A model for phosphocreatine resynthesis

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Nevill, Alan M., David A. Jones, David McIntyre, Gregory C. Bogdanis, and Mary E. Nevill. A model for phosphocreatine resynthesis. J. Appl. Physiol. 82(1): 329–335, 1997.—A model for phosphocreatine (PCr) resynthesis is proposed based on a simple electric circuit, where the PCr store in muscle is likened to the stored charge on the capacitor. The solution to the second-order differential equation that describes the potential around the circuit suggests the model for PCr resynthesis is given by

\[ PCr(t) = R - D \cdot \exp(-k_1 \cdot t) + c_1 \exp(-k_2 \cdot t) \]

where \( R \) represents the subjects’ PCr concentration at rest, \( D \) indicates the concentration of PCr at time 0 (postexercise/activity), \( c_1 \) and \( c_2 \) are rate constants, \( k_1 \) and \( k_2 \) are constants, and \( t \) is time. By using nonlinear least squares regression, this double-exponential model was shown to fit the PCr recovery data taken from two studies involving maximal exercise accurately. In study 1, when the muscle was electrically stimulated while occluded, PCr concentrations rose during the recovery phase to a level above that observed at rest. In study 2, after intensive dynamic exercise, PCr recovered monotonically to resting concentrations. The second exponential term in the double-exponential model was found to make a significant additional contribution to the quality of fit in both study 1 (\( P < 0.05 \)) and study 2 (\( P < 0.01 \)).

Eq. 1

The study was able to confirm that the model parameters \( a \) and \( b \) for each subject were sufficiently different to reject the assumption of common parameters for the group PCr resynthesis curve.

Nearly 20 years earlier, Harris et al. (8) proposed a “biphasic” model with common group parameters to represent a number of subjects’ PCr resynthesis as follows

\[ PCr(t) = R - D \cdot [c_1 \exp(-k_1 \cdot t) + c_2 \exp(-k_2 \cdot t)] \]

where \( k_1 \) and \( k_2 \) are rate constants of the two exponential terms (the parameters \( c_1 \) and \( c_2 \) are dimensionless, \( c_1 + c_2 = 1 \)). Although the details of the curve-fitting methods were not described, the authors divided the data into an early- and a late-recovery phase, and separate exponential curves were fitted to each phase. The authors reported a half time for the fast recovery component as 21–22 s, compared with 170 s for the slow component.

Because the recovery is occurring in a rapidly changing environment, the assumption that the rate of PCr resynthesis is described by a monoeponential model (Eq. 1) may be questioned, especially in the light of the observations of Söderlund and Hultman (14), who noted that, during recovery, PCr concentration in type II fibers was higher than in resting muscle before exercise. Similar findings were obtained in cat soleus muscle by Kushnerick et al. (10) as well as in the present study 1 described below.

Because it is impossible for the monoeponential curve to overshoot or undershoot the level observed at rest, in this paper, we shall consider an alternative double-exponential model for PCr resynthesis, originally proposed by Harris et al. (8), based on a simple analog electric circuit modified from that described by Meyer (13). This model explains the early rapid and subse-
quent slower PCr resynthesis observed by Harris et al. (8), McCann et al. (12), and Bogdanis et al. (3) and is able to successfully describe the overshoot in PCr resynthesis observed by Söderlund and Hultman (14), Kushmerick et al. (10), and in the present study 1. The model cannot be fitted directly by using usual linear-regression methods. However, standard statistical packages such as SPSS (16) or BMDP (1) have nonlinear least squares regression routines that can estimate the unknown parameters in such a model. This study illustrates the flexibility of the proposed model and of the SPSS nonlinear least squares curve-fitting software by analyzing examples taken from two contrasting studies: study 1, previously unpublished data, and study 2, that of Bogdanis et al. (3).

**METHODS**

The examples described and analyzed here are taken from two studies; the first, using 31P-magnetic resonance (MR) spectroscopy to investigate PCr resynthesis after maximal electrical stimulation of the anterior tibialis, and the second, using needle biopsy tissue from the vastus lateralis to examine PCr resynthesis (by using enzymatic assays of extracts from freeze-dried muscle) after intensive dynamic exercise. Study 1, with the use of 31P-MR spectroscopy after electrical stimulation of the anteritibialis, and the second, study 2, that of Bogdanis et al. (3). The examples described and analyzed here are taken from two contrast-studies: study 1, previously unpublished data, and study 2, that of Bogdanis et al. (3).

The analytical methods were similar to those described in Bogdanis et al. (3). Briefly, the exercise consisted of a 30-s maximal-cycle ergometer sprint with needle biopsy samples obtained from the vastus lateralis muscle before the 30-s sprint, immediately after, and again after 90 s, 3 min, and 6 min. The time delay between cessation of the sprint exercise and freezing of the sample in liquid nitrogen was 7, 7, and 5 s for subjects 1, 2, and 3, respectively. The concentrations of PCr in study 2 were recorded in millimoles per kilogram dry weight.

The model for PCr resynthesis. A simple modification of the first-order linear system described by Meyer (13) has been used to model the resynthesis of PCr (APPENDIX 1). The inclusion of an inductance into the circuit results in a second-order differential equation, the solution of which is given as follows

\[ \text{PCr}(t) = R - [d_1 \cdot \exp(-k_1 \cdot t) + d_2 \cdot \exp(-k_2 \cdot t)] \tag{4} \]

where \( R \) is the steady-state equilibrium level of PCr at rest and \( R - D \) (where \( D = d_1 + d_2 \)) is the depleted level of PCr at time 0, i.e., the same as the model originally proposed by Harris et al. (8).

Statistical methods. The SPSS nonlinear regression software was used to fit the proposed model (Eq. 4) to the PCr resynthesis data from studies 1 and 2. The curve-fitting process is iterative, and, hence, initial starting values were required. To overcome the limited number of observations per subject, especially in study 2, the three subjects' PCr data in each study were stacked and analyzed together. This enabled the examination of common parameters for some or all subjects and to increase the power of the test when comparing the quality of fit of the monoexponential (Eq. 1) and double-exponential models (Eq. 4). For the purpose of the nonlinear regression analyses, all the PCr data were expressed as a percentage of PCr at rest to provide a common resting value (100%) for all subjects. The structure of the SPSS data file required to analyze the PCr data from study 2 is given in APPENDIX 2, i.e., requiring the use of subject-indicator variables.

Half times were obtained for each subject by calculating the fitted double-exponential curves (Eq. 4) for the range of times, \( t = 0, 1, 2, 600, s \), and then simply reading off, to the nearest second, the time \( (t_h) \) when \( \text{PCr}(%) = 100 - D(%) \) from the list of calculated PCr values.

**RESULTS**

Study 1. The SPSS nonlinear least squares regression software was used to fit the monoexponential (Eq. 1) and the double-exponential (Eq. 4) models to the three subjects' PCr concentrations, allowing separate parameters for each subject (known as the saturated solutions). The mono- and double-exponential models explained 89.0 and 94.2% of the variance in the PCr recovery data, respectively, with 6 and 12 degrees of freedom (df). However, when a double-exponential model (Eq. 4) was fitted, allowing the parameters, \( d_1 \) and \( k_2 \), to be common for all three subjects, the model still explained 93.7% of the variance (with 8 df) in the PCr recovery data. The explained variance for the saturated monoexponential, and the additional two parameters for the double-exponential model, are partitioned and given in Table 1. The two additional parameters were found to make a significant contribution to the quality of fit (\( P < 0.05 \)). The three subjects' fitted parameters for the double-exponential model are given in Table 2, and the resulting PCr resynthesis curves are plotted in Fig. 1, A–C. Note the similarity between these curves and the solution to the hypothetical example, case 1, described in APPENDIX 1. In this case, the initial speed, \( dq/dt \), where \( q \) is the stored charge on the capacitor, was relatively fast resulting in an overshoot in \( q \) before returning to the equilibrium point.

Although the overshoot observed in the three examples in study 1 (see Fig. 1, A–C) was relatively small,
by examining the three subjects’ PCr concentrations after 200 s collectively, 12 of the 15 PCr concentrations were above those observed at rest (100%), with a mean percentage of 104.91% [SD (s) ± 9.09]. This indicates a significant overshoot when using either a parametric t-test (t = 2.09, P < 0.05) or a nonparametric sign test.

From Table 1, the residual error from fitting the double-exponential model (Eq. 4) to the subjects’ PCr data in study 1 was s = \sqrt{79.87} = 8.9% (percentage of PCr at rest). When transformed into the original units of PCr concentrations in study 1, this result represents a mean residual error of 2.41 mmol/l intracellular water.

Study 2. As in study 1, the SPSS nonlinear least squares regression software was used to fit the monoexponential model (Eq. 1) to the three subjects’ PCr concentrations from study 2, allowing separate parameters for each subject. The saturated monoexponential model explained 98.9% of the variance in the PCr recovery data, with 6 df. As there were only four PCr observations per subject and just three subjects, the saturated double-exponential model would require 12 df and thus could not be fitted. However, when a double-exponential model (Eq. 4) was fitted, allowing the parameters d1 and k1 to be common for all three subjects, the model still explained 99.9% of the variance in the PCr recovery data (using 8 df). The SPSS syntax and SPSS data file to fit the double-exponential model are given in Appendix 2 (note that to fit the saturated monoexponential model, the exponential term \([-d_1\times\text{exp}(k_1\times\text{time})]\) should be removed from the line, \text{COMPUTE PRED} = .

The explained variance for the saturated monoexponential model and the additional two parameters for the double-exponential models are partitioned and given in Table 3. As in study 1, the two additional parameters were found to make a significant contribution to the quality of fit (P < 0.01). The three subjects’ fitted parameters for the double-exponential model are given in Table 4 and plotted in Fig. 2, A–C. Note that these curves are similar to the solution of the hypothetical example, case 2, described in Appendix 1, where the initial speed or rate of PCr resynthesis, \(d_1/dt\), was relatively slow.

From Table 3, the residual error for the subjects in study 2 was \(s = \sqrt{1.92 \times 1.38} = 1.38\%\) (percentage of PCr at rest). When transformed into the original units of PCr concentrations in study 2, this represents a mean residual error of \(s = 1.03\) mmol/kg dry wt.

DISCUSSION

Meyer (13) proposed a simple electrical analog model to describe changes in PCr based on a first-order linear system. The resulting solution was a monoexponential model in time. However, in some situations, the kinetics may be more complex, resulting in the initially more rapid PCr resynthesis observed by some authors after heavy or maximal exercise (Refs. 3, 8, 12). In the present study, by introducing an inductance into the first-order linear system originally proposed by Meyer, an alternative double-exponential model for PCr resynthesis is obtained that is more flexible and fits the PCr data better when an early, more rapid, deceleration of PCr resynthesis occurs (e.g., Refs. 3, 8, 12).

The physiological interpretation of the added inductance is speculative. A number of factors will determine the rate of PCr resynthesis during recovery. These include the supply of oxygen to tissue and the removal of metabolites such as lactate and H\(^+\) (see Ref. 15). All of these factors will be affected by the blood supply to tissue. In the two studies described in the present article, the patterns of blood supply during recovery are different. In the first exercise paradigm (study 1), where the muscle was exercised under ischemic conditions, the blood flow would have increased rapidly after the release of the pneumatic cuff and then subsequently decreased back to a resting flow. In the second exercise paradigm (study 2), blood flow is likely to have been maximal at the end of dynamic exercise and would then decrease as the metabolites returned to resting values. In both studies, it is possible that the differential effect of oxygen supply and, in particular, the removal of H\(^+\) could vary or change the rate of PCr resynthesis during recovery. It is this varying or changing rate of PCr resynthesis that the introduction of inductance in the electric circuit accommodates in the model for PCr resynthesis.

Table 2. PCr at rest, the fitted parameters (asymptotic SD values) for the double-exponential model (Eq. 4), half times, and the SD about the fitted PCr resynthesis curve (% of PCr at rest) for each subject in study 1

| Subject | R | D, % | d1, % | d2, % | k1 | k2 | Half Time, s | s
|---------|---|-----|-------|-------|----|----|------------|---|
| 1 (DN)  | 29.38 | 81.0 (399) | 162.7 (194) | 0.0092 (0.006) | 81.7 (196) | 0.0042 (0.003) | 44 | 2.62
| 2 (D)   | 25.45 | 55.3 (393) | 137.0 (197) | 0.0063 (0.001) | 81.7 (196) | 0.0042 (0.003) | 69 | 2.27
| 3 (DT)  | 26.33 | 77.4 (393) | 159.1 (197) | 0.0068 (0.002) | 81.7 (196) | 0.0042 (0.003) | 68 | 2.35

R, rest; D, decrease in PCr; d1, d2 and k1 and k2, parameters; D, d1 + d2; s, SD about the fitted PCr resynthesis curve.
The solution to the resulting second-order differential equation is shown to be a constant, minus either the sum of or the difference between two negative exponential terms in time (Eq. 4). Although this model is similar to the biphasic model proposed by Harris et al. (8), the methods proposed in the present study have the added advantage that they describe an objective nonlinear curve-fitting technique that allows different models to be fitted to each subject’s resynthesis data separately, rather than fitting a common group resynthesis model to all subjects, as described by Harris et al. (8). The modeling of each subject’s PCr resynthesis data separately has been shown by Bogdanis et al. (3) to be necessary, and, indeed, it is generally accepted that any kinetic data should be modeled in this fashion.

As may be seen from Tables 1 and 2, when the double-exponential model (Eq. 4) was fitted to the PCr resynthesis data from studies 1 and 2, the resulting solutions explained 93.7 and 99.9% of the variance, respectively. The s values about the fitted models are relatively small, although the estimated error for study 1, found to be 2.41 mmol/l intracellular water, is considerably greater than for study 2, given by 1.03 mmol/kg dry wt. To obtain the same units as in study 1, the values in study 2 are multiplied by 0.364 (see Ref. 4) to give s = 1.03(0.364) = 0.375 liter intracellular water⁻¹. This probably reflects the measurement error of PCr when the 31P-MR spectrography methods are used, compared with PCr measurements using the needle-biopsy technique.

Not only did the double-exponential model (Eq. 4) explain 93.7 and 99.9% of the variance in PCr resynthesis data from studies 1 and 2, respectively, the quality of the fit was also empirically superior to the monoexponential model (Eq. 1). By fitting a double-exponential model (Eq. 4), allowing one of the exponential terms to have two common parameters for all three subject, the additional parameters were found to make a significant contribution to the quality of fit in both study 1 (P < 0.05) and study 2 (P < 0.01).

When comparing with preexercise values, Söderlund and Hultman (14) observed a higher concentration of PCr after exercise in type I and II fibers (in type II fibers P < 0.05). Kushnerick et al. (10) also observed an overshoot in PCr resynthesis in the slow soleus muscle in cats. A similar pattern of PCr resynthesis was observed in study 1, with the PCr concentration rising ~5% above that recorded at rest during the recovery phase of exercise.

Table 3. Analysis of variance describing the explained variance of the saturated monoexponential and the two additional parameters for the double-exponential model from study 2

<table>
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<tr>
<th>Source</th>
<th>df</th>
<th>SS</th>
<th>MS</th>
<th>F</th>
<th>P</th>
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<td></td>
<td>57,747.21</td>
<td>9,624.54</td>
<td>5,012.78</td>
<td>&lt;0.01</td>
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<tr>
<td>Double exponential</td>
<td></td>
<td>96.33</td>
<td>48.17</td>
<td>25.09</td>
<td>&lt;0.01</td>
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<tr>
<td>(common d₁ and k₁)</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Residual</td>
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<td>7.68</td>
<td>1.92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncorrected total</td>
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<td>57,851.23</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Corrected total</td>
<td>11</td>
<td>9,057.73</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

R² = 1 – residual SS/corrected SS = 0.99915.
phase in the three subjects. The transient overshoot phase in PCr resynthesis was found to be significant (P < 0.05) and was successfully modeled using the difference between two negative exponential terms. In contrast, the PCr resynthesis observed in the three examples analyzed in study 2 was successfully modeled with the sum of two negative exponential terms that must remain below the level of PCr recorded at rest throughout the recovery time.

It is well known that the solution to the differential equation (Eq. 4) will return to its equilibrium point from above, having previously passed through the equilibrium point, provided the initial velocity, dq/dt, is sufficiently large. In the electrical circuit, described in Fig. 3 of the APPENDIX 1, this can be caused simply by an initial surge in electric current. The physiological explanation for such an overshoot in PCr resynthesis, observed in study 1 and in the study of Söderlund and Hultman (14), is not clear. However, it is notable that in these two studies, in contrast to those of Harris et al. (Ref. 8; in their study 1) and Bogdanis et al. (3), the exercising muscle was occluded, and recovery was initiated by a sudden return of blood to the leg. It remains to be seen whether the more rapid initial rate of resynthesis was a direct consequence of the initial surge in blood flow or possibly was due to some potentiation of mitochondrial activity as a consequence of prolonged ischemia.

APPENDIX 1
A Model for PCr Resynthesis

Figure 3 shows a simple electrical circuit developed from that described by Meyer (13), containing a capacitance (C), a resistance (R), an inductance (L), and an electromotive force (emf; E). At time 0, the capacitor has been discharged to a low level q0 (equivalent to the depletion of PCr after heavy or maximal exercise), and the switch A is then closed to introduce a constant emf E into the circuit that allows the capacitor to be recharged.

All the components in this circuit were clearly described and interpreted physiologically by Meyer, with the exception of L. Briefly, Meyer defines the components as follows; the energy source (E), represents the free energy potential available in the mitochondria; the capacitance C is due to the creatine kinase reaction, i.e., PCr is analogous to stored charge on a capacitor (9); the resistor R is a function of the number and properties of the mitochondria in the cell; and the current (i) is the rate of oxidative phosphorylation. Meyer was able to show that, by equating step changes in current around the above circuit, excluding the L, the change in PCr concentration followed a monoexponential curve. The introduction of L into the system allows an additional reduction (deceleration) in oxidative phosphorylation that may be associated with certain physiological or metabolic changes after heavy or maximal exercise (e.g., the deceleration in blood flow and/or possibly other changes in enzyme activity as a result of H+ accumulation).

The potential described in Fig. 3 can be equated to give the second-order differential equation (Eq. 5), assuming that at any subsequent time the fall in potential at every point in the system remains constant (E) (e.g., see Refs. 2, 6)

\[ L \cdot \frac{d^2q}{dt^2} + R \cdot \frac{dq}{dt} + 1/C \cdot q = E \]  

It can be shown that the solution to this differential equation (Eq. 5) is the sum of two negative exponential terms (the complementary function) provided \( R^2 > 4L/C \), plus a constant term (the particular integral) found to be \( E/C \), i.e.

\[ q = E/C + A \cdot \exp \left( -k_1 \cdot t \right) + B \cdot \exp \left( -k_2 \cdot t \right) \]  

where \( k_1 \) and \( k_2 \) are given by \( R/2L \pm \sqrt{(R^2/4L^2 - 1/LC)} \), and A and B are arbitrary constants depending on the initial or starting conditions at time 0.

If in the model for PCr resynthesis we assume that each subject’s resting level of PCr (R) is the steady-state equilibrium level \( q = E/C \), the unknown parameters in Eq. 6 can be redefined as follows

\[ PCr(t) = R - \left[ d_1 \cdot \exp \left( -k_1 \cdot t \right) + d_2 \cdot \exp \left( -k_2 \cdot t \right) \right] \]  

This is Eq. 4 in the main text, where R is PCr at rest and R - D (where D = \( d_1 + d_2 \)) indicates the concentration of PCr at time 0. Under certain conditions, when the initial velocity (rate of change in PCr) is relatively large (equivalent to an initial surge of electric current in the circuit; Fig. 3), the solution, given by Eq. 6, will return to PCr at rest, having previously risen above the resting level R = E/C. Under such circumstances, the parameters \( d_1 \) and \( d_2 \) will have opposite signs.

Hypothetical Example

Consider a hypothetical example that leads to the following differential equation, a particular case of the differential equation (Eq. 5) (arbitrary units)

\[ \frac{d^2q}{dt^2} + 0.024 \cdot \frac{dq}{dt} + 0.0008 \cdot q = 0.08 \]  

It is easy to show that the general solution to Eq. 7 is given by

\[ q = 100 + A \cdot \exp \left( -0.02 \cdot t \right) + B \cdot \exp \left( -0.004 \cdot t \right) \]  

where A and B are constants depending on starting conditions. Without loss of generality, we shall assume that the charge on the capacitor (or the level of stored PCr) is depleted, i.e., \( q = 0 \) at time 0, and the rate of change dq/dt (or rate of PCr resynthesis) at this time 0 is initially either 1) relatively fast \((dq/dt = 2.96) \) or 2) relatively slow \((dq/dt = 0.88)\).

<table>
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<th>Subject</th>
<th>R</th>
<th>D, %</th>
<th>( d_1 ), %</th>
<th>( k_1 )</th>
<th>( d_2 ), %</th>
<th>( k_2 )</th>
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<td>59.68(5.04)</td>
<td>-0.0041(0.0004)</td>
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</table>

Table 4. PCr at rest, fitted parameters (asymptotic SD values) for the double-exponential model (Eq. 4), half times, and SD about the fitted PCr resynthesis curve (% of PCr at rest) for each subject in study 2
Differentiating \( q \) in Eq. 8 with respect to time \( t \) and substituting the starting values, we obtain two “simultaneous” equations to solve for the two unknowns \( A \) and \( B \).

In case 1, when the starting velocity \( \frac{dq}{dt} = 2.96 \) is more than three times that in case 2, the solution to the simultaneous equations give \( A = -160 \) and \( B = 60 \), and the equation for \( q \) becomes

\[
q = 100 - \left[ 160 \cdot \exp(-0.02 \cdot t) - 60 \cdot \exp(-0.004 \cdot t) \right] \quad (9)
\]

i.e., the constant 100 minus the difference between two negative exponential terms in time \( t \). However, in case 2, when the starting velocity was relatively slow (\( \frac{dq}{dt} = 0.88 \)), the solution to the simultaneous equations gives \( A = -30 \) and \( B = -70 \), and the equation for \( q \) becomes

\[
q = 100 - \left[ 30 \cdot \exp(-0.02 \cdot t) + 70 \cdot \exp(-0.004 \cdot t) \right] \quad (10)
\]

i.e., the constant 100 minus the sum of two negative exponential terms in time \( t \).

These solutions (Eqs. 9 and 10) are plotted in Fig. 4.

**APPENDIX 2**

**SPSS Syntax File**

```plaintext
*Nonlinear Regression.
MODEL PROGRAM
D21 = 50
D22 = 50
D23 = 50
K21 =
```

Fig. 3. Electric circuit used to describe the model for PCr resynthesis in muscle. E, energy source; \( q \), stored charge on the capacitor; \( C \), capacitance; i, electric current; A, switch; R, resistance; L, inductance.

Fig. 4. Solutions to hypothetical example with initial velocities either 1) fast (×) or 2) relatively slow (solid line), with horizontal line representing PCr at rest.
-0.01 K22 = -0.01 K23 = -0.01 D1 = 25 K1 = -0.02.

\[
\text{COMPUTE} \text{ PRED} = 100 - (s1*d21 + s2*d22 + s3*d23) * \exp((s1+k21 + s2+k22 + s3+k23)*\text{time}) - d1*\exp(k1*\text{time}).
\]

\[
\text{NLR pcr100}
\]

\[
\text{OUTFILE = 'C:\ WINDOWS\ TEMP\ SPSSFNLR.TMP'}
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\[
\text{PRED PRED} / \text{CRITERIA S5CONVERGENCE 1E-8 PCON 1E-8.}
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**SPSS Data File**

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