


FIG. 1 PROGRAM FLOW

SIMULATION		
20/1000	AGE/PXG/VA-AMB/VA-NHL	20/20
10 \ 0 \ 400 \ 40		
12 \ 10 \ 66.116 \ 55.4113		
14 \ 10 \ 34.8571 \ 63.2813		
16 \ 2 \ 55.9463 \ 45.348		
18 \ 7 \ 43.3954 \ 48.9691		
20 \ 7 \ 39.9689 \ 50.0529		
22 \ 5 \ 46.5964 \ 45.3994		
24 \ 5 \ 49.7152 \ 42.9367		
26 \ 6 \ 47.1 \ 43.3835		
28 \ 6 \ 46.6278 \ 43.0503		
30 \ 3 \ 60.8556 \ 36.7487		
32 \ 8 \ 43.8085 \ 42.8984		
34 \ 6 \ 46.727 \ 41.2812		
20/1000	AGE/PXG/VA-AMB/VA-NHL	20/20
36 \ 8 \ 40.5826 \ 44.0792		
38 \ 7 \ 42.467 \ 42.7498		
40 \ 10 \ 33.5826 \ 48.0349		
42 \ 0 \ 74.2272 \ 31.0767		
44 \ 10 \ 41.8613 \ 40.6615		
46 \ 6 \ 48.6404 \ 37.4365		
48 \ 7 \ 47.5224 \ 37.3763		
50 \ 8 \ 43.6146 \ 38.6871		
52 \ 7 \ 46.5576 \ 37.0042		
54 \ 8 \ 44.1166 \ 37.5778		
56 \ 0 \ 87.4919 \ 25.5567		
58 \ 12 \ 39.884 \ 37.5991		
60 \ 8 \ 42.9173 \ 36.4725		
20/1000	AGE/PXG/VA-AMB/VA-NHL	20/20
62 \ 8 \ 44.4849 \ 35.5413		

FIGURE 2. SAMPLE PRINTOUT OF SIMULATION

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