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by

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## 1. Introduction

In certain operations, such as brain and eye surgery, involuntary muscle movements can be disastrous. Such operations require that steady levels of patient drug-induced muscle relaxation (or paralysis) be maintained. The provision of muscle relaxation allows the surgeon to make best use of a small incision and gain access to deep structures with minimal tissue damage.

Muscle relaxant drugs are conventionally administered by bolus injections. The anaesthetist's experience and judgement are called for to determine the size of the bolus dose. Such manual control tends to proceed by over-paralysis and usually fails to maintain steady relaxation levels. When over-paralysis does occur at the end of an operation, antagonist drugs, such as neostigmine, are administered to reverse the neuromuscular block. These drugs, although efficient in counteracting the overdosing of relaxant agents, give rise to post-operative complications when used in large amounts.

This work is aimed at providing quantitative measurement of the degree of muscle paralysis and closed-loop control of steady drug administration at very small infusion rates. Feedback control of the continuous infusion of muscle relaxant drugs offers the advantages of precise control of the degree of paralysis and the decrease in the undesirable side-effects by virtue of the reduction of the total relaxant dosage (Cass et al [4], Asbury et al [1], Brown et al [3], Linkens et al [9]).

The level of muscle relaxation can be measured either in terms of an evoked electromyogram (EMG) or an evoked tension response (Lan et al, [7]). The former method has been adopted in this research using supramaximal stimulation at a frequency of 0.1 Hz at the ulnar nerve above the elbow. The resulting EMG is measured using electrodes inserted



in the foreleg (note that the clinical results reported in this paper were obtained in trials on a dog). The EMG signals are amplified 1000 times with a bandwidth of 8 Hz to 10 kHz, rectified, integrated and finally stored in a sample-hold amplifier. Details of the electronic signal conditioning can be found in (Brown et al [3]). Calibration of the system at zero paralysis is performed by adjustment of the EMG gain amplifier to give a rectified, integrated EMG (RIEMG) signal of 5 volts amplitude (i.e. 0% paralysis).

A number of drugs, all of which act to block the neuromuscular transmission, are commonly administered to induce muscle relaxation, and the drug used in this research, pancuronium bromide, is of the competitive (or non-depolarising) type (Laurence and Bennett [8]).

## 2. Initial Feedback Control Trials and Identification Studies

Brown et al [3] achieved satisfactory regulation with a mean of 74% paralysis for an 80% set point in human trials using a simple proportional gain feedback controller. This offset (steady state error) was successfully removed upon the introduction of an integral action into the control structure (using a fixed PI controller), although these authors reported occasional oscillations in the closed-loop response.

It is known from the literature that there is a considerable time-delay between first administration of the drug and the commencement of paralysis. This initial delay is also known as the 'margin of safety' (Paton and Waud [14]) whereby about 70% of the receptor sites must be occluded before paralysis commences. This produces a highly non-linear characteristic involving pharmacodynamics which may be modelled in terms of a Hill equation (Sheiner et al [15], Whiting and Kelman [21]), in contrast to the linear pharmacokinetics representing drug distribution into the blood (Hull et al [6]).

The successful implementation of closed-loop regulation of paralysis in humans (Brown et al [3]) prompted the use of the same techniques in trials on dogs to investigate the long-term pharmacokinetics of pancuronium bromide and its interactions with other drugs such as tranquilisers (Linkens et al [10]). The fact that there are considerable differences

in dynamics between individual subjects and there being no possibility of manually tuning PI parameters during an operation which lasts about an hour make it desirable to identify the dose-response model for muscle relaxation. Identification of the system dynamics for a range of subjects will improve the design of fixed regulators and assist that of alternative adaptive controllers.

Off-line identification (Linkens et al [10]), using a generalised least squares package (Billings and Sterling [2]) applied to data recorded from trials on dogs with PRBS excitation, showed that pancuronium dynamics may be modelled as a two time-constant process. These studies also revealed the presence of a pure time-delay. Note that the identification has concentrated on a linearised model about an operating point and hence the subsequent results give a good insight into the pharmacokinetics of the relaxant drug.

A linear two time-constant time-delay model has been used in this research in simulation studies to describe the pharmacokinetics of the drug pancuronium as part of an overall non-linear muscle relaxant model in which the pharmacodynamic characteristic is included in the form of a dead-zone (to account for the margin of safety) in cascade with a saturation element (to denote the fact that paralysis cannot increase beyond 100%).

## 3. Feedback Control via Simulation

A simulation package, PSI, (Van den Bosch [18]) which includes a hill-climbing optimization procedure was used to simulate the overall non-linear muscle relaxant system. A discrete PID controller was designed with an integral of absolute error as the cost function. Allowing the controller to operate from switch-on (i.e. before the margin of safety was taken up), the optimized response shown in figure 1 for mid-range parameters (taken from Linkens et al [10]) was obtained. The sensitivity of the controlled system to parameter changes was investigated and produced unacceptable oscillations such as those shown in figure 2 (when the model time-delay was changed from 2 to 4 minutes).

The pure time-delay in the relaxant dynamics makes conventional three-term control very difficult particularly when the delay varies widely from subject to subject. This has pointed to the inclusion of a Smith predictor scheme (Smith [17]) in an overall control structure in which the optimized PID controller provides the primary control action. Using the same model parameters as before, the results for the same conditions as those for figures 1 and 2, upon the introduction of a Smith predictor, are shown in figures 3 and 4 respectively.

The Smith predictor algorithm has also been formulated as an external Fortran segment to the simulation and comparable results to those in figures 3 and 4 have been obtained. For this purpose, a digital control package PSICON (Linkens et al [11]) provides the controller + Smith predictor algorithm as a separate Fortran segment in a multi-tasking environment and includes finite ADC/DAC accuracies.

The well-known sensitivity of Smith predictor schemes to mismatched model/plant parameters suggests that some form of adaptive control is required for muscle relaxation control. Because of the unknown and possibly varying time-delay, an explicit pole-assignment self-tuner (Wellstead et al [19]) has been opted for rather than an implicit self-tuner with optimal control objective (Clarke and Gawthrop [5]). An additional advantage of the explicit self-tuner is that process dynamics are estimated directly, and this is important in muscle relaxant investigations since not only is good control required but also a knowledge of relaxant dynamics is likely to have clinical importance. This ability to identify the pharmacokinetics without using blood samples is of paramount importance in the case of new relaxant drugs, such as NC45, for which there is no known assay method for determining drug concentrations in the blood.

The off-line PRBS identification studies (Linkens et al [10]) have shown that the noise present in the system is nearly white, so that the pole-assignment self-tuner should converge to unbiased estimates of the process parameters without there being a necessity to use the extended least squares estimators (Wellstead and Sanoff [20]) which allow for coloured noise contamination.

To allow for the heavy non-linearity in the system, the self-tuning algorithm is 'jacketted' so that when the response is outside its linear operating region, identification is frozen and control is switched to a fixed PID controller. The simulation results reported here, involving self-tuning control were obtained using a 2 microcomputer version of PSICON, muPSI (Linkens et al [12]). This approach uses two Research Machines 380Z microcomputers, one providing the self-tuning algorithm as a separate Fortran segment driving a continuous system simulation language on the other. Inter-machine communication is via an ADC/DAC interface. An example of the output response to a step demand of 80% paralysis is shown in figure 5. The corresponding parameter estimates are shown in figure 6.

The linear model, assumed to describe the pharmacokinetics of the drug pancuronium, was the result of the PRBS identification studies (Linkens et al [10]), which suggested a two-compartment model. Hull et al [6] have, however, proposed a 3-compartment model for the same drug. A compromise through which both suggestions can be accounted for is to require that if the 3rd compartment does exist, then the additional time constant it introduces into the pharmacokinetic model must be faster than the fastest one in the 2nd order model. Thus, an arbitrary choice of a 3rd time constant equal to one tenth of the fastest time constant of the original 2nd order model was made and the resulting 3rd order system was simulated again in muPSI. The controller program is not instructed of this change in the model order, i.e. it still assumes a two-compartment system. The resulting response (figure 7) and corresponding parameter estimates (figure 8) clearly justify the original assumption of a 2nd order model. Although a non-minimum phase system is identified, good control is still maintained and the pole-assignment property (Wellstead et al [19]) is verified. The simulation studies were used to 'initialise' the self-tuner before the eventual self-tuning control of pancuronium administration in dogs. The word 'initialise' in this context means finding sensible values for quantities such as the covariance matrix and forgetting factor in the recursive least squares algorithm and the closed-loop poles which the overall controlled system is required to have i.e. the poles assigned.

Before the actual on-line control of pancuronium administration in dogs, both control approaches, i.e. Smith predictor and self-tuning, were tested in real-time with the non-linear relaxant dynamics being simulated on an analogue computer controlled by a microcomputer programmed to provide the controller algorithms. The results obtained using this real-time simulation were satisfactory enough to encourage the real-life implementation of both control strategies.

## 4. Clinical Trials (Menad [13])

With the dog anaesthetised and intubated, the front and back legs were accessible for measurement and control of the degree of muscle relaxation. An intravenous cannula, inserted in the left back leg, was used for steady infusion of pancuronium via a peristaltic pump with a small dc motor driven from the controller (provided by a 380Z microcomputer). The drug concentration was set to 1 mg in 20 ml of 0.9% saline solution.

While the RIEMG was sampled every 10 seconds, adjustments to the drug infusion rate were made at one minute intervals. The RIEMG was thus re-sampled with a period of 1 minute. This re-sampled output value constitutes the arithmetic mean of the 6 most recent RIEMG values. Such processing of data (averaging) is equivalent to low-pass filtering (Slate [16]).

### Results

Figure 9 shows the output response (RIEMG) and the motor drive signal for the following cases, under Smith predictor control:

(1) a set point of 80% paralysis (from t = 0 to t = 34 mins)

(2) a set point of 40% paralysis (from t = 34 to t = 55 mins)

and (3) a set point of 80% paralysis, with the primary PID controller replaced by a high proportional controller (from t = 55 to t = 84 minutes). In cases (1) and (2), the control structure successfully maintained steady levels of 72.8% and 36.4% relaxation respectively. The very high proportional gain in case (3) has, as would be expected resulted in a 17.5% overshoot. Even in this case, however, control is regained after about 12 minutes and the response has almost settled to a mean

level of 74% paralysis. A non-linearly varying offset on the ADC may account for the steady state offset present in the above 3 cases.

Note. All the self-tuning control trials are for a set point of 60% paralysis. The forgetting factor in the recursive least squares routine was fixed to 0.995 throughout. The self-tuner assumes control when the RIEMG reaches 50% of the set point i.e. (30% paralysis) and the recursive least squares estimation is started as soon as the RIEMG begins to fall.

Shown in figure 10 is a photographic reproduction of a chart recording of the RIEMG and motor drive signals under self-tuning control. This shows the type of noise sometimes present in the RIEMG signal. A satisfactory performance is demonstrated, though the speed of response needs to be improved.

To speed up the response, a different set of closed-loop poles was assigned and another trial was conducted. The resulting system response is shown in figure 11. The 'kink' at the 53rd minute was due to a syringe needing to be changed. The system nevertheless regained control after about 15 minutes. A relatively fast response with good steady state properties is demonstrated. The parameter estimates (figure 13) describe a 2-time constant process with $T_1 = 1.2$ minutes and $T_2 = 18$ minutes. The change in the b-parameters at $t = 53$ minutes, i.e. when the syringe was changed, demonstrates the self-tuning property i.e. that the parameter estimates have subsequently converged to their correct values. This can be attributed to the absence of noise in this trial (in contrast to figure 10).

The well-known 'blow-up' of the recursive least squares routine in the absence of sufficient excitation has prompted the use of a slow sinewave superimposed on the set point to provide such continuous excitation. With the same set of closed-loop poles (i.e. those of the case of figure 11) assigned, a trial was conducted for a 60% set point with a sinewave perturbation. A Smith predictor control structure is now used to provide control over the non-linear region (as opposed to such control being provided by a PID controller). The resulting response is shown in figure 13. This shows a clear improvement in the speed of response and again good steady state behaviour.

To check the validity of the self-tuning property, a 170 minute long trial in which the drug concentration was halved at t = 106 minutes was conducted. Owing to the length of the chart recording of the input and output signals and there being a need for photographic reproduction of such a recording, only times 0 to 87 minutes and 125 to 170 minutes are shown (figs. 14 and 15) i.e. the time at which the concentration change occurred is not shown. However, the parameter estimates for this trial were logged onto a disc (for the whole trial) and plotted off-line. These are shown in figure 16. While the identified system time-constants remained almost constant (as demonstrated by the steady a-parameters in figure 16), the open-loop gain of the system as calculated from the b-parameters has changed from 3.1 at t = 106 minutes to 1.3 at the end of the trial. This reduction by almost a factor of ½ in the open-loop gain demonstrates the validity of the self-tuning property since the drug concentration is part of the overall loop gain.

## 5. Conclusions

Control, dead-time compensation, and on-line identification and control have all successfully been applied to the field of relaxation management in anaesthesia. As well as providing better control, the closed-loop control approach is giving insight into the classic pharmacokinetic compartmental modelling problem and providing a test environment capable of quantifying interacting effects from other drugs. Provided care is taken to 'jacket' the self-tuner, self-tuning control of muscle relaxation is shown to be feasible, safe and efficient. As well as being a satisfactory control strategy in its own right, the Smith predictor structure, when used to provide the above-mentioned 'jacketting' greatly improves the system's speed of response.

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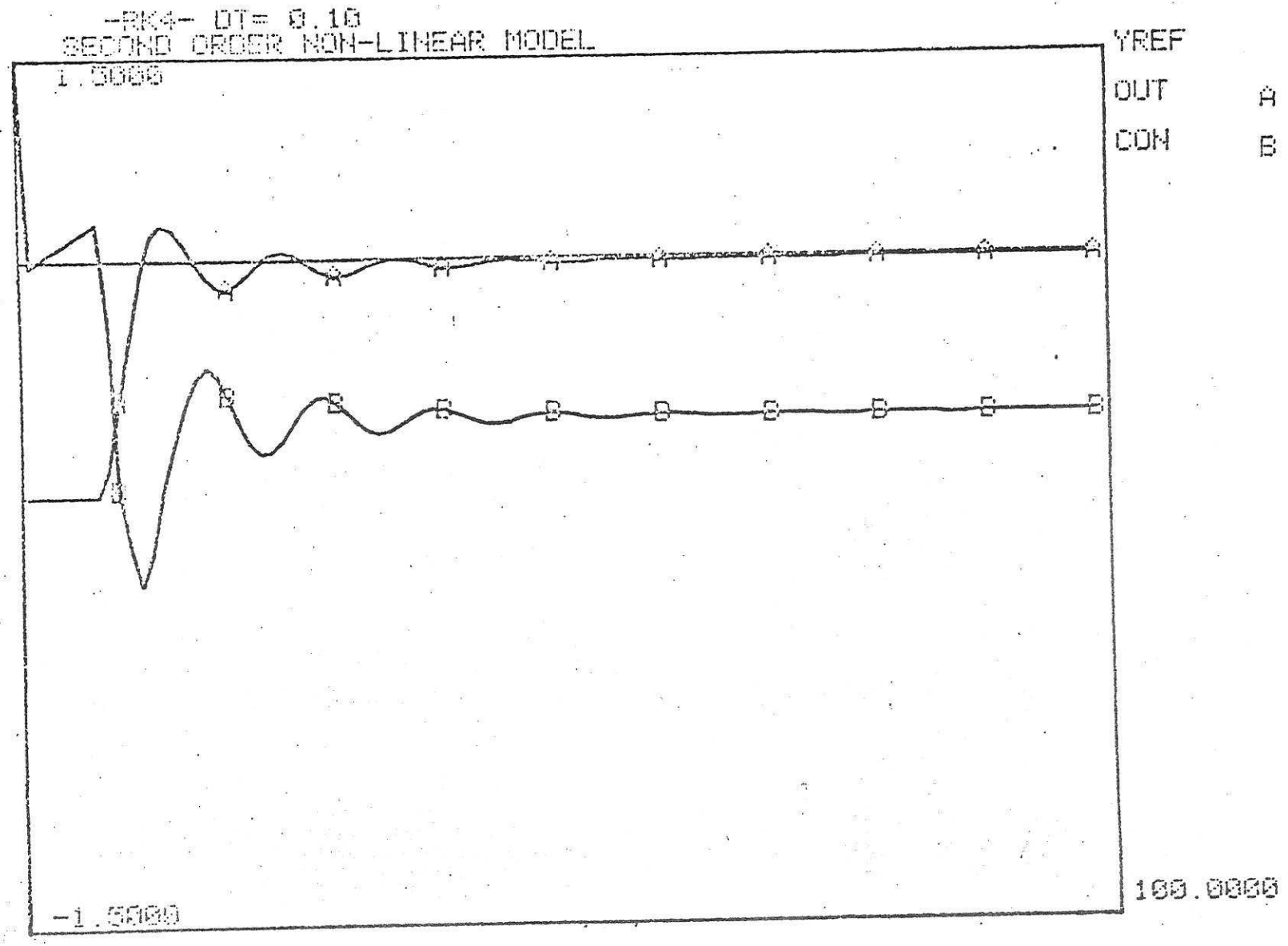
Figure Captions

| | |
|---|---|
| Figure 1 | Closed-loop response of the simulated system under optimised PID control |
| Figure 2 | System response under PID control when delay = 4 min. |
| Figure 3 | System response under Smith predictor control (matched conditions) |
| Figure 4 | System response under Smith predictor control with mismatch conditions |
| Figure 5 | Self-tuning control of non-linear model. |
| Figure 6 | Parameter estimates relating to Figure 5 |
| Figure 7 | Self-tuning control with underparameterised model |
| Figure 8 | Parameter estimates relating to Figure 7 |
| Figure 9 | Dog Trial: RIEMG and Motor Drive Signals. |
| Figure 10 | Chart recording from clinical self-tuning trial |
| Figure 11 | Self-tuning control, including drug disturbance |
| Figure 12 | Parameters relating to Figure 11 |
| Figure 13 | Self-tuning control, plus initial Smith predictor regime |
| Figure 14 | Self-tuning control with persistent excitation |
| Figure 15 | Continuation of trial in Figure 14 |
| Figure 16 | Parameters relating to trials depicted in Figures 14 and 15 |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CON B
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FIG.1

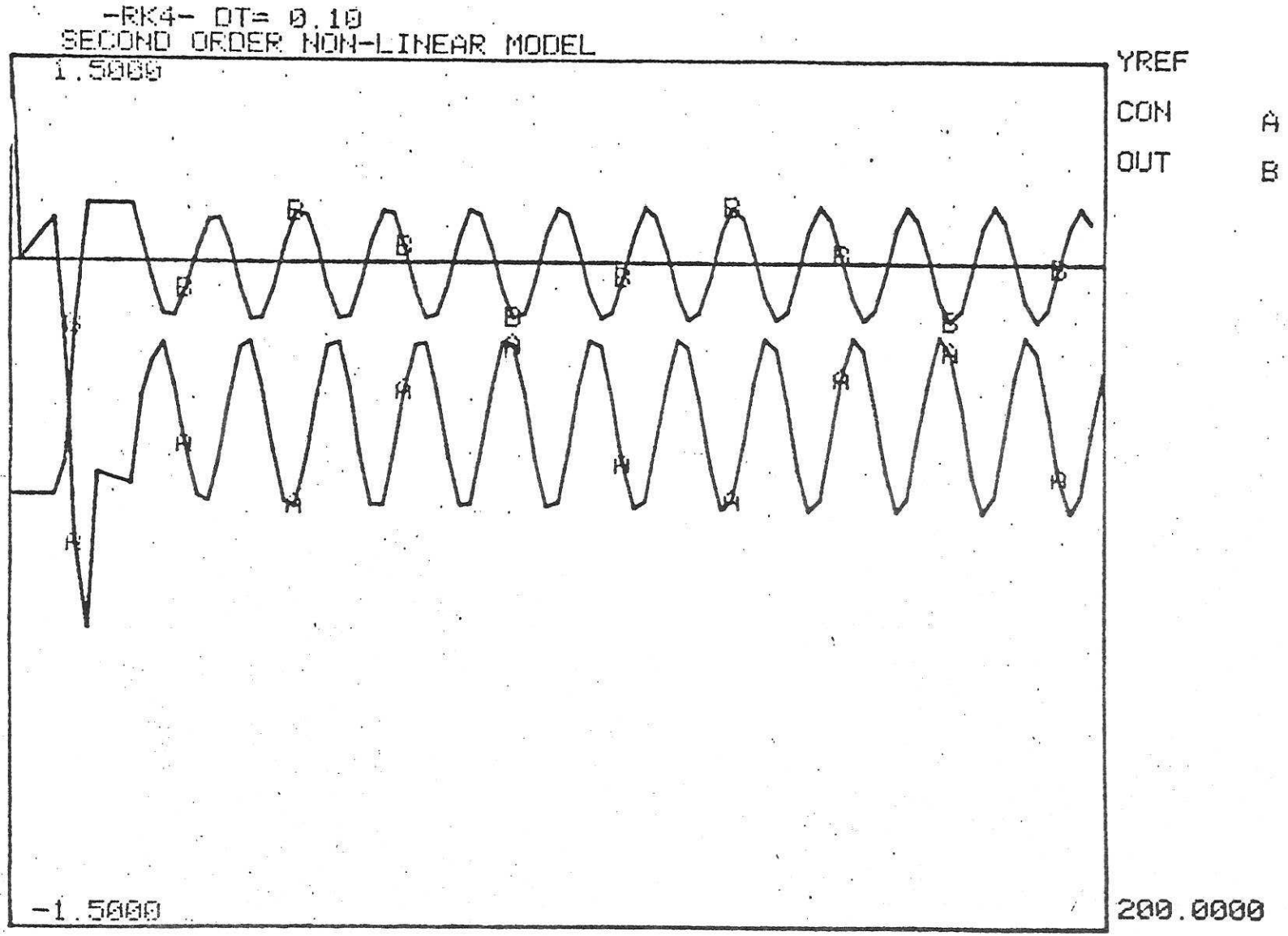
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Fig 2

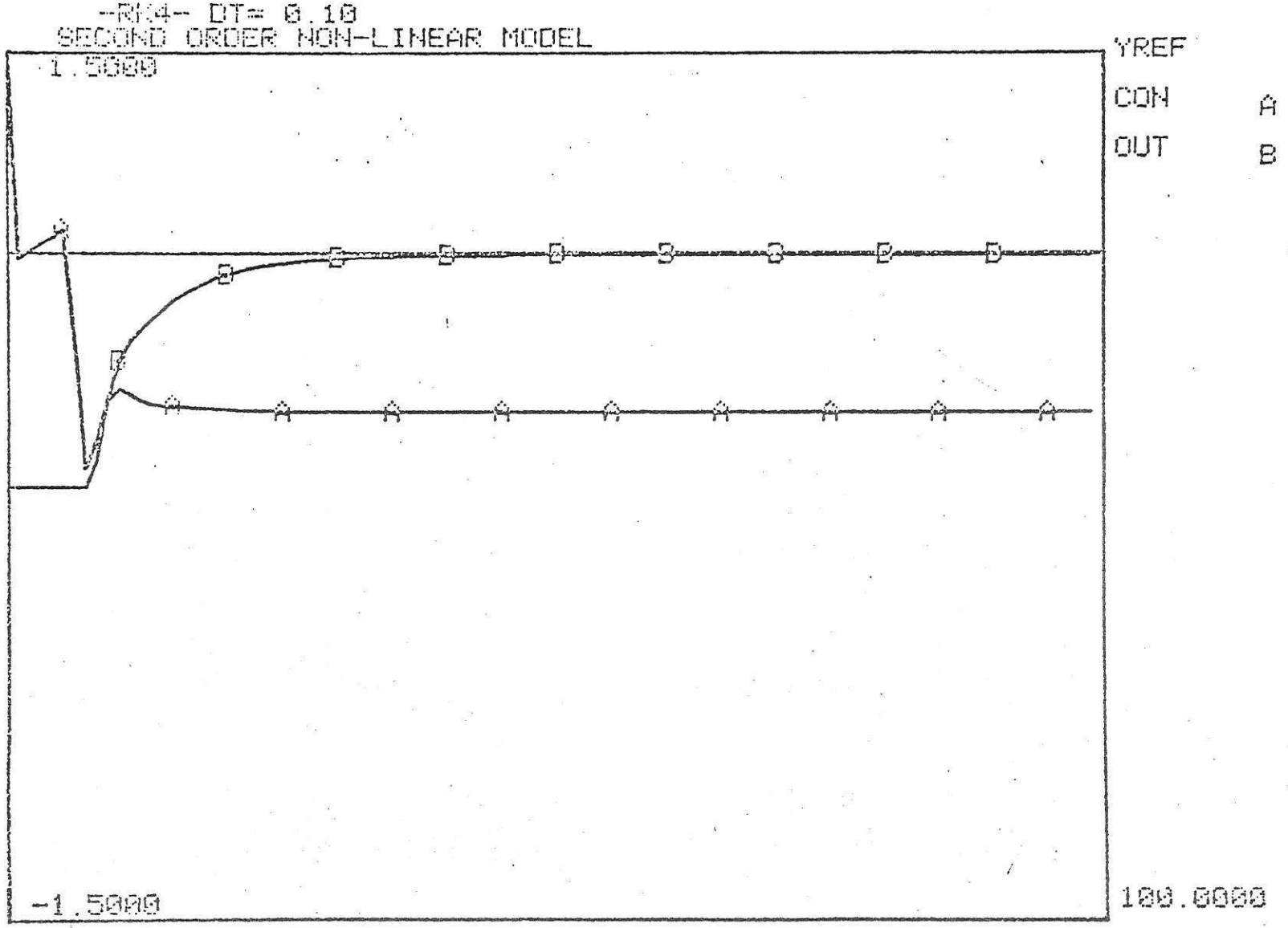
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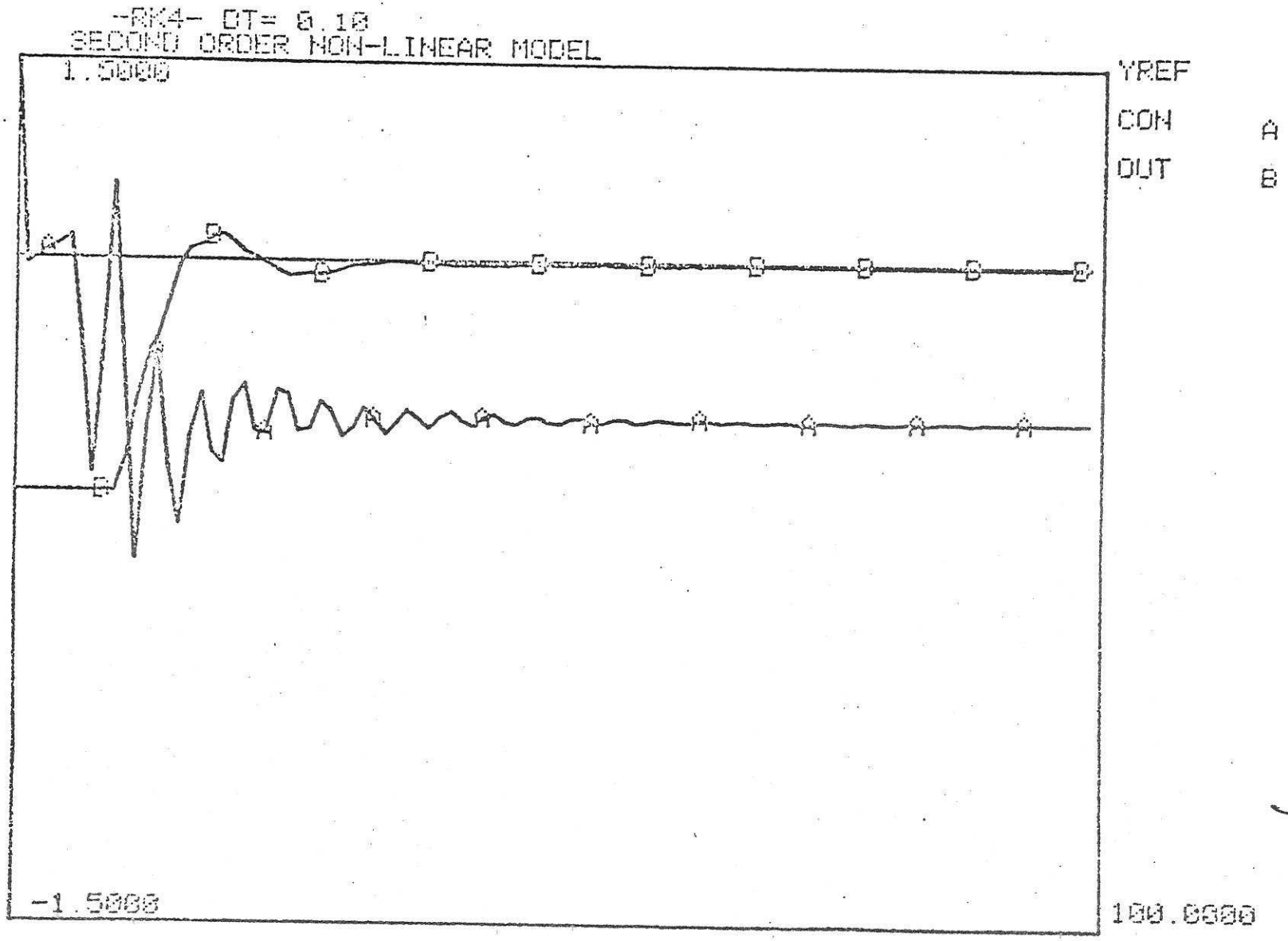
Fig 3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OUT B
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Fig 4

SELF-TUNING CONTROL OF MUSCLE RELAXATION

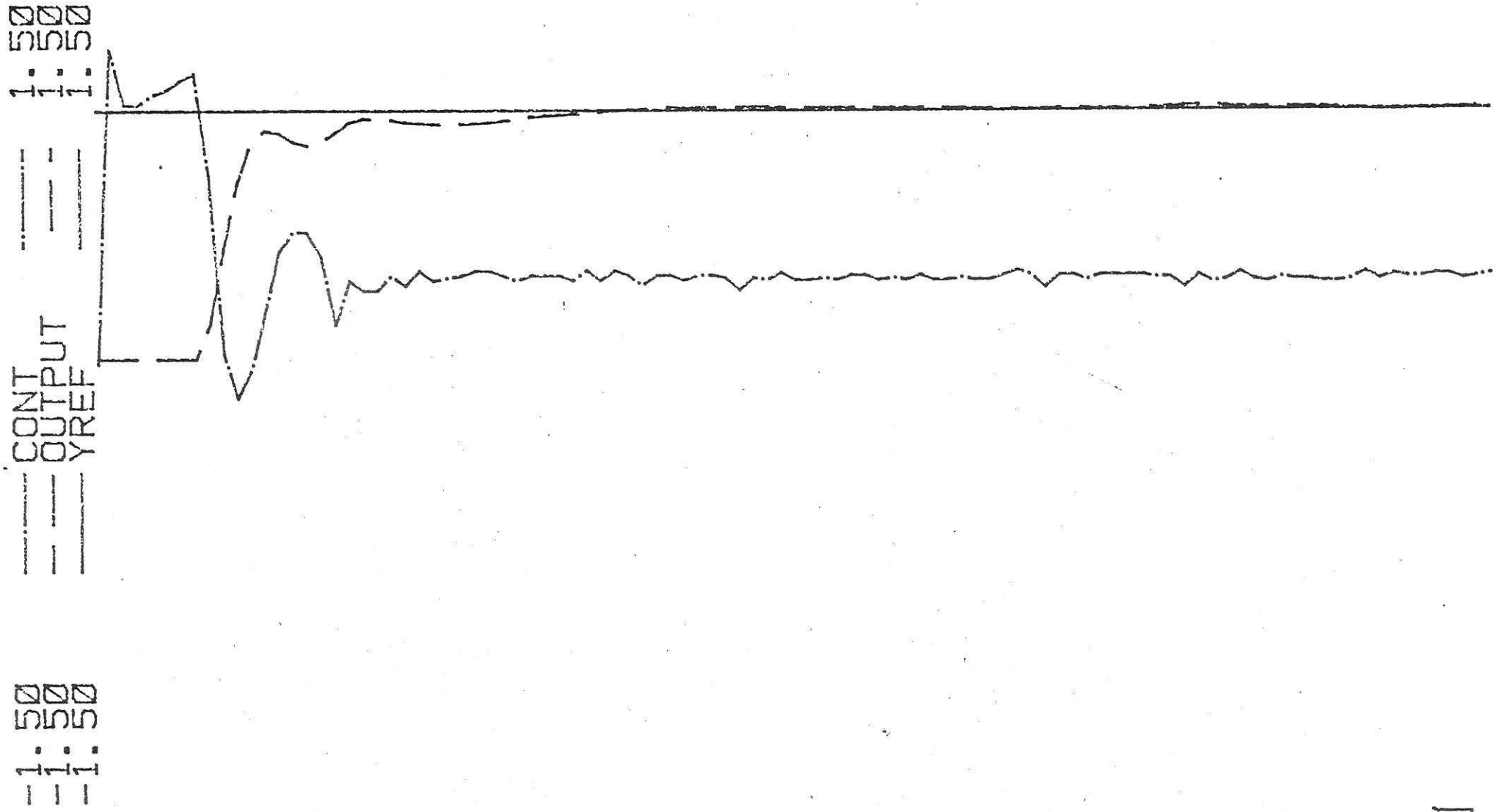



Fig 5

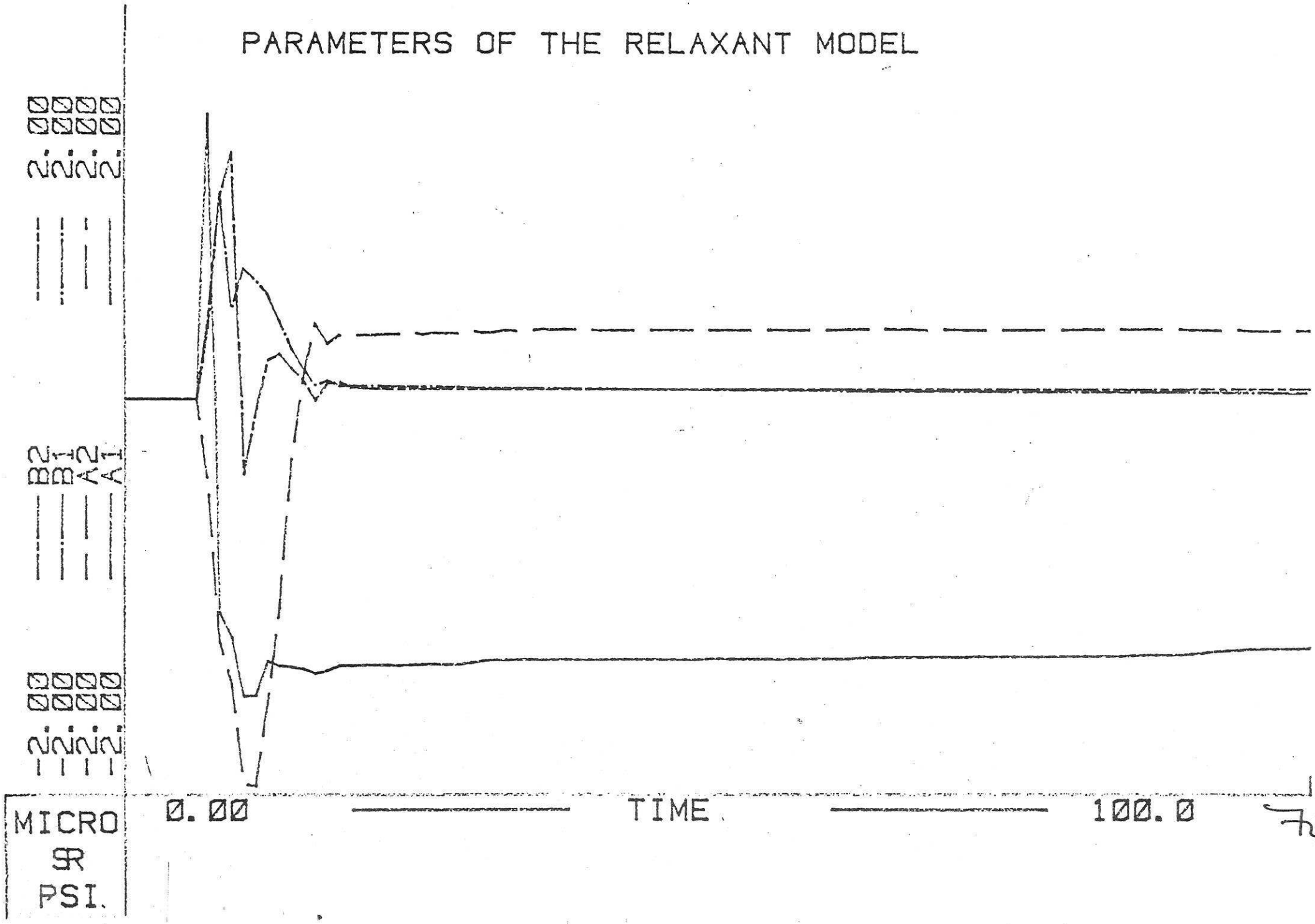



Fig 1

SELF-TUNING CONTROL OF MUSCLE RELAXATION

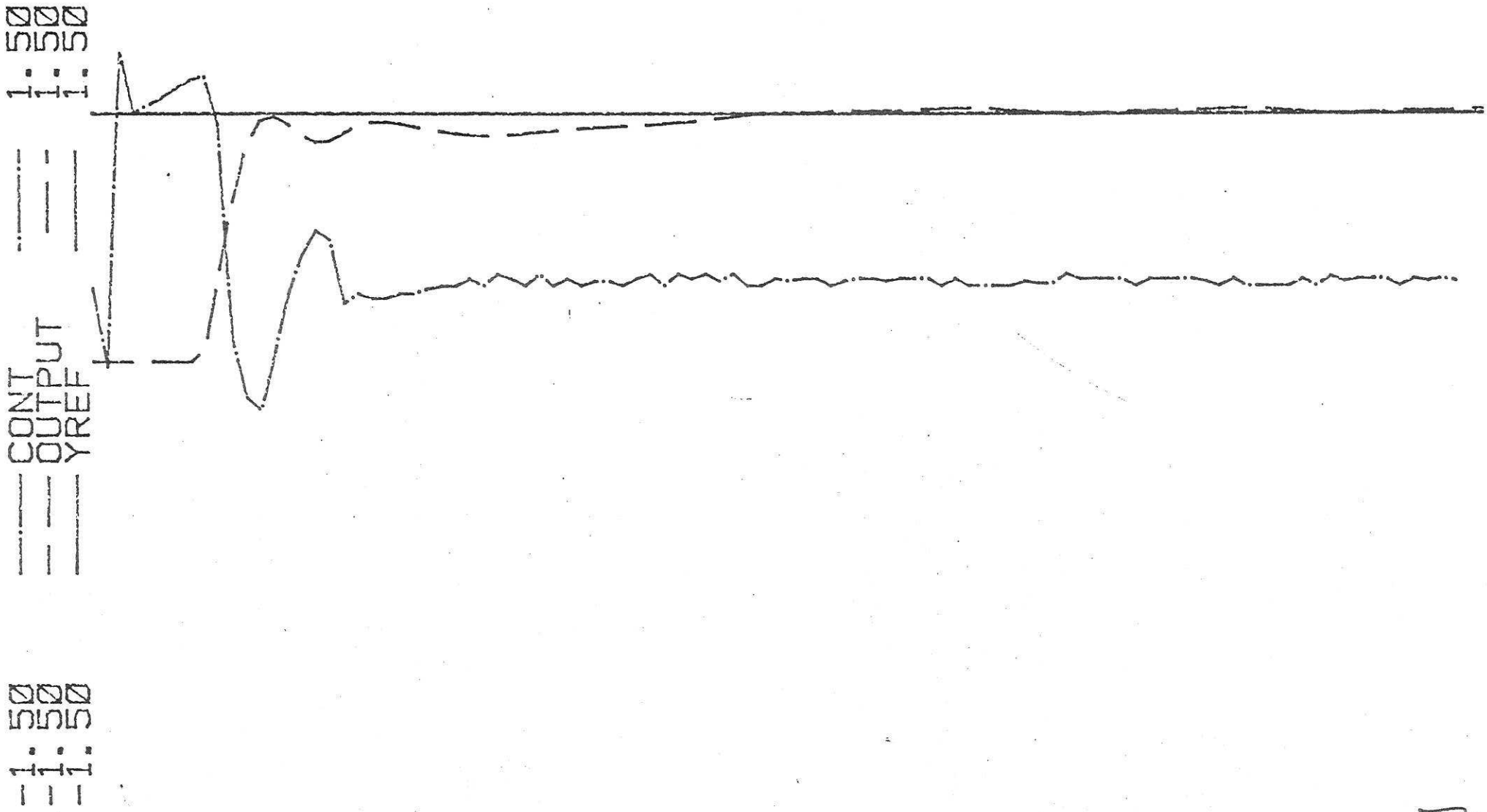
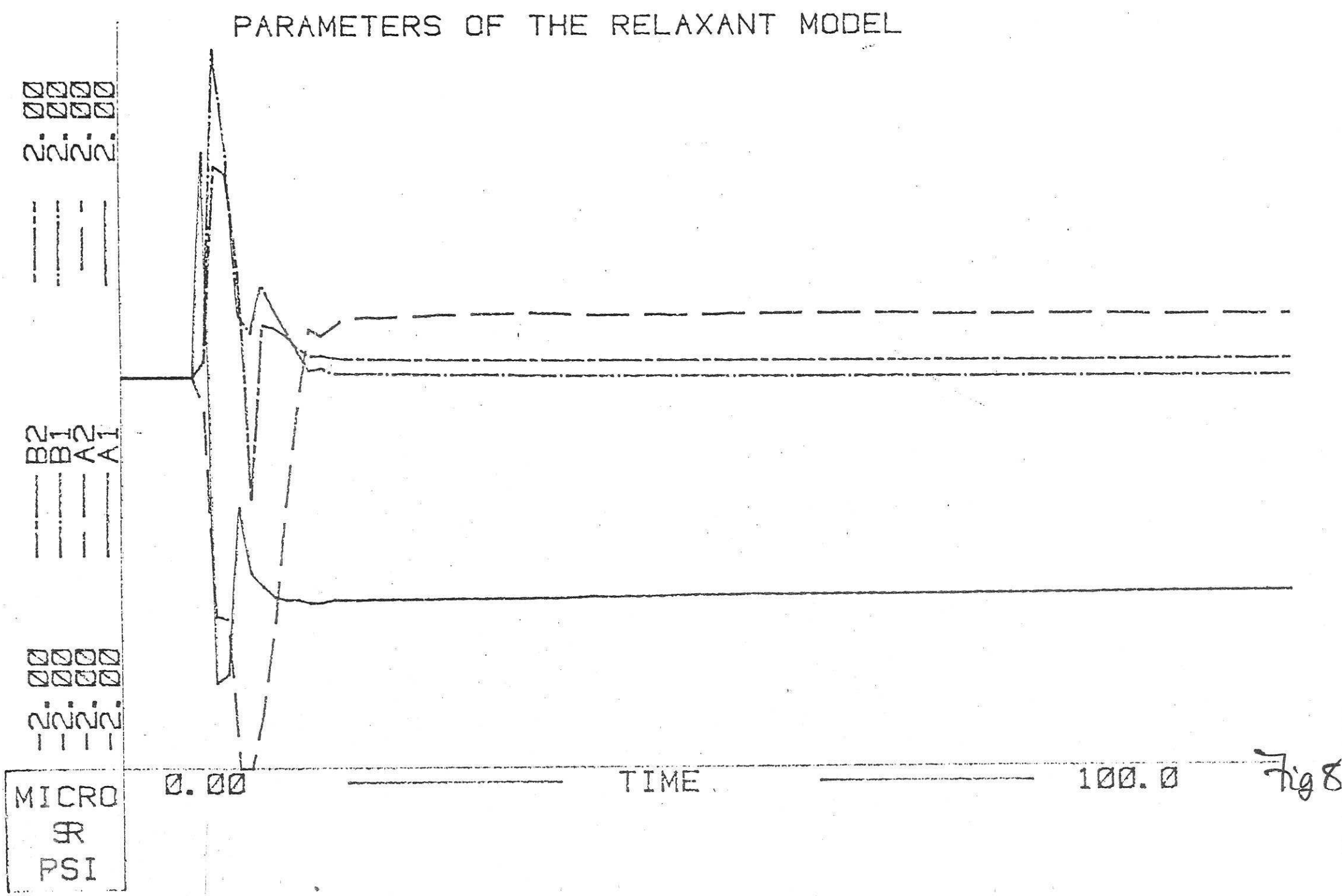



Fig 7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A2
A1
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PSI
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TIME
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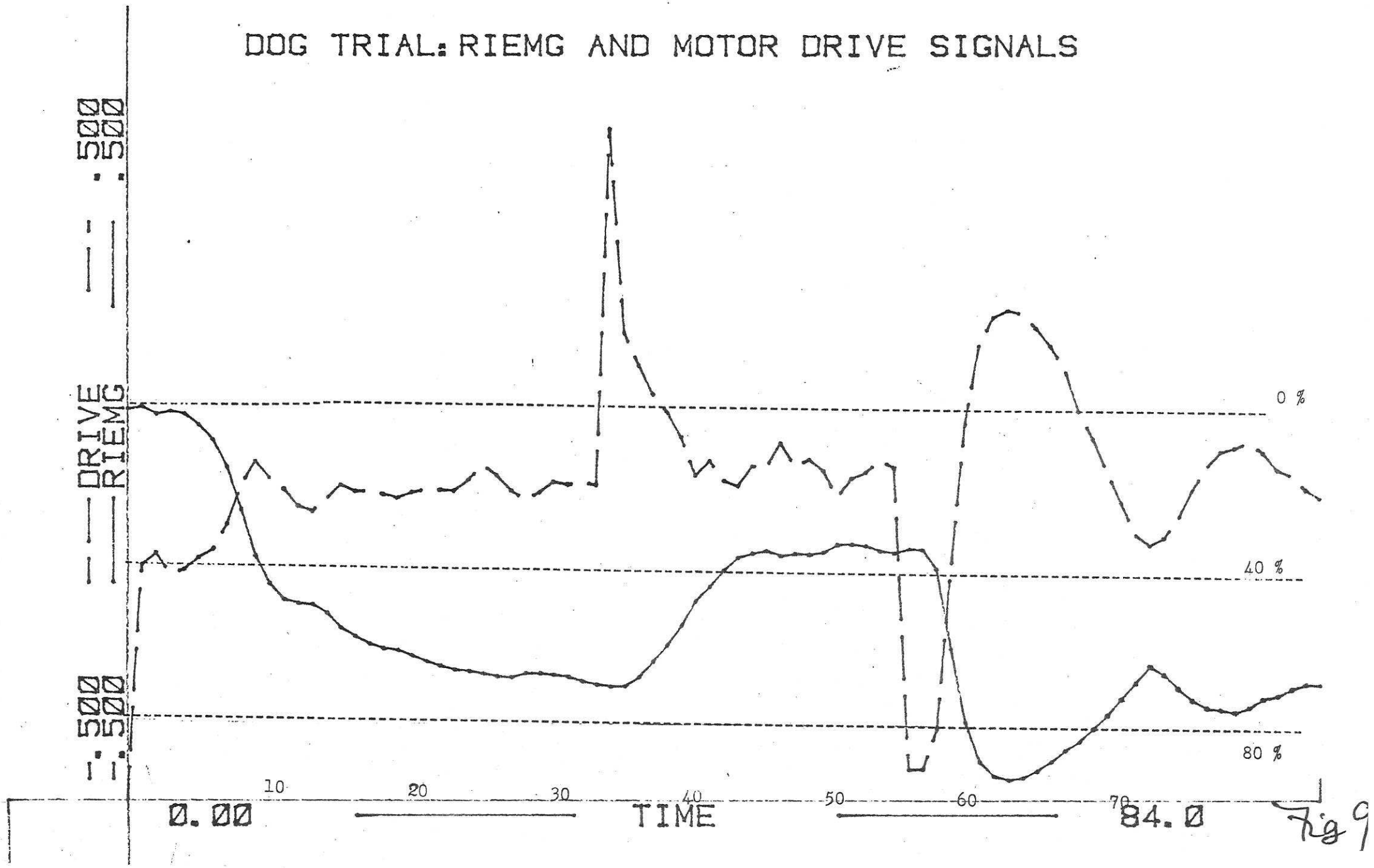
Fig 8


DOG TRIAL: RIEMG AND MOTOR DRIVE SIGNALS
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.500
DRIVE
RIEMG
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.500
0 %
40 %
80 %
10
20
30
40
50
60
70
0.00
TIME
84.0

Fig 9

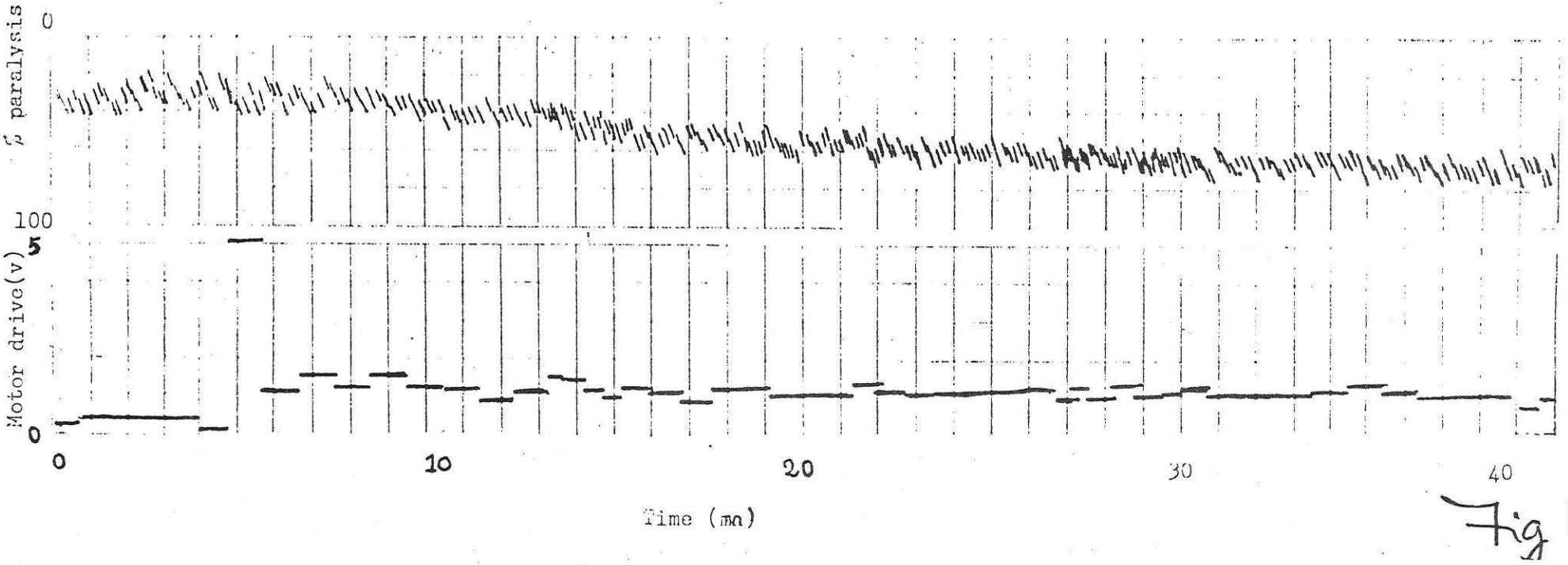
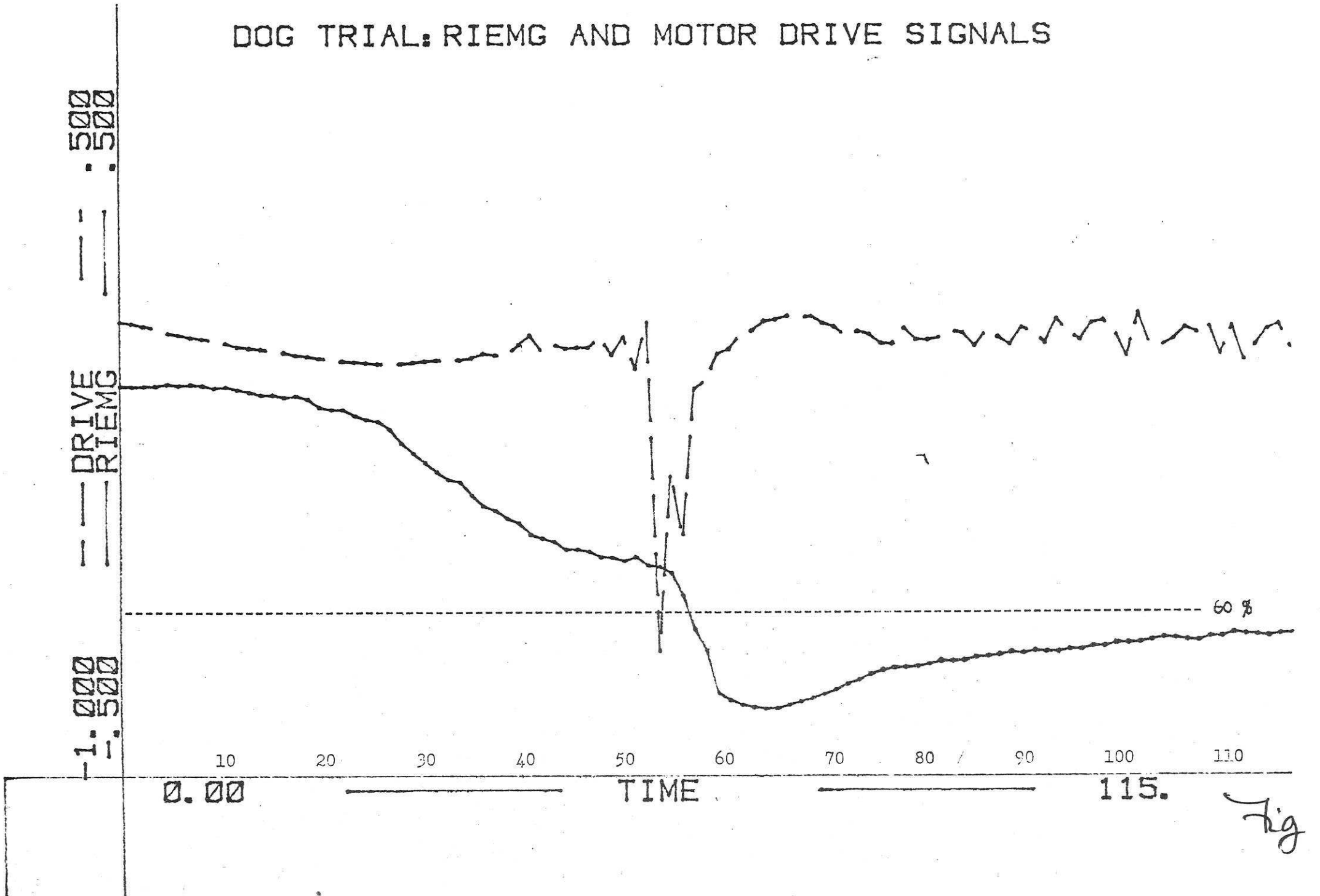



Fig 1c


DOG TRIAL: RIEMG AND MOTOR DRIVE SIGNALS
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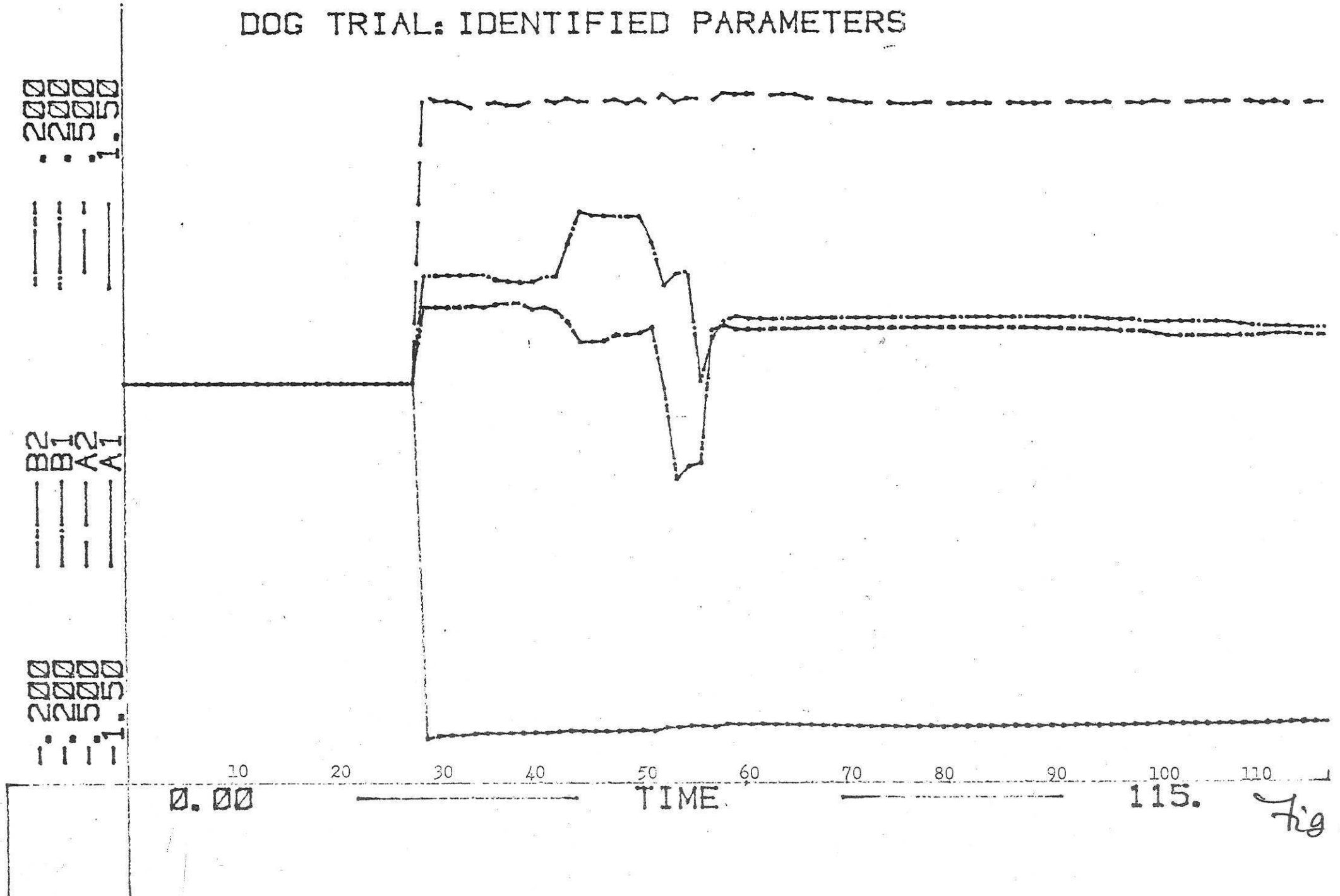
.500
DRIVE
RIEMG
-1.0000
-1.500
60 %
10
20
30
40
50
60
70
80
90
100
110
0.00
TIME
115.

Fig 11


DOG TRIAL: IDENTIFIED PARAMETERS
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B2
B1
A2
A1
1.
10
20
30
40
50
60
70
80
90
100
110
0.00
TIME
115.

Fig 12

Drive(v)
% paralysis
0
5
10
20
30
60
0

Fig 14

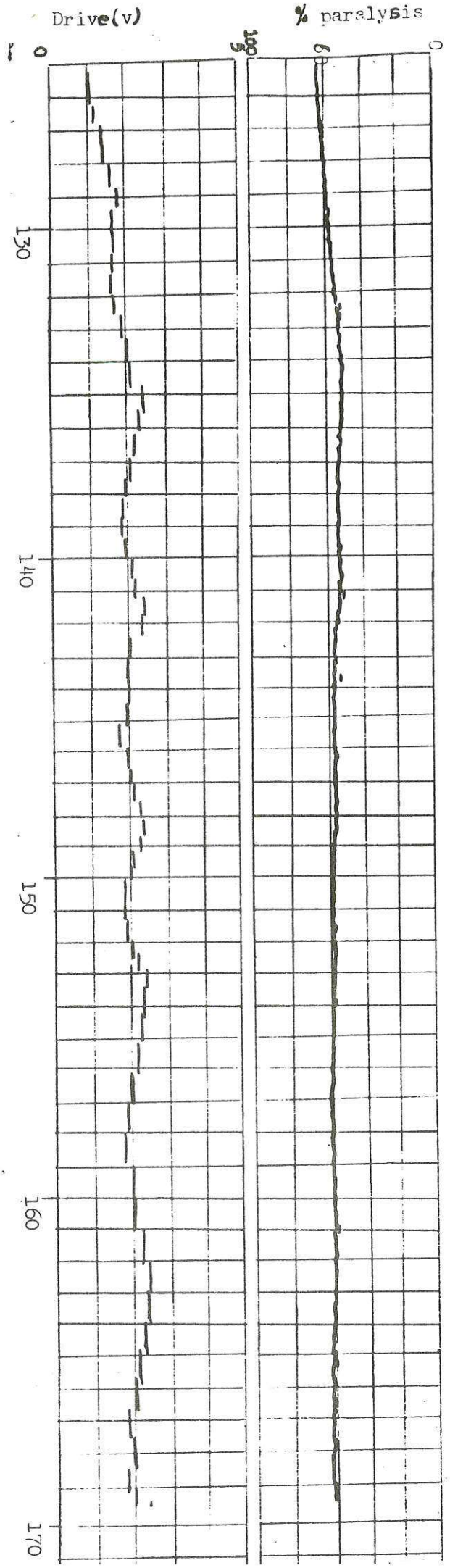
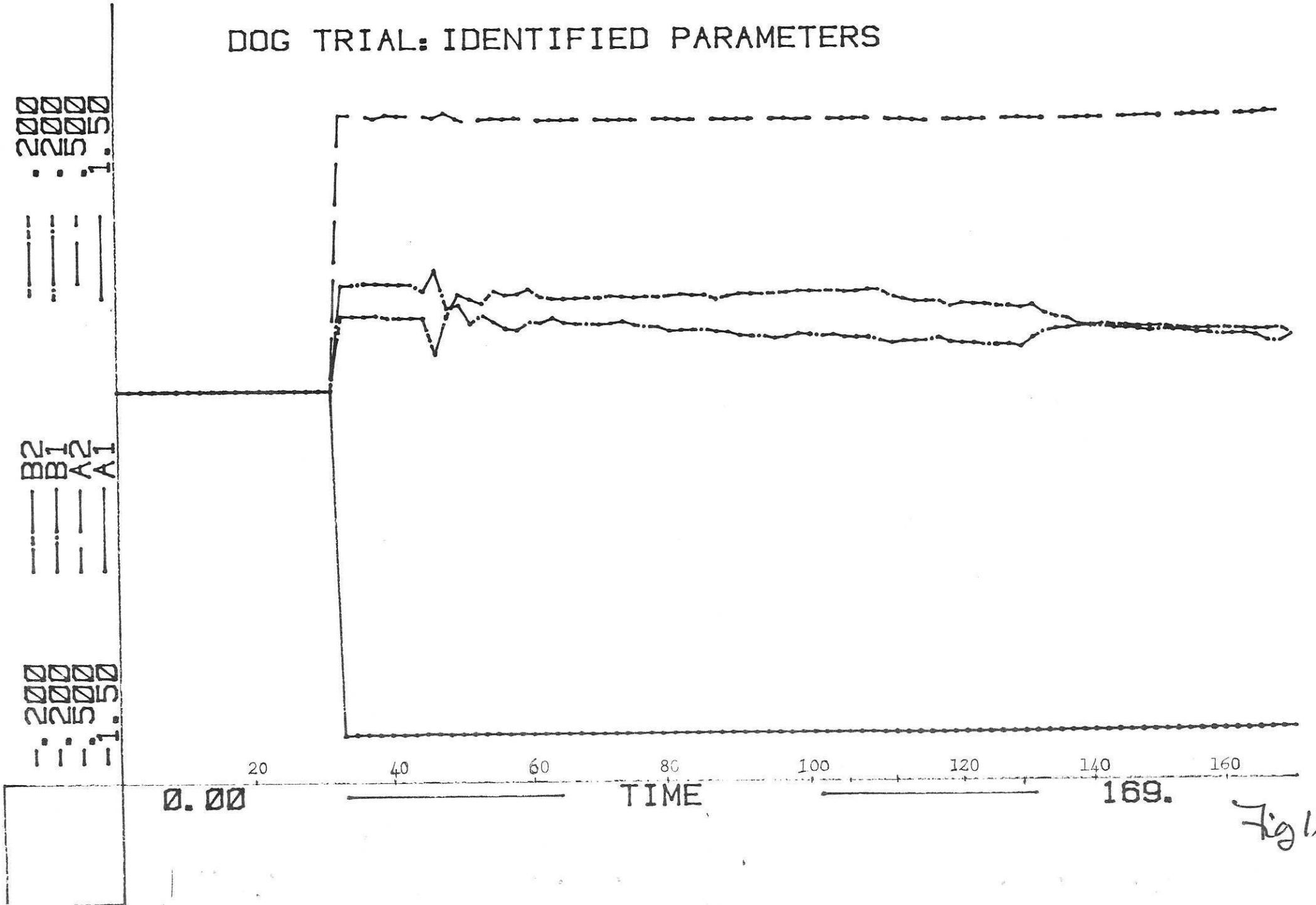



Fig 15.


DOG TRIAL: IDENTIFIED PARAMETERS
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TIME
169.

Fig 16