Mathematical Performance of Reliability Estimation in Step – the Secretion of Glutamate and Dopamine Due to the Stress Effect in Terms of Ketamine

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Abstract

In this paper, generally experiences various stresses, which either accelerate or decelerate the part's failure, during its lifetime. However, in conventional reliability analysis, the influence of varying stresses is seldom explicitly included into reliability estimation. Time-varying stress accelerated life testing (ALT) is to study the failure time and failure mode of a part under pre-planned changing stresses. Comparing to the constant stress ALT, time-varying stress ALT is able to further reduce testing time, as well as estimate product lifetime under a similar varying stress operation condition. This is highly desirable given the pressure to shorten a product's time-to-market. For example, Ketamine (18 mg/kg, s.c.) evoked a significant release of glutamate and DA, although the glutamate response was slower in onset compared with DA. Pretreatment with either systemic (3 mg/kg s.c.), but not DA, release. When applied directly to the mPFC via the dialysis probe, ketamine had no effect on glutamate release but did significantly enhance the release of DA. Local ketamine, on the other hand, does not increase glutamate but does increase DA release. This suggests that ketamine acts outside of the mPFC to enhance glutamate, but within the mPFC to enhance DA release. The origin of the ketamine effect on mPFC glutamate is currently not known.

Key Words: Stress effects, Glutamate, Dopamine, Ketamine, ALT ,SSA ,CDM.

AMS Classification: 60J65, 60G57

In this paper ,we have used the following notations

ALT	Accelerated Life Test
SSALT	Step Stress Accelerated Life Test
CDM	Cumulative Damage Model
MLE	Maximum Likelihood Estimation
T	Failure time
β	Shape parameter of the Weibull distribution
η	Scale parameter of the Weibull distribution
x(t)	Stress level as a function of t
F(t)	Cumulative failure function
R(t)	Reliability function
a,b	Parameters in the inverse power function
I(t)	Integrated standardized time used in the reliability function
u	$u = \beta \ln I(t)$
$\hat{\theta}$	Estimator of θ
$\mathrm{Var}\hat{\theta}$	Asymptotic variance of the θ estimator

K_α	The α upper percentile point of a standard s–normal distribution
θ_U	upper bound of θ
θ_L	lower bound of θ
LR(θ)	likelihood ratio function on θ

1. Introduction

The pioneering work for varying stress ALT modeling has been done and [7]. Assumed that under higher stress, the mean product life time would linearly shrink with a constant factor corresponding to the stress level, and proposed a tampered random variable model for simple step stress ALT (SSALT) in the framework of Bayesian decision theory. [7], suggested that the life-stress model must take into account the cumulative effect of the applied stresses when dealing with data from accelerated tests with step stresses. The cumulative damage is additive, and the remaining life of test units depends only on the current stress & the current cumulative distribution function, regardless of the damage accumulation history. Alternatively, [6] developed a tampered failure rate model. [5] proposed another model known as the KH model for step-stress ALT, which is based on a time-transformation of the exponential model and presented a generalized accelerated life model for step stress testing, and a general likelihood function formulation of step stress models.

Most of the above varying stress ALT models are based on step-stress loading; however, the stresses experienced by a product in service usually are not just simple step stresses. Some products may undergo a repeated cyclic stress loading; some may undergo a ramp, or cyclic-ramp-constant stress loading, or a nonrepeating pattern stress loading. For example, insulation under AC voltage sees a sinusoidal stress[4]. The varying stress ALT for such a product loads a specimen with the same stress pattern at high stress levels to obtain the accurate reliability estimation.

In this paper, we develop an analytical expression of the reliability function, and its confidence bounds based on the cumulative damage model (CDM) for a part under varying stress loading. This generalizes the previous work on ALT and SSALT modeling. We prove the nonmonotonicity of the confidence bounds on the reliability function by examining the limiting values of upper and lower bounds. We also demonstrate the importance of appropriately assigning a confidence level for parameter estimation when facing limited data.

2. Cumulative damage model

In this paper, the Weibull distribution, and the inverse power function are considered. To derive the confidence bound of the reliability function under a varying stress loading, we will briefly describe the cumulative damage model proposed by Nelson [7], which was initially used for analyzing SSALT data. The failure time (T) of a product under a certain stress level follows a Weibull distribution, where two parameters β and η are used to characterize the shape, and the scale of the distribution (when β=1 an exponential distribution is obtained). It is assumed that β is a constant, and η is a function on the stress level,

i.e. $F(t; \eta; \beta) = 1 - \exp[-(t/\eta(x))^{\beta}]$ (1)

and $\eta(x) = (a/x)^b$ (2)

where x is the stress level, and η has an inverse power function on x. Parameters β, a and b are unknown. Combining (1) &(2), the reliability function can be written as

$$R(t) = \exp[-(x/a)^b t]^{\beta} \quad (3)$$

If we view (t/ η)in (1) as a standardized failure time, and the parameter η as the shrinking or expanding factor to the original failure time comparing with a natural reference stress , the expression in the bracket in (3)

can be seen as the standardized cumulative exposure time to the constant stress, x with respect to the natural reference point. In a step-stress accelerated life test, the stress level is moved to the next stage at a pre-specified time if the part in test has not failed yet; so the standardized cumulative exposure time is $\sum_i [(x_i/a)^b \Delta t_i]$, where Δt_i is the duration of testing under stress x_i . In a linear-stress accelerated life testing, the stress amount is a linear function on time, i.e., $x= x_0+\lambda t$, so the standardized cumulative exposure time is $\int ((x_0+\lambda t)/a)^b dt$ .This can be used to model the ramp range when the stress level is changed from one to another level .

In general, let I(t) denote the integrated standardized time

$$I(t) = \int_0^t \{\frac{x(\varepsilon)}{a}\}^b d\varepsilon \qquad (4)$$

and the reliability function becomes ,

$$R(t) = e^{-[I(t)]^\beta} = e^{-e^u} \qquad (5)$$

where $u = \ln[I(t)]^\beta = \beta \ln I(t)$. R is a decreasing function on u.

3. Confidence Bounds of Reliability Function

The confidence bounds on the parameters, and a number of other Quantities, such as the reliability, and the percentile, can be obtained based on the asymptotic theory for maximum likelihood estimation (MLE). Denote $\hat{\theta}$ as the maximum likelihood estimator of parameter θ . By the invariance property of MLE, a function of ML estimators is still a ML estimator of the function, so the MLE of u & R are

$$\hat{u} = u(\hat{\beta}, \hat{a}, \hat{b}) = \hat{\beta} \ln \int_0^t \{\frac{x(\varepsilon)}{\hat{a}}\}^{\hat{b}} d\varepsilon \qquad (6)$$

and $$\hat{R} = e^{-e^{\hat{u}}} \qquad (7)$$

Based on the large sample s-normal approximation, the upper, and lower limits of u with the confidence level of 100(1-α) % are respectively

$$u_U = \hat{u} + K_\alpha \sqrt{Var(\hat{u})} \qquad (8)$$

and $$u_L = \hat{u} - K_\alpha \sqrt{Var(\hat{u})} \qquad (9)$$

where K_α is the α upper percentile point of a standard s–normal distribution, and $Var(\hat{u})$ is the asymptotic variance of the ML estimator of u. Here, u is a function on parameter vector □, where □ = [a,b,β].

Therefore

$$Var(\hat{u}) = \left(\frac{\partial u(\square)}{\partial \square}\right)' \sum_{\hat{\square}} \left(\frac{\partial u(\square)}{\partial \square}\right) \qquad (10)$$

After defining $$L(t) = \int_0^t \{\frac{x(\varepsilon)}{a}\}^{\hat{b}} \ln\{\frac{x(\varepsilon)}{a}\} d\varepsilon \qquad (11)$$

it is easy to show that , $$\frac{\partial u}{\partial \beta} = \ln I(t) \qquad (12)$$

$$\frac{\partial u}{\partial a} = -\beta b / a \qquad (13)$$

and $$\frac{\partial u}{\partial b} = \beta \frac{L(t)}{I(t)} \qquad (14)$$

$$\text{Let } p(t) = \frac{L(t)}{I(t)} \qquad (15)$$

Then the upper and lower limits of u become equations are given below.

$u_U = \hat{\beta}\text{In } \hat{I}n(t) + K\alpha$

$$\sqrt{(In^2\, I(t)\,)var\,\hat{\beta} + (\frac{\hat{\beta}\hat{b}}{\hat{a}})^2 var\,\hat{a} + \hat{\beta}^2\hat{p}(t)^2\,\text{var}\hat{b} - 2\,\frac{\widehat{(\beta}\,\hat{b}\;\text{In}\hat{I}(t)covar(\hat{\beta},\hat{a})}{\hat{a}} + 2\,\hat{\beta}\,\hat{p}(t)\text{In}\,\hat{I}(t)covar(\hat{\beta},\hat{b}) - 2\,\frac{\hat{b}\,\hat{\beta}^2}{\hat{a}}\,\hat{p}(t)covar(\,\hat{a},\,\hat{b})}$$

and

(16)

$u_L = \hat{\beta}\text{In } \hat{I}n(t) - K\alpha$

$$\sqrt{(In^2\, I(t)\,)var\,\hat{\beta} + (\frac{\hat{\beta}\hat{b}}{\hat{a}})^2 var\,\hat{a} + \hat{\beta}^2\hat{p}(t)^2\,\text{var}\hat{b} - 2\,\frac{\widehat{(\beta}\,\hat{b}\;\text{In}\hat{I}(t)covar(\hat{\beta},\hat{a})}{\hat{a}} + 2\,\hat{\beta}\,\hat{p}(t)\text{In}\,\hat{I}(t)covar(\hat{\beta},\hat{b}) - 2\,\frac{\hat{b}\,\hat{\beta}^2}{\hat{a}}\,\hat{p}(t)covar(\,\hat{a},\,\hat{b})}$$

(17)

Therefore, the corresponding upper, and lower confidence bounds on the reliability function are

$$R_U = e^{-e^{uL}} \quad (18)\ ,$$

and

$$R_L = e^{-e^{uU}} \quad (19)$$

Equation (7) is the reliability estimation of a part subject to varying stresses. The impact of stress is explicitly modeled into the formula by continuously shrinking or expanding the part's in-use time comparing to a natural reference stress level. Accordingly, (18), and (19) are respectively the upper, and lower confidence bounds of the reliability estimation of a part under the natural reference stress level.

4.Application

Recent preclinical discoveries have brought into focus the potential utility of group II metabotropic glutamate receptor agonists in the treatment of schizophrenia Specifically, phencyclidine's (PCP) neurochemical and behavioral effects in rats were reversed by pretreatment with the mGluR2/3 selective agonist LY354740 [3]. PCP, a noncompetitive *N*-methyl-D-aspartate channel blocker with known psychotomimetic properties in humans , increased glutamate release in medial prefrontal cortex , activated locomotion, and impaired working memory in rats. Pretreating animals with LY354740 reversed each of these effects suggesting that mGluR2/3 agonists may have potential in treating the symptoms of PCP psychosis in humans, and possibly schizophrenia via a novel mechanism of action, i.e. by attenuating glutamatergic neurotransmission in the mPFC. Known antipsychotics such as clozapine and haloperidol, however, were without effect in blocking PCP-evoked glutamate release in the mPFC [1]. We should also note that not all evidence supports over activity of glutamate systems in schizophrenia. In fact, the opposite case has also been suggested. For example, biochemical analysis of brains and cerebrospinal fluid from schizophrenics have revealed, in some cases, decreased concentrations of glutamate and increased cortical glutamate receptors [3].

Data are reported as percentages of baseline, not corrected for *in vitro* recovery. All time-course data obtained on glutamate and DA release were analyzed with repeated measure analysis of variance (ANOVA) using either a one-factorial design for detection of change in release across time within a single treatment or a two-factorial design for comparison of two treatment groups (with treatment as the between factor and time as the within factor).

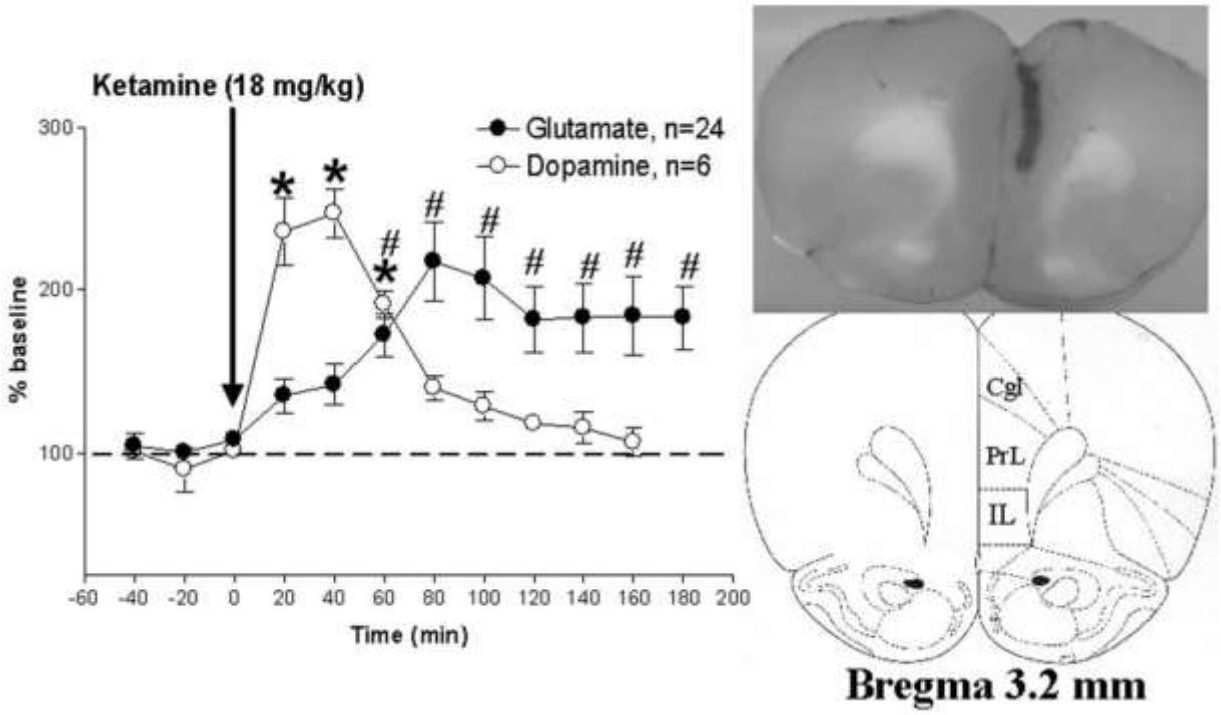
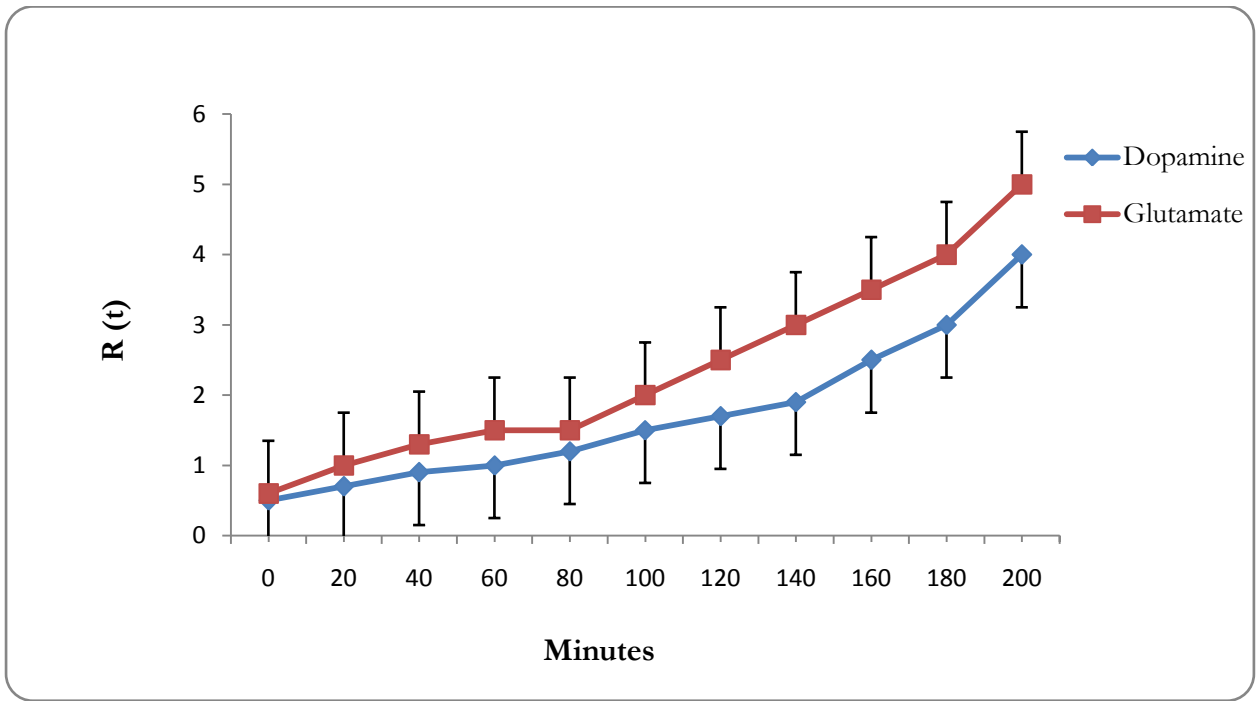


Figure 1.

Figure 1 .Left: Effects of ketamine on glutamate and DA release in the mPFC of the awake rat. Data (mean_S.E.M.) are reported as percentage of baseline. Under the current testing conditions basal glutamate was calculated to be 50 ± 24 pg/μl dialysate and DA was calculated to be 0.02 ± 0.01 pg/μl dialysate. Right: Representative coronal section showing the spread of dye from the active portion of the dialysis membrane to the surrounding tissue in an individual subject with an appropriately placed microdialysis probe (top). Drawing of the rat brain depicting the regions of the mPFC assayed by the microdialysis probe (bottom).

5. Mathematical Result



6. Conclusion

From the medical report glutamate-release studies, 24 control animals received an 18 mg/kg s.c. ketamine challenge injection (Figure 1).

These 24 animals are a compilation of three separate groups, each serving as a control group for one of three treatment groups;

1) systemic LY379268 (3 mg/kg)

2) local LY379268 (1 μ M) and 3) TTX (1 μ M).

Here we report on the pooled data (24 subjects). In the section to follow individual control groups are analyzed with respect to their treatment group. The ANOVA conducted on the pooled data revealed a significant increase in glutamate release ketamine challenge. Dunnett's post hoc comparisons revealed a delayed yet long-lasting increase in glutamate release reaching statistical significance by 60 min and remaining elevated throughout the 180-min sampling period (P<0.05). Ketamine (18 mg/kg) also produced a significant increase in dialysate DA concentrations. Dunnett's post hoc comparisons revealed an immediate increase in DA reaching statistical significance by 20 min and returning to baseline values by 80 min (P<0.05).From the Mathematical model the Glutamate and Dopamine increases rapidly (gradually) with time which coincides with the above medical report.

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