IOSR Journal of Engineering (IOSRJEN) **www.iosrjen.org**
ISSN (e): 2250-3021, ISSN (p): 2278-8719
Vol. 04, Issue 04 (April. 2014), ||V6|| PP 08-15

Mathematical Model for finding the maximum value of growth hormone (GH) deficiency in Patients with Fibromyalgia by using Gaussian Process

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Abstract: - An important problem in reliability engineering is to predict the failure rate, that is, the frequency with which an engineered system or component fails. This paper presents a new method of estimating failure rate using semiparametric model with Gaussian process smoothing. This method is able to provide accurate estimation based on historical data and it does not make strong a priori assumptions of failure rate pattern.(e.g., constant or monotonic).Our experiments of applying this method in power system failure data compared with other models show its efficacy and accuracy. This method can be used in estimating reliability for many other systems, such as software systems or components. Adult growth hormone (GH) deficiency is a well described syndrome with many features reminiscent of fibromyalgia. There is evidence that GH deficiency as defined in terms of a low insulin-like growth factor – I (IGF-1) level occurs in approximately 30% of patients with fibromyalgia and is probably the cause of some morbidity. It seems most likely that impaired GH secretion in fibromyalgia is related to a physiologic dysregulation of the hypothalamic – pituitary – adrenal axis (HPA) with a resulting increase in hypothalamic somatostatin tone. It is postulated that impaired GH secretion is secondary to chronic physical and psychological stressors. It appears that impaired GH secretion is more common than significant GH deficiency with low IGF-1 levels. The severe GH deficiency that occurs in a subset of patients with fibromyalgia is of relevance because it is a treatable disorder with demonstrated benefits to patients. Finally we conclude our Mathematical results that the figure – A is well fitted in the Gaussian process and the maximum value of growth hormone deficiency at the time has been obtained. This will be helpful for the medical professional.

Keywords: *Estimation theory, Gaussian processes, GH, IGF – 1.* ***Mathematical subject classification:*** *60 G_{xx}, 62H_{xx}, 62$P_{xx.}$*

I. INTRODUCTION

Reliability is one of the most important requirements of the smart grid and other sustainable energy systems. By smart grid, we refer to an automated electric power system that monitors and controls grid activities, ensuring the two-way flow of electricity and information between power plants and consumers – and all points in between [9].How to accurately and effectively evaluated system reliability has been a long – time research challenge. One commonly used indicator for system reliability is failure rate, which is the frequency with which an engineered system or component fails. To estimate the failure rate, historical failure information and /or testing of a current sample of equipment are commonly used as the basis of the estimation. After these data have been collected, a failure distribution model, a cumulative distribution function that describes the probability of failure up to and including time t,is assumed (e.g., the exponential failure distribution or more generally, the weibull distribution)and used to estimate the failure rate. Our experimental results indicate that using an exponential or weibull distribution prior may not be as effective for power grid failure modeling as a particular semiparametric model introduced in this work. This semiparametric model does not assume a constant or monotonic failure rate pattern as the other models do. We introduce Gaussian smoothing that further helps the semiparametric model to closely resemble the true failure rate. We applied this method to power network component failure data and compared its blind-test estimation results with the subsequent real failures. We also compared it with other models during these experiments. In all of these cases, the semiparametric model outperformed the other models.

II. BACK GROUND ON RELIABILITY ANALYSIS

The failure rate can be defined as the total number of failures within an item population, divided by the total time expended by that population, during a particular measurement interval under stated conditions

[14].We use $\lambda(t)$ to denote the failure rate at time t,and R(t) to denote the reliability function (or survival function),which is the probability of no failure before time t.Then the failure rate is:

$$\lambda(t) = \frac{R(t) - R(t+\Delta t)}{\Delta t \, . R(t)}$$

As Δt tends to zero, the above λ becomes the instantaneous failure rate, which is also called hazard function (or hazard rate) h(t) :

$$h(t) = \lim_{\Delta t \to 0} \frac{R(t) - R(t+\Delta t)}{\Delta t \, . R(t)}$$

A failure distribution F(t) is a cumulative failure distribution function that describes the probability of failure up to and including time t:

$$F(t) = 1 - R(t), t \geq 0$$

For system with a continuous failure rate, F(t) is the integral of the failure density function f(t):

$$F(t) = \int_0^t f(x)dx \, .$$

Then the hazard function becomes

$$h(t) = \frac{f(t)}{R(t)}$$

2.1. Weibull and Exponential Failure Distribution

For the weibull failure distribution, the failure density function f (t) and cumulative failure distribution function F(t) are

$$f(t;\lambda,k) = \begin{cases} \frac{k}{\lambda}\left(\frac{t}{\lambda}\right)^{k-1} e^{-\left(\frac{t}{\lambda}\right)^k} & t \geq 0 \\ 0, & t < 0 \end{cases}$$

$$F(t;\lambda,k) = \begin{cases} 1 - e^{-\left(\frac{t}{\lambda}\right)^k}, & t \geq 0 \\ 0, & t < 0 \end{cases}$$

Where k > 0 is the shape parameter and $\lambda > 0$ is the scale parameter of the distribution. The hazard function when $t \geq 0$ can be derived as

$$h(t;\lambda,k) = \frac{f(t;\lambda,k)}{R(t;\lambda,k)} = \frac{f(t;\lambda,k)}{1 - F(t;\lambda,k)} = \frac{k}{\lambda}\left(\frac{t}{\lambda}\right)^{k-1}$$

A value of k < 1 indicates that the failure rate decreases over time. A value of k = 1 indicates that the failure rate is constant (i.e., k/λ) over time. In this case, the weibull distribution becomes an exponential distribution. A value of k > 1 indicates that the failure rate increase with time.

III. SEMIPARAMETRIC MODEL WITH GAUSSIAN SMOOTHING

We consider the semiparametric estimation of the longitudinal effect of a blip treatment (i.e., a single "all – or – nothing" treatment occurring at a precisely recorded time) on a system with recurring events (e.g., immediately – recoverable failures in a mechanical / electronic system).The estimand is the effect of the most recent blip treatment on the future arrival rate. The method assumes that the effect of treatment is to scale the underlying rate, and is thus an extension of Cox regression with internal covariates, using the Gaussian process to provide much-needed smoothing. Although the method applies to any blip treatment, we focus on estimating the effect of an event (failure) on future failures. For example, an association of an event with an immediate increase in failure rate provides a finely –detailed explanation for "infant mortality" which can be compared with parametric models such as the weibull.

3.1. Probability and Regression Model

We assume each of N units is under observation for some interval of time [0, T].The method can be easily adapted to allow for units with missing observation periods (known in advance).Let $\mathbb{T}$ denote the (finite) set of times at which an event occurs. The unit to fail at time t (if any)is denoted as $i(t)$;ties are broken in preprocessing, if necessary, by randomly selecting tied units and shifting their failures by one second. For any unit j under observation at time t denote by $\tau_{t,i}$ the time of the treatment (which is here the time of previous outage).It turns out to be important to remove "unobserved " units (i.e. those for which $t - \tau_{t,i}$ is unknown due to left – truncation of the study);thus ,the index - set of fully observed units at time t is given by $\Re(t)$,and commonly called the " risk set ".Note that if the mechanism for observation is independent of the treatment and failure processes (i.e., if it is fixed in advance),this does not introduce bias [1].We consider the non – parametric rate model as follows:

$$\lambda(t;i) = \lambda_0(t)\psi(t - \tau_{t,i});$$

$\psi(.) = e^{\phi(.)}$

That is , 20 seconds after treatment the effect will be to make failure $\psi(20) = e^{\phi(20)}$ times more likely. The full likelihood is then [4]:

$l(\lambda_0(.), \psi(.)) = \left(\Pi_{t \in \mathbb{T}} \lambda_0(t) \psi(t - \tau_{t,i})\right) \times e^{-\int_0^T \Sigma_{j \in \Re(t)} \lambda_0(t) \psi(t - \tau_{t,i})\, dt}$

The estimation proceeds in two steps, detailed in Appendix B. The λ_0 term is first shown to be estimated as 0 at all times t $\notin$ $\mathbb{T}$.Thus,conditioning on the failure times ,the λ_0 term is cancelled out (since it affects all units equally).This allows convenient estimation of $\psi(t) = e^{\phi(t)}$. After the estimation of $\psi(t)$,the λ_0 term may be estimated by a weighted non parametric estimator (which uses the estimate of ψ) .For simplicity, in this paper we fit the λ_0 as a constant (within each network) by using the method of moments (Appendix C).Since only the time since last treatment is tracked , it is implicitly assumed that any prior treatments are immediately " forgotten" by the system upon administration of a new treatment. The connection between the hazard λ and the distribution function is detailed in Appendix A. The information reduction induced by the Cox frame work should be very useful, especially in the Gaussian process setup which scales as O (p^3) in the number of predictors. To achieve further reduction of data for numerical stability and to expedite cross – validation, we "bin " values of $t - \tau_t$, (which can be viewed as the predictors of $\phi(t - \tau_t)$) into percentiles.

3.2. Gaussian Process

We apply a Gaussian process prior to the values $\phi(t)$ with a radial basis function. After the standard marginalizing of the prior [21] on to $t \in \mathbb{T}$, the $\phi(t)$ are normally distributed with mean 0 and covariance matrix K with $K_{t,t'} = a\, e^{-(t-t')^2/b}$

This marginal prior distribution will be referred to as π.The parameters a, b are the marginal variance and so – called "characteristics time – scale '' respectively. We use the parameter values a = 5, b = 1.10^3 based on good performance on the training data.Aternatively, cross – validation on a grid search on these parameters can be used to obtain approximate "point estimates '' of a, b.Details of the fitting process are in Appendix D.The smoothed fit using the Gaussian process prior. It is much better than the unsmoothed fit.

IV. APPLICATION

It is common for physicians who are unfamiliar with the complexity of the fibromyalgia syndrome to view the patient's symptoms as a result of a hormonal deficiency. The fatigue, mental sluggishness, and muscle pain of hypothyroidism are reminiscent of fibromyalgia complaints. In general, routine endocrine test results are normal in fibromyalgia. Perhaps the most striking "endocrine"finding in fibromyalgia is its predominance in women [25].However, there is no obvious relation to life – time changes in estrogen secretion because fibromyalgia occurs in teenagers and postmenopausal women. In addition, estrogen replacement does not alleviate the symptoms of fibromyalgia. A Para diagrams to explain the complexity of fibromyalgia symptomatology proposes that it is a stress-related syndrome in which a disordered hypothalamic-pituitary-adrenal (HPA) axis acts as a final common pathway linking of fibromyalgia to other stress-related somatic and psychiatric syndromes [8,19,26]. There are close links between the HPA and the HP- growth hormone (GH) axis. For instance,corticotropin releasing factor (CRF) stimulates the release of hypothalamic somatostatin, which acts to restrain the pituitary secretion of GH.This views discusses the evidence for disturbances in GH secretion and their postulated link to a disordered HPA axis in patients with fibromyalgia.

4.1 Physiology of the hypothalamic – pituitary growth hormone / insulin-like growth Factor-1 axis.

The GH /Insulin-like growth factor – I (IGF-1) axis is subject to exquisite regulation by multiple internal physiologic variables and external cues [23].GH is the only pituitary hormone that is influenced by stimulatory and inhibitory hypothalamic hormones. The normal pulsatile secretion of GH depends on the tonic balance of stimulatory GH-releasing hormone (GHRH) and inhibitory somatostatin. Under normal circumferences, GH produced only when GHRH is secreted in the setting of low levels of somotostatin tone. Therefore, the regulation of GH secretion depends on the relative amounts of GHRH and somoatostain that are released from the hypothalamus into the hypothalamic – hypophyseal portal venous system.GH secretion has a diurnal pattern of secretion that is linked to stages 3 and 4 of the sleep cycle [24],but this association is less evident with older age.Furtheremore ,intentional sleep deprivation almost totally abolishes GH production .The increased pulsatile GH secretion that occurs during deep sleep (in stages 3 and 4) is postulated to result from reduced hypothalamic somatostain tone combined with increased GHRH release. There is an exponential decline in the daily GH secretion rate as a function of age, such that every 7 years of age beyond 18 to 21 years of age results in an approximately 50% decline. There is negative correction between the daily GH secretion rate and body mass index (BMI).For each increase in BMI of 1.5kg/m^2, there is a 50% decrease in the amount of GH secreted daily. Studies using GHRH-stimulation and pyridostigmine (to reduce somatostain tone) indicate that

combined defects in GHRH release and somatostain excess are involved in the GH deficiency that often accompanies obesity. At puberty and throughout adulthood, gonadal steroid hormone concentrations in blood positively influence the intensity of GH secretion. The major mediator of most GH-related anabolic activity is IGF-1.Insulin-related growth factor-I is secreted mainly by the liver in response to GH release. It has a half-life of approximately 21 hours and does not exhibit much diurnal variation; its plasma level is considered to reflect the integrated pulses of GH hormone secretion over the previous 48 hours [16].

4.2 Adult growth hormone deficiency

Growth hormone deficiency in adults has been associated with a miscellany of symptoms that are similar to those described by patients with fibromyalgia, such as low energy [15],poor general health reduced exercise capacity[13],muscle weakness ,cold intolerance ,impaired cognition ,dsthymia ,and decreased lean body mass .Furthermore,GH is important in maintaining muscle homeostasis. It was theorized that suboptimal levels may factor into the impaired resolution of muscle microtrauma in patients with fibromyalgia [3].The treatment of GH deficiency in adult has been reported to improve quality of life and energy level [5] ,reduced pain ,improve depression ,enhance self-esteem ,improve cholesterol and low-density lipoprotein levels ,enhance cognitive psychometric performance augment stroke volume and improve exercise capacity and muscle strength [13].

4.3 Growth hormone treatment in patients with fibromyalgia

This study has reported on the use of GH replacement therapy in patients with fibromyalgia and low levels of IGF-1[4](Fig.1).In this study,50 patients with fibromyalgia were enrolled in a 9-month,double-blind,placebo-controlled trial. There was a prompt increase in IGF-1 levels within the first month in all patients receiving GH injections, which was sustained throughout the 9 – month trial. The placebo group showed no such increase. Only the group treated with GH achieved a significant improvement between baseline and finish. There was a significant improvement of the group treated with the GH compared with the placebo group. No unexpected adverse reactions occurred in the group treated with GH.Carpaltunnel syndrome symptoms occurred in 28 % of the patients with GH at some time during the treatment period (only one control patient had such symptoms).Carpal tunnel syndrome symptoms were managed by reducing the GH dose. No patients were experiencing carpal tunnel syndrome symptoms at the end of the study. Although no patient had a complete remission of symptoms, several patients on GH experienced an impressive improvement in their function ability; In general, there was a lag of approximately 6 months before patients started to note improvement. All the patients who experienced improvement on GH suffered a version of symptoms over a period of 1 to 3 months after stopping GH treatment. A preliminary study of

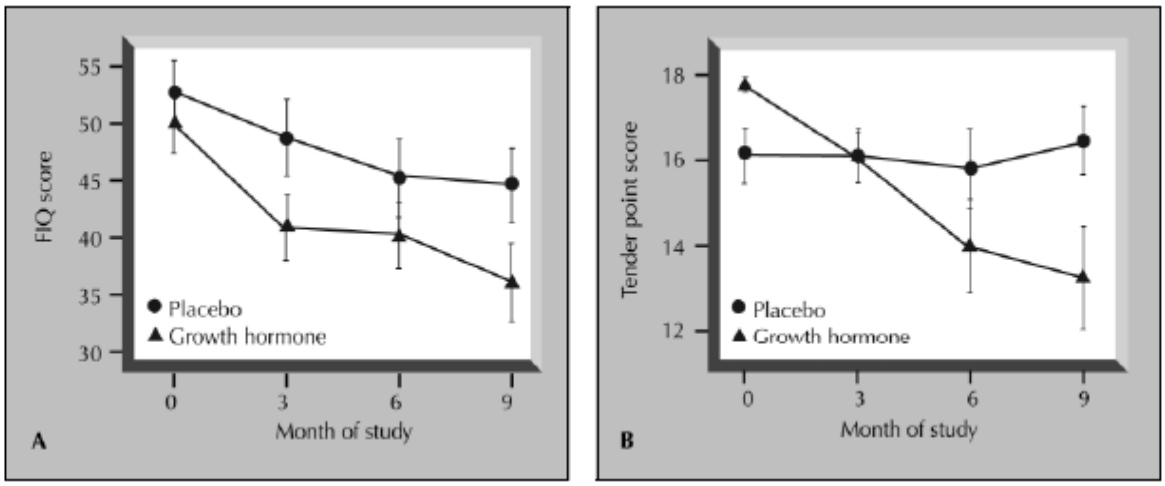


Figure - 1 - A, The fibromyalgia Impact Questionnaire (FIQ).**B,** Number of tender points. Clinical results of a 9 – month controlled trial of growth hormone therapy in patients with fibromyalgia. The FIQ and the number of fibromyalgia tender points improved significantly toward the end of the study period. The values shown are the means and standard deviations.

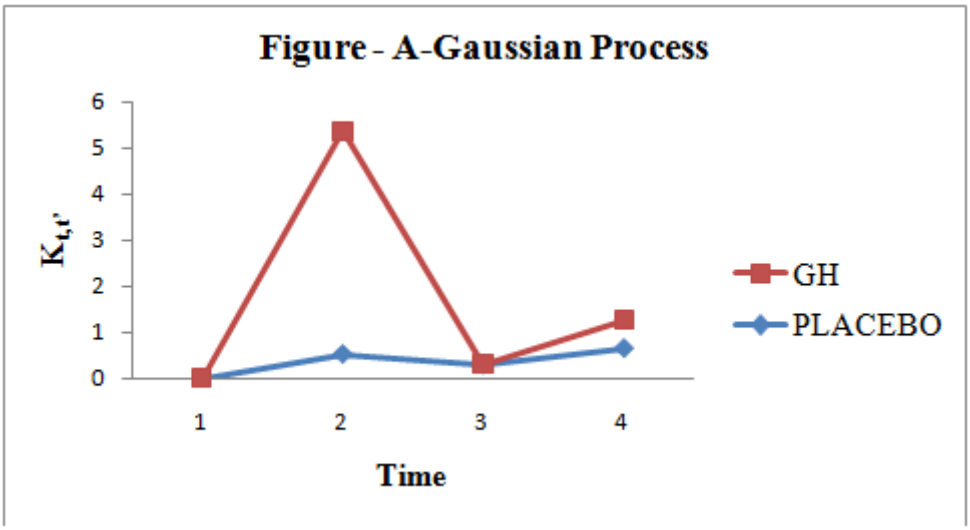
supplement GH therapy in patients with chronic fatigue syndrome has reported somewhat similar and encouraging results[17].There have been concerns about elevated IGF-1levels being associated with an increased risk of some cancers [7,16,22,27].However,GH therapy aims to normalize, not increase,IGF-1 levels. It is possible that the low IGF-1levels associated with older age have protective effect on the development of

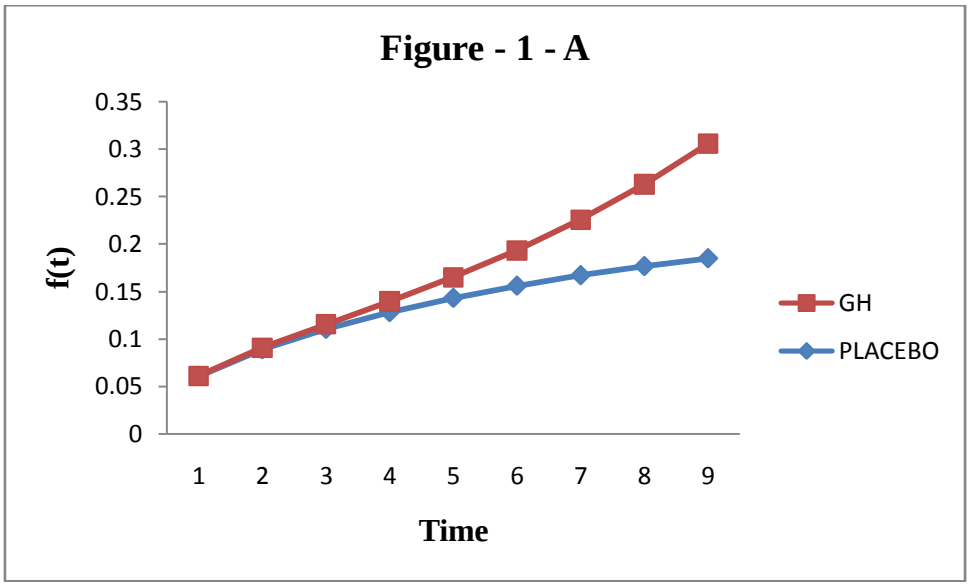
some cancers. If this notion is correct, then normalization of IGF-1 levels could put some patients at increased risk of developing cancer.However,adult GH deficiency is associated with an increased mortality rate as a result of accelerated atherosclerotic cardiovascular disease [5].Because fibromyalgia affects 2% to 4% of all adults, it must be a major contributing factor to many cases of adult GH deficiency, with consequences for an impaired quality life, increased morbidity rate, and sometimes mortality.Unfortunately,GH therapy is very expensive and beyond the means of most patients with fibromyalgia and the budgets of most third party payers. The decision to treat patients with fibromyalgia with GH supplementation must await confirmatory long-term studies of its efficacy and side affects profile.Hopefully,a better understanding of the pathophysiologic basis for GH deficiency in fibromyalgia will yield novel approaches for treating patients with GH-deficient fibromyalgia that is more physiologic than daily GH injections.

4.4 Possible causes of growth hormone deficiency in patients with fibromyalgia

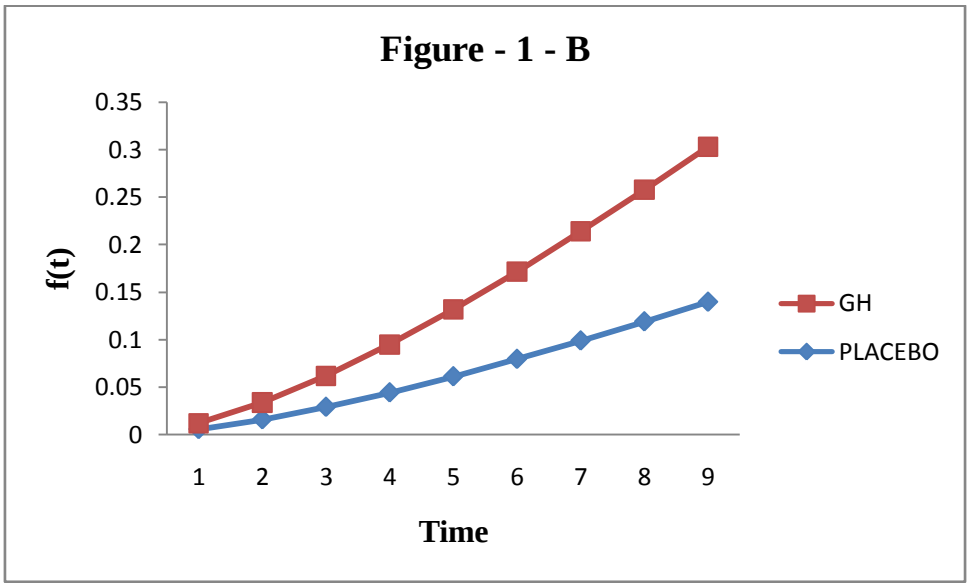
The complexity of the GH response has been noted. Low IGF-1 levels in patients with fibromyalgia are unlikely to have an anatomic cause. It seems most likely that the problem is a physiologic GH deficiency. Unlikely healthy controls, patients with fibromyalgia were unable to mount a GH response to exercise, deposit reaching an anaerobic threshold. However, when patients with fibromyalgia were administered pyridostigmine 1 hour before exercising, they were able to mount a reasonable GH response [20].Because pyridostigmine is known to reduce a somatostatin tone in the hypothalamus ,this result is compatible with the notion that GH deficiency in fibromyalgia is potentially reversible problem that has a physiologic basis (i.e, increased hypothalamic somatostatin tone).The effects of HPA axis dyregulation secretion are postulated to be relevant to GH deficiency in fibromyalgia [18].Rheumatologists are familiar with the growth retardation that occurs in some children with juvenile rheumatoid arthritis or systemic lupus erythematosus who have been treated with long – term corticosteroids. This stunting is caused by the inhibitory effect of iatrogenic hypercortisolemia on GH secretion. Cortisol inhibits GH production through the mechanism of an increased density of beta-adrenergic receptors, with resulting stimulation ofadenyl cyclase and somatostatin release [58].Corticotrophin-releasing hormone is the major mediator of the HPA / sympathetic response to physical and psychological stressors. Neeck and Riedel have hypothesized that a stress-induced increase in CRF is the common denominator linking the disturbed HPA axis and reduced GH secretion in fibromyalgia. The critical link is the observation that CRF increases hypothalamic somatostatin tone. It seems difficult to reconcile the well – described association of hypercortisolemia and defective GH production with the HPA defect described in fibromyalgia, namely a hypcortisolemic response to stressors. This paradox may be a result of the diverging consequences of acute versus chronic stressors. Therefore, in the case of persistent CRF secretion, its physiologic effects on cortisol secretion ultimately become blunted[12].Maybe the subpopulation of patients with fibromyalgia with defective neuroendocrine and sympathetic stress responses has reached this "third stage" of Selye's general adaption syndrome. There are several other examples of human stress-related disorders that exhibit an impaired cortisol secretion, such as chronic pelvic pain syndrome [10].chronic fatigue syndrome, post-traumatic stress disorder [11], and overtraining syndrome .All these conditions are characterized by an increase in central HPA function with a paradoxic blunting of the adrenal cortisol response. It appears that fibromyalgia is one of several other chronic disorders that are characterized by a hypoactive stress response in terms of HPA axis and a reduced sympathetic response [6].

V. MATHEMATICAL RESULT

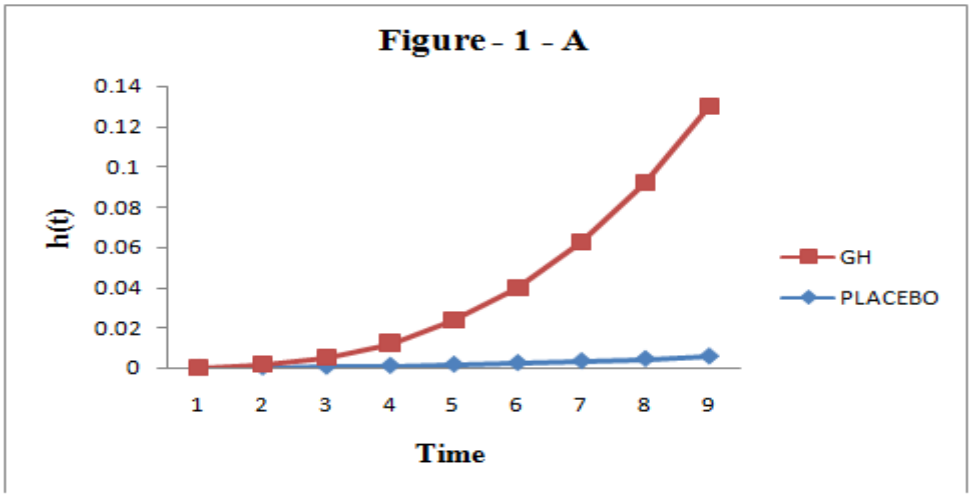




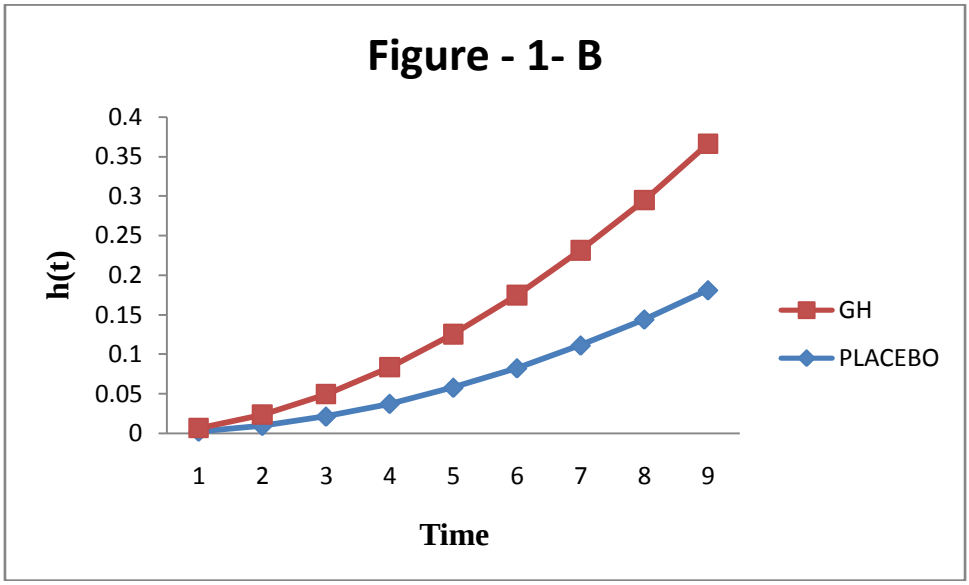
Probability density function for Placebo and GH deficiency patients corresponding to figure -A



Probability density function for Placebo and GH deficiency patients corresponding to figure -B



The values of Hazard rate for Placebo and GH deficiency patients corresponding to figure -A



The values of Hazard rate for Placebo and GH deficiency patients corresponding to figure -B

VI. CONCLUSION

This paper presented a new method of estimating failure rate using a semiparametric model with Gaussian process smoothing. The method is able to provide accurate estimation based on historical data and it does not make strong a priori assumptions of the failure rate pattern (e.g., constant or monotonic). Our empirical studies of applying such an approach in power system failure data and a comparison of this approach will other existing models show its efficacy and accuracy. This method may also be used in estimating reliability for many other systems, such as software systems or components. It is impossible to arrive at any definitive conclusions as to the link between HPA axis dysfunction and GH deficiency in fibromyalgia. Nevertheless, the presence of a Mathematically significant GH deficiency in a subpopulation of patients with fibromyalgia seems well-established. Understanding its links with chronic stress may provide some insights into mechanisms where by environmental stressor and developmental factors interact with inherited susceptibility to modify gene expression, and ultimately generate symptoms [6, 20]. Finally we conclude our Mathematical results in the figure – A is well fitted with the Gaussian process and the maximum value of Growth Hormone deficiency at the time has been obtained. This will be helpful for the medical professional.

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