Influence of experimental conditions on visco-hyperelastic properties of skeletal muscle tissue using a Box–Behnken design

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Abstract (186 words)

The Mechanical characterization of skeletal muscles is strongly dependent on numerous experimental design factors. Nevertheless, significant knowledge gaps remain on the characterization of muscle mechanics and a large number of experiments should be implemented to test the influence of a large number of factors. In this study, we propose a design of experiment method (DOE) to study the parameter sensitivity while minimizing the number of tests. A Box-Behnken design was then implemented to study the influence of strain rate, preconditioning and preloading conditions on visco-hyperelastic mechanical parameters of two rat forearm muscles. The results show that the strain rate affects the visco-hyperelastic parameters for both muscles. These results are consistent with previous work demonstrating that stiffness and viscoelastic contributions increase with strain rate. Thus, DOE has been shown to be a valid method to determine the effect of the experimental conditions on the mechanical behaviour of biological tissues such as skeletal muscle. This method considerably reduces the number of experiments. Indeed, the presented study using 3 parameters at 3 levels would have required at least 54 tests per muscle against 14 for the proposed DOE method.

1. Introduction

Skeletal muscle is a complex tissue that can be affected by numerous neurological and musculoskeletal diseases. Relevant constitutive models can allow for the monitoring and the understanding of a disease development. To this end, significant research efforts have been made to understand its biomechanical properties. At the tissue scale, the majority of experimental studies are made by using uniaxial testing machines. Whole or sectioned muscles were thus both subjected to either tension (Calvo et al., 2010; Mohammadkhah et al., 2016; Wheatley et al., 2016a) or compression (Böl et al., 2014; Jalal and Zidi, 2018; Pietsch et

al., 2014). Muscle tissue exhibits a highly nonlinear behaviour and may be described by hyperelastic (Calvo et al., 2010; Gras et al., 2012; Johansson et al., 2000; Latorre et al., 2018) and visco-hyperelastic (Calvo et al., 2014; Gras et al., 2013; Van Loocke et al., 2008; Wheatley et al., 2016a) constitutive laws. Note that the experimental conditions could influence the mechanical behaviour of muscle tissue such as strain rate, preloading, preconditioning, hydration, lubrication, ambient temperature, sectioning, bathing, etc... No experimental conditions consensus has been reached from literature yet, and for numerous factors, the incidence on mechanical behaviour has been poorly documented. For instance, some authors used to preconditioned samples (Calvo et al., 2014; Gras et al., 2012; Nagle et al., 2014; Pietsch et al., 2014; Van Ee et al., 2000) whereas others have considered that precondition can lead to permanent deformation (Van Loocke et al., 2008) and consequently do not precondition the samples (Böl et al., 2016; Jalal and Zidi, 2018; Mohammadkhah et al., 2016; Takaza et al., 2013). Furthermore, most of the studies described the application of a preload before testing, but the amount of preload can greatly vary between studies. Thus, preload have ranged from corresponding force of half of the sample mass (Takaza et al., 2013), and 1/40 (Mohammadkhah et al., 2016) to 1/1000 of a maximal load obtained on preliminary tests (Abraham et al., 2013).

Note that the influence of some experimental conditions such as tissue conservation (Böl et al., 2016; Jalal and Zidi, 2018; Van Ee et al., 2000) or sectioning and bathing muscle (Abraham et al., 2013) was investigated on skeletal muscle passive behaviour. Abraham et al. (2013) shown a significantly different viscous tissue response between a section of muscle tissue or a whole muscle as well as between dry or wet testing conditions. Consequently, it is crucial to investigate the influence of various experimental conditions in order to better control mechanical tests. However, numerous factors could be studied which could lead to a

large number of tests. Traditionally this type of studies has been performed by monitoring the influence of one factor at a time on an experimental response. While only one factor is changed, others are kept at a constant level. Usually, studies are performed with at least 6 tests per group (Abraham et al., 2013; Jalal and Zidi, 2018; Van Loocke et al., 2008; Wheatley et al., 2016b). In this way, for example, studies with four parameters that could take three different values would then require 72 tests.

Design of experiments (DOE) is a potential means to evaluate the effect of factors on the response while minimizing the number of required experiments. Basically, the method consists in changing the value of several factors at the same time in a specific sequence. Note that DOE is widely used in some disciplines such as chemistry (Bezerra et al., 2008; Ferreira et al., 2007) or food research (Deng et al., 2016; Tajabadi et al., 2016). Although this method is rarely used in biomechanics, it is noticeable that some DOE sensitivity analysis based on finite element analyses was used on bone and cartilage tissues (Bahraminasab et al., 2013; Isaksson et al., 2009; Wang et al., 2005).

The purpose of this paper is to propose an affordable approach to study the parameter sensitivity while minimizing the number of necessary tests. In this way, as we know that viscoelastic behaviour depends on strain rates (Van Loocke et al., 2008), we choose to investigate the effect of this parameter as well as preconditioning and preloading conditions. A Box–Behnken designs (Box and Behnken, 1960) is then proposed to address this issue.

2. Material and methods

2.1 Sample preparation and tensile tests

Rat flexor carpi radialis (FCR) and palmaris longus (PL) muscles (N=14) was extracted from the forearm of 15 healthy rats by an authorized person in accordance with the local ethic

committee ANSES/ENVA/UPEC (n°13/12/16-10). After sacrifice of the animals, the muscles were harvested from the forearm of each animal. The muscles were then stored in saline solution at 4°C until testing. Testing was conducted within 6 hours after the death of the animal in order to minimize *rigour mortis* effect (Böl et al., 2016; Van Ee et al., 2000; Van Loocke et al., 2006).

After positioning of the muscle between mechanical jaws, the initial sample height was recorded using a calibrated camera, then muscles images were acquired for both front and side view. Hence, under the assumption that the muscle cross-sections were rectangular, the average cross-section area (CSA) was determined from these images by a custom Matlab scripts (Matlab® R2017b, The Mathworks, Inc). FCR and PL muscles were respectively 9.8±1.6mm (8.3±2.0mm) high with an average CSA of 9.1±2.3mm² (3.2±1.9mm²).

Tensile tests were conducted by the uniaxial mechanical testing system (MTS Insight, MTS Systems Corporation) by using a 100N force sensor controlled by data processing software. Global strain was recorded during experiments through internal measure of crosshead movement. The slippage was reduced with sandpaper added between muscle and jaws (Calvo et al., 2010). It should be emphasized that the experiments were recorded by front and side cameras in order to inspect slippage at large strain.

Before testing, the muscles were or were not subjected to preconditioning cycles and preloading, depending on Box–Behnken design as presented below in the experimental designs section. The experiments consisted of 4 steps, the sample was first loaded at a chosen strain rate up to 10% strain and kept constant for 300 seconds to allow stress relaxation in the sample. The muscle was unloaded until a preloading force and then finally stretched again at the same strain rate than initial ramp up to first onset of slippage. Those slipping were

115 determined afterward by both video inspection and substantial decrease/inflection of stress. In
116 what follows, the first and second period of stretch is named T1 and T2 respectively.

117 *2.2 Experimental designs*

118 Preconditioning, preloading and strain rates were chosen as varying factors. In order to
119 minimize the number of tests, an experimental design is proposed. Each parameter can take 3
120 values chosen to represent the diversity of values within the literature. First, the
121 preconditioning cycles varied between 0 (Böl et al., 2016; Mohammadkhah et al., 2016), 5
122 (Calvo et al., 2014) and 15 cycles (Nagle et al., 2014; Pietsch et al., 2014). Cycles have been
123 set at a strain rate of 0.5mm/s. Then, preloading varied between 1/1000 (Abraham et al.,
124 2013), 1/40 and 1/20 (Mohammadkhah et al., 2016) of a maximum load. Since we were
125 limited by our sensor sensitivity, a no-preload condition was chosen to represent the very low
126 preloading (1/1000 of maximal load). Preliminary tests enabled us to prescribe 0,03N and
127 0.07N preloads that corresponded to roughly 1/40 and 1/20 of a maximum load. Finally, the
128 strain rate varied between 0.05% (Mohammadkhah et al., 2016), 0.5% (Jalal and Zidi, 2018)
129 and 10% (Van Loocke et al., 2008) per second.

130 A Box–Behnken experimental design with three independent variables at three levels was
131 performed to study the influence of the parameters on the visco-hyperelastic behaviour
132 described in the next section. For statistical calculations, each variable was coded as three
133 levels: -1, 0, and 1 as shown in Tab.1. The protocol was implemented for each muscle,
134 consisting of 14 experimental points carried out in random order with two repeats of the
135 centre of the design as illustrated in Fig. 1.

136

137

2.3 Visco-hyperelastic model

Since we have just tested skeletal muscle by uniaxial tensile test, we chosen a hyperelastic isotropic model (Bosboom et al., 2001; Gras et al., 2012; Wheatley et al., 2016). We used first-order Ogden's model coupled with second-order Maxwell's model (Jalal and Zidi, 2018). The visco-hyperelastic model is briefly described in Supplementary material S1.

2.4 Statistics

The experimental data of Box–Behnken design were statistically analysed using Matlab2017b® software. A three-way ANOVA was performed with preconditioning cycles, preload force and strain rates as factors. Experiments were also fitted to a second-order polynomial model :

$$Y = a_0 + \sum_{i=1}^{3} a_i F_i + \sum_{i=1}^{3}\sum_{j=1}^{3} a_{ij} F_i F_{j,} \tag{7}$$

where Y is the output $\left[\mu, \alpha, E_0, \tau_k, \gamma_k, \gamma_T, \lambda_{\max}\right]$ with $\lambda_{\max}$ the ultimate elongation before any slippage, F_i are preconditioning cycles (F_1), preload force (F_2), strain rates factors (F_3) and a_0, a_i, a_{ii}, a_{ij} are respectively central, linear, quadratic and interaction coefficients. Finally, the coefficient of determination r^2 and adjusted coefficient of determination r_a^2 were obtained.

3. Results

3.1.Model Fitting

An illustrative example of the stress-time response is shown in Fig. 2a. This test was carried out on FCR muscle with all parameters at central levels, that is to say with 5 preconditioning cycles, 0.03N preload force and strain rate at 0.5 %L0/s. The fitting of the first and second

158 stretch period using first Ogden's model is presented Fig. 2b and Fig. 2d respectively. The
159 stress relaxation fitting by Maxwell's model is given Fig. 2c. We observe that the fitting was
160 correctly performed for both first tensile part $(r^2 = 0.98 \pm 0.02)$ and relaxation
161 $\left(r^2 = 0.985 \pm 0.015\right)$ when using respectively (1) and (2) whereas the fitting of the second
162 tensile part is less suitable $\left(r^2 = 0.96 \pm 0.04\right)$ when using (1). The fitting of this last part is
163 particularly incorrect for small strain which is a region of interest in order to estimate
164 instantaneous modulus. Therefore, in what follows, the hyperelastic parameters were obtained
165 from the fitting of the initial 10% ramp (T1).

166

167 *3.2. Box-Behnken experiment*

168 An ANOVA and second-order polynomial regression were conducted on Box-Behnken
169 experiments with as outputs results $\left(\mu(T_1), \alpha(T_1), E_0(T_1)\right)$ for the first tensile part, $\left(\tau_k, \gamma_k, \gamma_T\right)$
170 for relaxation part and the ultimate elongation λ_{max}. The second-order model coefficients a_0
171 to a_{33} were obtained for both muscles. Central $\left(a_0\right)$ and linear (a_1 to a_3), coefficients, as well
172 as coefficients of determination (r^2, r_a^2) and p-value for preconditioning cycles, preloading
173 and strain rates factors are given in Tab.2 and Tab.3 for respectively PL and FCR muscles.

174

175 For hyperelastic contribution, in the case of FCR muscle, we note a non-significant trend of
176 strain rate on $\mu(T_1)$ and $\alpha(T_1)$ ($\left(p = [0.05 - 0.1]\right)$). For viscoelastic contribution, in the case
177 of both muscles, we found a strong influence of strain rate on τ_1, γ_1 $\left(p \le 0.01\right)$ and a
178 significant influence on γ_T ($p \le 0.05$).

Eq. (8) and (9) show the relationship between the 3 factors and the output τ_1 for respectively PL and FCR muscles. Response surfaces are presented in Fig.3a-c for PL muscles and in Fig.3d-f for FCR muscles. They were obtained by varying 2 factors within the experimental range [-1 1] and holding the other one at the central level [0].

$$\tau_1 = 3.94 - 0.64F_1 - 0.17F_2 - 2.70F_3 + 0.88F_1.F_3 + 0.09F_1.F_2 - 0.04F_2.F_3 - 0.89F_1^2 + 0.65F_2^2 + 0.68F_3^2, \quad (8)$$

$$\tau_1 = 3.74 - 0.01F_1 - 1.09F_2 - 3.44F_3 + 0.70F_1.F_3 + 0.54F_1.F_2 - 1.47F_2.F_3 - 0.76F_1^2 + 0.19F_2^2 + 1.26F_3^2, \quad (9)$$

4. Discussion

This study was motivated by the importance of the experimental conditions on the mechanical response of muscle subjected to the relaxation-tensile test. The study factors include preload, preconditioning cycle and strain rate. The only factor affecting the behaviour of both muscles is strain rates. Indeed, this parameter has been shown to have a great impact on viscoelastic properties, and more specifically on τ_1, γ_1 and γ_T parameters. Higher the strain rates, the most the stress relaxed in a short period of time. Therefore, whether it is for PL or for FCR muscles the coefficient of τ_1 in the polynomial model before F3 (strain rates) is negative and larger in absolute value. On the contrary, the coefficient γ_1 and γ_T of the polynomial model before F3 are positive and also higher in absolute value. These results are consistent with previous work demonstrating that the viscoelastic contributions, which corresponds to γ_T, increased with the strain rate in muscle compression tests (Van Loocke et al., 2008). A trend towards significance can be noted between an increase of strain rates and an increase of $\mu(T_1)$ as well as a decrease of $\alpha(T_1)$ ($p = 0.07$ and $p = 0.094$) for FCR muscles. Note that a

similar trend can be observed for PL muscles but without statistically significant. We can note that Sun et al. (1995) did not show behavior differences in the context of small strain. Thus, it is not surprising to show only slight differences due to strain rate. Consequently, these similarities with previous work strongly suggest that this method is robust enough to be used as tools to determine the effect of experimental conditions on mechanical tests. The main interest of this method is to substantially reduce the number of experiments. Indeed, if we applied the usual single variable method with at least 6 tests per group (Jalal and Zidi, 2018; Van Loocke et al., 2008; Wheatley et al., 2016b), this study with 3 parameters at 3 levels would required at least 54 tests per muscle against 14 for the DOE proposed method.

It should be noted that only the second-order polynomial regression with a coefficient of determination r^2 above 0.8 should be considered according to Joglekar and AT May (1987) (Joglekar and May, 1987). Nevertheless, the more coefficients, the higher will the r^2 value will be. Thus, the adjusted coefficient of determination r_a^2 was also determined, this coefficient is corrected by including a penalty for the numbers of predictors variables (here 9). In that respect, although correlation for τ_1, γ_1 and γ_T results are acceptable for FCR muscle with $r_a^2 \geq 0.8$, correlations for PL muscles should be made carefully ($r_a^2 \geq 0.657$, $r_a^2 \geq 0.674$ for τ_1 and γ_T results).

Furthermore, it is worth noting that neither the preloading nor the preconditioning does not seem to have a significant effect on the visco-hyperelastic skeletal muscle behaviour. It is important, nevertheless, to nuance such a conclusion. Indeed, it is difficult to isolate one factor without others factors interaction. For instance, the preconditioning of sample may (depending on experimental device) require a substantially longer handling involving an increased tissue drying. Thus, the initial preconditioning study would, in fact, be an

investigation including preconditioning and drying. Clearly, more works have to be done considering more parameters carefully chosen while using the proposed DOE. Finally, none of these factors seems to have an influence on the ultimate elongation value (λ_{max}). This observation means that the specimen slippage that is an experimental limitation does not seem to be affected by those factors.

5. Limitations

(see Supplementary material S2).

6. Conclusion

A Box–Behnken design was proposed to investigate the influence of strain rates, preconditioning and preloading conditions on mechanical behaviour were investigated on two rat forearm muscles. Visco-hyperelastic parameters are derived from the Ogden model coupled with Maxwell's model. The results showed that strain rate affects the behaviour of both muscles. These results are consistent with previous work suggesting that design of experiment is a valid method to determine the effect of experimental conditions on the mechanical behaviour of skeletal muscle subjected to tensile test. This method lets considerably reduce the number of experiments. Thus, it may be worth investigating the effect of various experimental factors such as drying, jaws tightening, and also testing temperature.

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Conflict of interest statement

No conflict of interests is associated with the present study.

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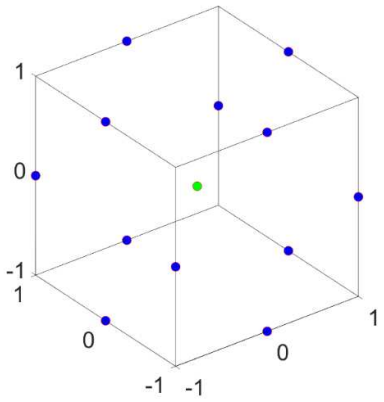
Fig. 1. Schematic illustration of Box-Behnken design. Blue points were only completed once whereas green point was repeated twice.

Fig. 2. Illustrative examples (FCR centre point) of stress-time response (a), stress-stretch fitting using first-order Ogden's model for first $r^2 = 0.98 \pm 0.02$ (b) and the second tensile part $r^2 = 0.96 \pm 0.04$ (d), and stress-time fitting using second-order Maxwell's model $r^2 = 0.985 \pm 0.015$ (c).

Fig. 3. Response surface and contour plot showing the effect of preload, preconditioning cycles and strain rates ($\dot{\varepsilon}$) on first relaxation time τ_1 on PL (a-c) and FCR (d-f) muscles.

Fig. 1.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0
-1
1
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1

Fig. 2.

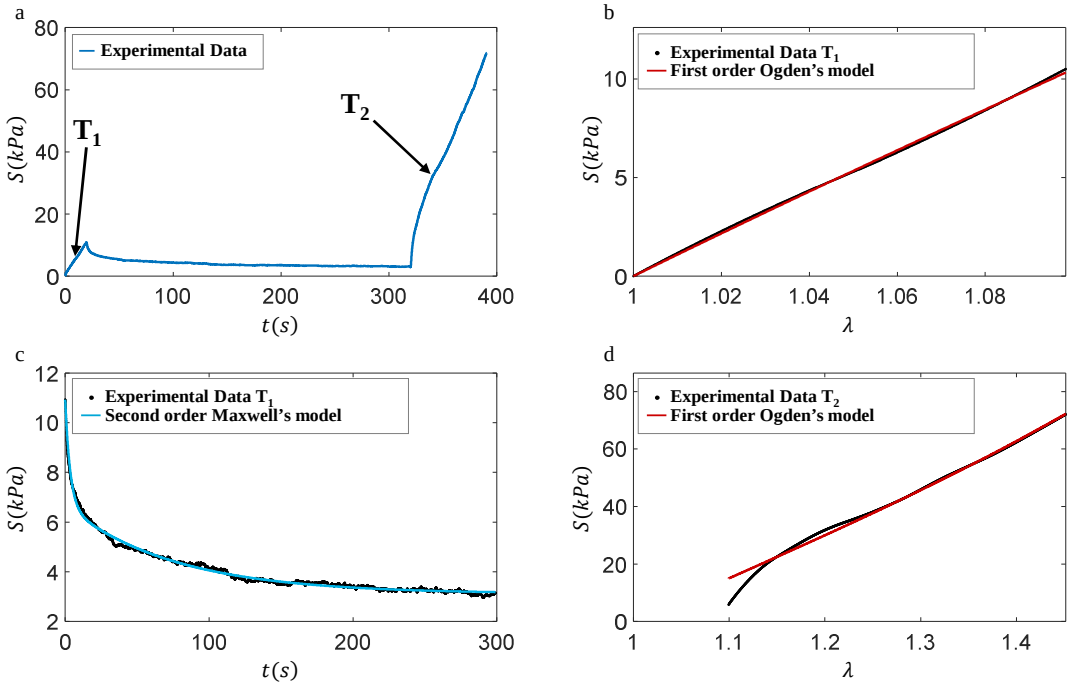
a
Experimental Data
T1
T2
S(kPa)
t(s)
b
Experimental Data T1
First order Ogden's model
S(kPa)
λ
c
Experimental Data T1
Second order Maxwell's model
S(kPa)
t(s)
d
Experimental Data T2
First order Ogden's model
S(kPa)
λ

Fig. 3.

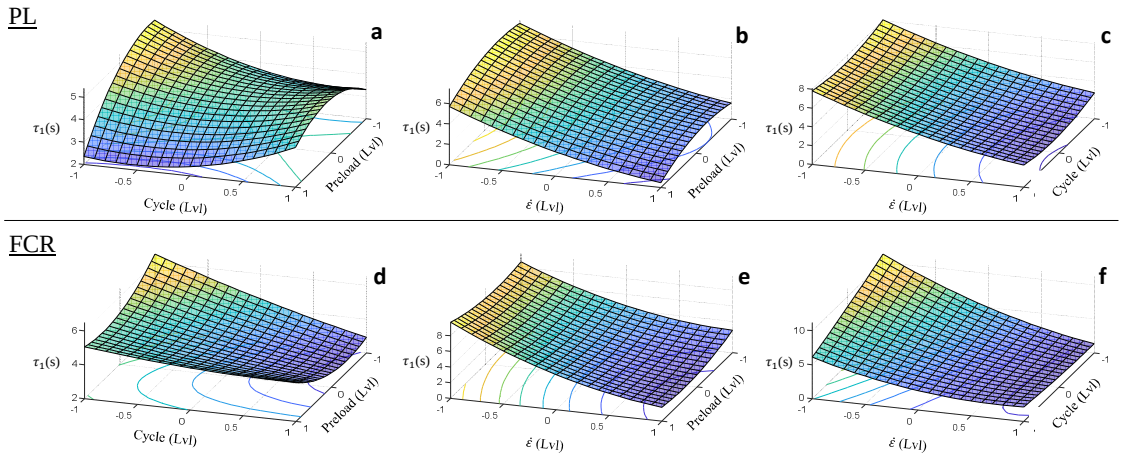

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Table 1 :

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Table 3

Central (a_0) and linear $(a_1$ to $a_3)$ coefficients of the second-order polynomial model for outputs obtained on FCR muscles mechanical tests. Coefficients of determination r^2 and adjusted coefficient of determination r_a^2 of polynomial model. P-values for preload, preconditioning cycles and strain rates $(\dot{\varepsilon})$ obtained by ANOVA.

Table 1.

Variables	Levels		
	-1	0	1
Preconditioning cycles	0	5	15
Preload Force (N)	0	0.03	0.07
Strain rate (%L_0/s)	0.05	0.5	10

Table 2.

	a_0	a_1	a_2	a_3	r^2	r_a^2	**P-Value Preload**	**P-Value Cycle**	**P-Value** $\dot{\varepsilon}$
$\mu(T_1)$	263,60	218,04	82,25	190,64	0,674	-0,061	0,359	0,848	0,393
$\alpha(T_1)$	0,53	-0,42	-0,76	-4,30	0,855	0,530	0,461	0,756	0,569
$E_0(T_1)$	180,13	225,86	213,52	-142,93	0,728	0,117	0,223	0,178	0,290
γ_1	0,39	-0,03	0,03	0,19	0,964	0,882	0,740	0,250	0,002
τ_1	3,94	-0,64	-0,17	-2,70	0,894	0,657	0,240	0,637	0,002
γ_2	0,40	-0,05	0,01	0,04	0,734	0,136	0,449	0,192	0,540
τ_2	94,79	-24,36	6,58	-8,68	0,934	0,784	0,201	0,407	0,631
γ_T	0,79	-0,07	0,04	0,23	0,900	0,674	0,530	0,182	0,023
λ_{max}	1,53	-0,14	-0,05	0,06	0,628	-0,209	0,122	0,731	0,284

Table 3.

	a_0	a_1	a_2	a_3	r^2	r_a^2	**P-Value Preload**	**P-Value Cycle**	**P-Value** $\dot{\varepsilon}$
$\mu(T_1)$	38,20	32,85	70,25	103,83	0,834	0,462	0,519	0,592	0,070
$\alpha(T_1)$	6,54	1,02	2,24	-5,97	0,677	-0,050	0,465	0,512	0,094
$E_0(T_1)$	122,05	11,81	20,14	18,97	0,907	0,697	0,119	0,471	0,790
γ_1	0,38	0,01	-0,01	0,13	0,991	0,970	0,256	0,317	0,000
τ_1	3,74	-0,01	-1,09	-3,44	0,957	0,860	0,738	0,365	0,001
γ_2	0,33	0,04	0,02	-0,06	0,905	0,690	0,033	0,415	0,030
τ_2	84,12	2,38	-8,76	-16,56	0,650	-0,138	0,473	0,652	0,147
γ_T	0,71	0,04	0,02	0,07	0,972	0,910	0,006	0,370	0,010
λ_{max}	1,38	0,00	0,02	0,04	0,545	-0,479	0,802	0,903	0,907