Neurons' Firing Features

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1 Introduction

The understanding of the main functions of the brain, those that preside over the transmission and the elaboration of the sensory stimuli, the memorization and the classification of the information, have multiple repercussions of practical and immediate nature, from the disciplines in medical field, like the study of the cerebral dysfunctions, to those in computer science-technological field, as an example the study of the automatic systems for elaboration, memorization, classification and acknowledgment of information.

Because the neurons are the primary functional unit of the nervous system, the study of their behavior is important to understand how the brain functions. Neurons are electrically excitable cells that process and transmit information. They typically respond to a stimulus by producing complex spike sequences that reflect both the intrinsic dynamics of the neuron and the temporal characteristics of the stimulus. The action potential (spike) generation also depends on the recent history of cell firing. For a few milliseconds just after an action potential has been fired, it may be virtually impossible to initiate another spike. This is called the absolute refractory period.
Moreover neurons can fire in two distinct modes, tonic and burst. This firing mode strongly affects the nature of the signal that is relayed to the cortex. In tonic mode, a cell's firing rate quite accurately and linearly reflects the amplitude and duration of an excitatory input. In contrast, burst firing is characterized by high-frequency of action potentials and represents a less linear relay of its input. The complexity of their behavior doesn't permit to describe the spiking patterns deterministically, so that they are treated probabilistically. The statistical characteristics of the spiking patterns are rich in information on the neuron's way of functioning, and for this they are studied in depth.

The signal emitted from the neurons for the passage of the information runs along pathways that connect the various zones of the brain. Neuronal processing in cerebral cortex and signal transmission from cortex to brain stem have been studied extensively, but little is known about the feedback pathways that ascend from brain stem to cortex.
In this context Professor Peter L. Strick, Co-director of the Center for the Neuronal Basis of Cognition (CNBC) at the University of Pittsburgh, discovered the existence of an ascending pathway coursing from the superior culliculus (SC) to the frontal eye field (FEF) via mediodorsal thalamus(MD), using anatomical methods. Dr. Marc Sommer, Assistant Professor in the department of Neuroscience at the CNBC, and his lab, discovered what this

pathway does (sends feedback information about orienting to the FEF). One of the main goals of his lab is to understand it even better, and compare it with other feedback pathways. Their overall hypothesis is that the pathway from SC has an influence on FEF neurons. To test this hypothesis, they look for evidence of its strength. Do MD and FEF neurons respond as if dominated by the influence of SC? Or do MD and FEF neurons act differently from the SC, implying they get big influences from other inputs too (such as visual cortex)? They are trying to answer these questions by studying the statistics of firing patterns: the inter-spike interval (ISI) distributions, the probability density of the time interval between two adjacent spikes.

Our role in this project has been to estimate the ISI distribution that reflects the influence of the refractory period and the ability of some cells to fire in the two distinct modes, tonic and burst. Two models are considered, a simpler one where the ISI are modeled utilizing the sum of a normal distribution, that capture the effect of the refractory period, and an exponential distribution, that represents the "true" ISI; the second is a mixture model, that is a combination of other probability distributions, in this case is given by the sum of a normal distribution and a mixture of two exponential distributions, to allow to reproduce the tonic and burst behavior. Once estimated the parameters for the two models for every neuron, pertaining to the three brain areas cited , we performed goodness of fit test for each model and model selection test for classifying the neurons as able to fire in the two modes or not. The goal is to understand if the characteristic of firing in tonic and regular mode is predominant only in one part of the brain, or if this feature influences the behavior of the neurons along the pathway.

2 Data Set

Our data set is composed of all single neuron data from three different part of the brain; superior culliculus (SC), frontal eye field (FEF) and mediodorsal thalamus(MD).
For every neuron we have the ISI distribution, that is the distribution of the time interval between two spikes expressed in microseconds (ms), during the control period with two different time windows, one of 100 ms, the other one of 350 ms. For time window equal to 100, we have 24, 47, and 20 data files for SC, FEF, and MD, respectively. And for time window equal to 350, we have 34, 72, and 39 data files for SC, FEF, and MD, respectively. In the control period the behavior of the neurons is not effected by any external factor, such as visual stimuli, permitting to have a good idea of their natural functioning.

The FEF is located in prefrontal cortex, the part of the cerebral cortex (or gray matter) that is important for making decisions. The main function of the FEF is to integrate lots of information (vision, memory, state of the body) and come to a decision about where to look next. It gets heavy input from the primary visual cortical areas further back (posterior) in the cerebral cortex. Also it gets major input from the pathway of interest: it gets direct projections from mediodorsal thalamus (MD), from neurons that in turn get input from the superior colliculus (SC).

MD is a zone of the thalamus. The thalamus is a large mass of gray matter deeply situated in the forebrain. All information that reaches the cerebral cortex (gray matter) of the brain from below must be relayed by neurons of the thalamus. In general, MD thalamus is reciprocally interconnected with all of the prefrontal cortex (the decision area of cortex). So in diseases like schizophrenia where prefrontal cortex is damaged, MD is damaged by association. The part of MD that is connected with the FEF is a tiny, concentrated volume of neurons.

The SC sits on top of the brainstem. In general, it is critical for orienting the body. All animals, even the lowest lizards and frogs, have an SC or something very much like it. Activity in the SC causes the eyes and head to move, as if looking for something. This is "orienting", or directing the computational power of the whole brain toward a specific object of interest in the world. The SC gets massive information from all over the brain and sends commands down to the lower brainstem centers that move the eye muscles and neck muscles. The SC is interesting in this study because it, also, sends a big projection up to the MD, onto relay neurons that in turn project to the FEF. This pathway goes "the wrong way" – instead of helping to orient the body, it seems to be sending information to the cerebral cortex, "telling" the cortex that the body or eyes are about to move.

3 Experiment

During the experiment, the monkey faced a tangent screen on which visual stimuli were projected by an LCD monitor. Visual stimuli were 0.3 by 0.3 blue or red spots ($(0.6cd/m^2)$) with dim ambient room light. Personal computers controlled the presentation of visual stimuli and recorded at 1 kHz the eye position the occurrence of action potentials, and the timing of task events.

Each task is composed of 3 parts, the control period, the visual stimulus and the movement. The control period is at the very beginning of the trial. This is when the animal is just looking around, just waiting, and not engaged in a formal task. Then there is the usual stimulus given by the spotlight, and in the end the saccade movement. A rapid intermittent eye movement occurs when the eyes fix on one point after another in the visual field. At the end of each trial, the monkey is rewarded. The Control data, the data from the control period, are critical because they tell us how much the processes of the neurons fluctuate in the steady state, when nothing in particular is happening in the visual world or with regard to eye movements.

More specifically, the data we have consist of (1) Control 100, (2) Control 350, (3) Entire Trials, (4) Fixation, (5) Mem, (6) Sac, and (7) Vis. (1) and (2) are explained in the previous paragraph, and the difference is the width of time window; thus, Cont350 has longer ISIs and larger data sets. (3) Entire Trials contain all the ISI in each trial from start to end. (4) Fixation is a time period when the monkey is steadily looking at the central fixation spot, waiting for the peripheral visual target to appear. (5) Mem is a 200ms period when the monkey remembers the location of the visual target. (6) Sac is a 100ms period leading up to the start of the saccadic eye movement. And (7) Vis is a 100ms period during the visual response of the neurons. And we are given those 7 types of data sets for each of the three different brain areas, FEF, SC, and MD. Although there are 7 types, we will focus on (1) and (2) for those three brain areas.

4 Methods

4.1 Single and Dual Process Models

As with other types of memory-less situations, inter-spike intervals (ISIs) have an exponential distribution. However, an ISI consists of two components: 1) refractory period and 2) actual ISI. A refractory period is a time interval when a neuron fires a spike and takes a rest for sometime, and it cannot fire another spike during a refractory period. And refractory periods are considered to be normally distributed. Actual ISIs are the ones that have an exponential distribution. Thus, we are considering a convolution model of a normal (with mean μ and variance σ^2) plus an exponential (with mean β), which we call the single process model. The probability density function is;

$$f_s(x) = \frac{1}{\beta} e^{-\frac{x}{\beta}+\frac{\mu}{\beta}+\frac{\sigma^2}{2\beta^2}} \Phi\left(\frac{x-\mu-\frac{\sigma^2}{\beta}}{\sigma}\right)$$

where Φ is the cumulative distribution function of a standard normal. Thus the model has three parameters, and we will estimate them by taking the maximum likelihood approach. See Appendix A for the details of deriving the function.

Another underlying assumption is that a neuron has two stages that it switches between with some probability, and therefore it has two exponentials for the actual ISI. We call it the dual process model. Now the probability density function is as follows (we use rate parameters λ for this model to avoid confusion with β in the single process model);

$$f_d(x) = (1-p)\lambda_0 e^{-x\lambda_0+\mu\lambda_0+\frac{\sigma^2\lambda_0^2}{2}} \Phi\left(\frac{x-\mu-\sigma^2\lambda_0}{\sigma}\right) + p\lambda_1 e^{-x\lambda_1+\mu\lambda_1+\frac{\sigma^2\lambda_1^2}{2}} \Phi\left(\frac{x-\mu-\sigma^2\lambda_1}{\sigma}\right)$$

And p is the probability that an ISI comes from the exponential with λ_1. This model has 5 parameters, and we again will take the maximum likelihood approach to estimate them. The rate estimate for the burst mode should be larger than that of the regular mode, because a larger rate means more spikes in a unit time period.

To determine the "goodness" of our estimators we looked for their consistency and how fast they should converge to the true values of the parameters (more details in the Appendix). For doing that we looked at the mean squared error MSE and at the rate at which it decreases as n, the sample size, increases.
As we can see from the Figure 1, MSE for the model with three parameters, (μ, σ, β), it decreases rapidly, from a value of $MSE = 3067$ with a simple size $n = 30$ to a value of $MSE = 85$ for $n = 50$, only 20 data points more, but really a better estimate. Currently, we do not have the same kind of plot for the dual model, but the estimate indicates that we need more than 100 observations to attain the same accuracy as the single model.

4.2 Analysis

Now we show how these two models actually fit with one data set. Applying the grid search to find the best initial values and then using nlm function in R, we find estimates to be: $\hat{\beta} = 12.02$, $\hat{\mu} = 4.502$, $\hat{\sigma^2} = 5.129$, $\hat{\lambda_0} = 0.1059$, $\hat{\lambda_1} = 0.0590$, $\hat{p} = 0.3414$. The dotted line

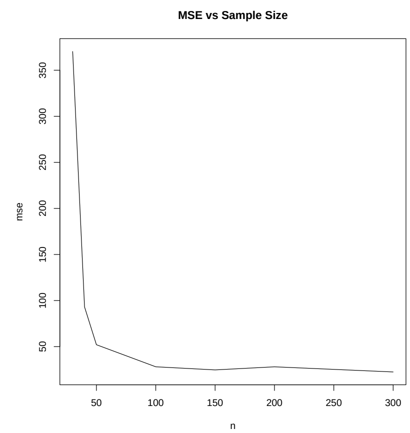

Figure 1: MSE for the single process model

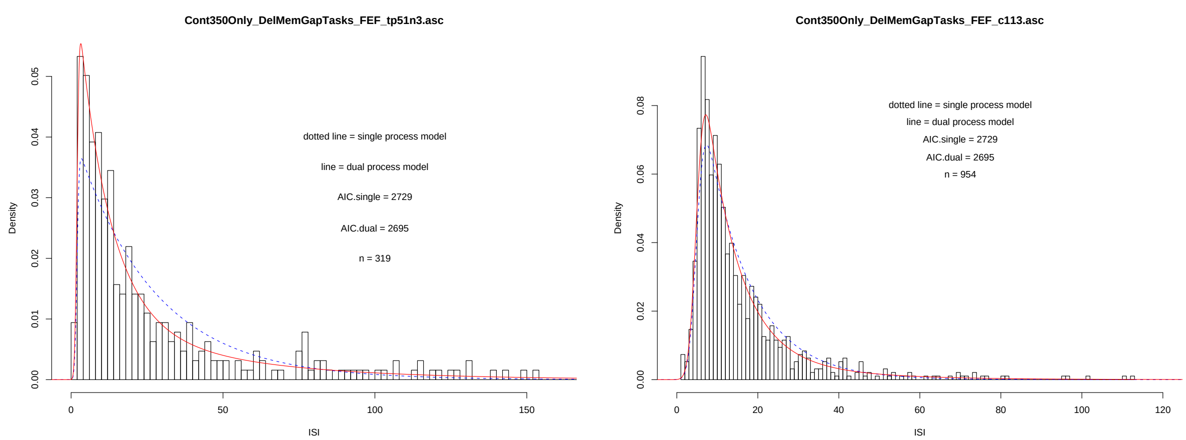

Figure 2: Two estimates

describes the density estimate for the single process model, and the line for the dual model. As can be seen in the plot, the two models have produced similar lines. In fact, many of the data sets give two lines very close to eath other.

The second data set shown here have estimates; $\hat{\beta} = 25.72$, $\hat{\mu} = 1.938$, $\hat{\sigma^2} = 0.3492$, $\hat{\lambda_0} = 0.0966$, $\hat{\lambda_1} = 0.0228$, $\hat{p} = 0.4599$. In this data set, the two models give somewhat different density estimates. It can be checked even visually.

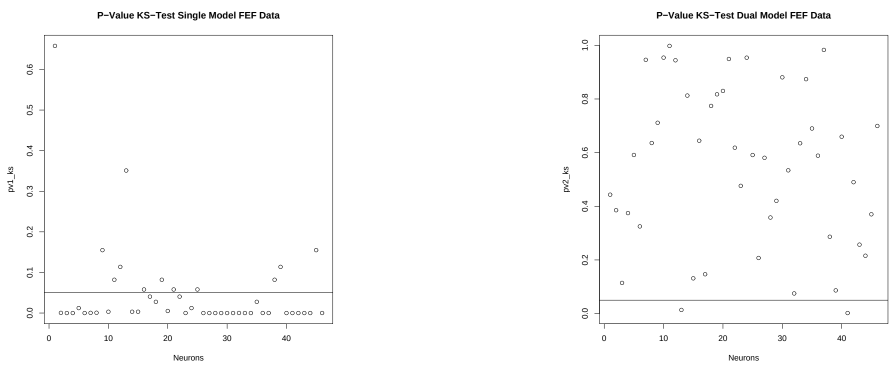

Figure 3: P-values for KS test for the single (left) the dual model (right) in Cont100 FEF

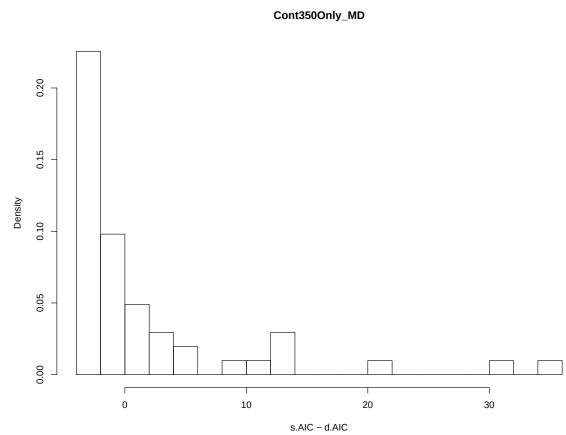

Figure 4: Histogram of the AIC difference

4.2.1 Kolmogorov-Smirnov test

First, we see whether or not those two models fit our data adequately by applying the Kolmogorov-Smirnov test. The details of this method is described in Appendix A. Figure 4 shows the p-values for testing the single process model for Cont100 FEF data sets. Those p-values that are smaller than 0.05 mean that the single process model does not fit those data files adequately. 26% of the Cont100 FEF data files resulted in the acceptance of the single model. Figure 5 shows that the dual process model fit 95% of the data files adequately, which indicates the improvement made by applying the dual process model rather than the single process model. Other acceptance percentages for Cont100 are: 12.5% for SC single, 100% for SC dual, 65% for MD single, and 100% for MD dual.

4.2.2 AIC (Akaike Information Criterion)

Our goal is to find the best model for ISI ditributions of each neuron, so that we can classify neurons based on the ability of having one or two modes . One of the measurements often used in model selection is AIC, which is defined as $AIC = -2l + 2k$, where l is the loglikelihood and k is the number of parameters in the model, and the second component is

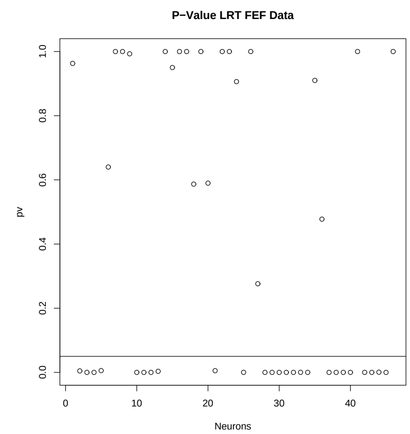

Figure 5: P-values for LRT for FEF Cont100

the penalization term. The smaller the AIC value is, the better the fit is. The plot shows the difference between the two models' AIC scores in the Cont350MD data files. A large difference indicates that the dual process model fits far better than the single process model. For this analysis, we employ the ordinary interpretation; that is, we choose the model that gives a smaller AIC value. Thus, those neurons whose AIC difference values are greater than 0, we would choose the dual process model. However, this method does not provide us with the significance of the difference, i.e., we would not know how big a difference should be in order for us to prefer one model over the other. Thus we move on to the loglikelihood ratio test in the subsequent subsection.

4.2.3 LRT

Because the single is the nested model of the dual process model, that is, we can set $p = 0$ in the dual model and construct the single model, we decide to use the loglikelihood ratio test (see the appendix for details) to measure the preference of one model over the other. Figure 7 shows taht 45% of the neurons in the FEF data have p-values greater than 0.05, which indicates that the single model is adequate for those neurons. For 58% of the neurons in SC, the single model is adequate enough, and the percentage for MD is 70%. By comparison, we notice that the AIC conclusions agree with those from LRT.

5 Conclusion and Further Work

As noted in the analysis section, 42% of SC, 30% of MD, and 55% of FEF preferred the dual process model over the single process model. Dr. Marc Sommer noted that if the influence of the SC is strong, then the ISI statistics of MD and FEF neurons should be similar to those of SC neurons. And that is not what we are observing in our analysis, thus our plausible interpretation is that the effect of the SC is rather weak. And this statistically different activity pattern indicates that MD probably has some inputs from an area different from SC, and that FEF probably has a somewhat large number of inputs from some area besides

SC.

For future studies, it might be interesting to see similarities and differences of the probability of switching between the two modes (regular and burst) betweeen the neurons belonging to the same area and between different brain areas, or to investigate the possibility of two different distributions for the two modes instead of sharing one distribution as in our analysis. We can also compare the regular and bursty Poisson rates. It may be worth trying the local variation, which measures how much variation exists between adjacent ISIs, as was done in Shinomoto, S., Shima, K., and Tanji, J. (2003). We may try other data files such as Entire Trial that are different parts of the experiment.

6 Appendix A

6.1 Single Process Model Probability Density Function

Let $Y \sim \mathrm{N}(y;\mu,\sigma^2)$ and $Z \sim \exp(z;\beta)$. Then $f_Y(y) = \frac{1}{\sqrt{2\pi}\sigma}e^{-\frac{(y-\mu)^2}{2\sigma^2}}$ and $f_Z(z) = \frac{1}{\beta}e^{-\frac{z}{\beta}}$ and $F_Z(z) = 1 - e^{-\frac{z}{\beta}}$

Now, with letting the Φ denote the cumulative ditribution function of the standard normal, the cumulative distribution function of $X = Y + Z$ is;

$$
\begin{aligned}
F_X(x) = P(X \le x) = P(Y + Z \le x) &= \int P(Z \le x - y \cap Y = y)dy \\
= \int_{-\infty}^{x} F_Z(x-y)f_Y(y)dy &= \int_{-\infty}^{x}(1 - e^{-\frac{x-y}{\beta}})\frac{1}{\sqrt{2\pi}\sigma}e^{\frac{(y-\mu)^2}{2\sigma^2}}dy \\
= \int_{-\infty}^{x}\frac{1}{\sqrt{2\pi}\sigma}e^{-\frac{(y-\mu)^2}{2\sigma^2}}dy &- e^{-\frac{x}{\beta}}\int_{-\infty}^{x}\frac{1}{\sqrt{2\pi}\sigma}e^{-\frac{y}{\beta}}e^{\frac{-y^2+2y\mu-\mu^2}{2\sigma^2}}dy \\
= \Phi\left(\frac{x-\mu}{\sigma}\right) - e^{-\frac{x}{\beta}+\frac{\mu}{\beta}+\frac{\sigma^2}{2\beta^2}}&\int_{-\infty}^{x}\frac{1}{\sqrt{2\pi}\sigma}exp\left(\frac{-(y-(\mu+\frac{\sigma^2}{\beta}))^2}{2\sigma^2}\right)dy \\
&= \Phi\left(\frac{x-\mu}{\sigma}\right) - e^{-\frac{x}{\beta}+\frac{\mu}{\beta}+\frac{\sigma^2}{2\beta^2}}\Phi\left(\frac{x-\mu-\frac{\sigma^2}{\beta}}{\sigma}\right)
\end{aligned}
$$

By differentiation;

$$
\begin{aligned}
f_X(x) &= \frac{1}{\sqrt{2\pi}\sigma}e^{-\frac{(x-\mu)^2}{2\sigma^2}} + \frac{1}{\beta}e^{-\frac{x}{\beta}+\frac{\mu}{\beta}+\frac{\sigma^2}{2\beta^2}}\Phi\left(\frac{x-\mu-\frac{\sigma^2}{\beta}}{\sigma}\right) - e^{-\frac{x}{\beta}+\frac{\mu}{\beta}+\frac{\sigma^2}{2\beta^2}}\frac{1}{\sqrt{2\pi}\sigma}e^{-\frac{(x-\mu-\frac{\sigma^2}{\beta})^2}{2\sigma^2}} \\
&= \frac{1}{\sqrt{2\pi}\sigma}e^{-\frac{(x-\mu)^2}{2\sigma^2}} + \frac{1}{\beta}e^{-\frac{x}{\beta}+\frac{\mu}{\beta}+\frac{\sigma^2}{2\beta^2}}\Phi\left(\frac{x-\mu-\frac{\sigma^2}{\beta}}{\sigma}\right) - \frac{1}{\sqrt{2\pi}\sigma}e^{-\frac{(x-\mu)^2}{2\sigma^2}} \\
&= \frac{1}{\beta}e^{-\frac{x}{\beta}+\frac{\mu}{\beta}+\frac{\sigma^2}{2\beta^2}}\Phi\left(\frac{x-\mu-\frac{\sigma^2}{\beta}}{\sigma}\right)
\end{aligned}
$$

6.2 Dual Process Model Probability Density Function

Here we have two exponentials, Z_0 and Z_1 with rate parameters λ_0 and λ_1, respectively. Now let Z be the mixture of Z_0 and Z_1, with p equal to the probability that the ISI comes from Z_1. Now,

$$f_Z(z) = (1-p)\lambda_0 e^{-\lambda_0 z} + p\lambda_1 e^{-\lambda_1 z}$$

And

$$F_Z(z) = (1-p)(1-e^{-\lambda_0 z}) + p(1-e^{-\lambda_1 z})$$

And following the same way as the single process model we derive;

$$f(x) = (1-p)\lambda_0 e^{-x\lambda_0+\mu\lambda_0+\frac{\sigma^2\lambda_0^2}{2}}\Phi\left(\frac{x-\mu-\sigma^2\lambda_0}{\sigma}\right) + p\lambda_1 e^{-x\lambda_1+\mu\lambda_1+\frac{\sigma^2\lambda_1^2}{2}}\Phi\left(\frac{x-\mu-\sigma^2\lambda_1}{\sigma}\right)$$

6.3 MSE

The quality of a point estimate can be assessed by the mean squared error (MSE), defined by

$$MSE = E_\theta(\hat{\theta}_n - \theta)^2$$

where the $E(.)$ refers to the expectation with respect to the distribution

$$f(x_1, ..., x_n; \theta) = \prod_{i=1}^{n} f(x_i; \theta)$$

that generate the data.
The MSE can be written as

$$MSE = bias^2(\hat{\theta}_n) + V_\theta(\hat{\theta}_n)$$

where the bias of an estimator is defined as

$$bias(\hat{\theta}_n) = E_\theta(\hat{\theta}_n) - \theta$$

that is $\hat{\theta}_n$ is unbiased estimator for θ if $E(\hat{\theta}_n) = \theta$. V_θ is the variance of the estimator.
If the $bias \longrightarrow 0$ and $V \longrightarrow 0$ as $n \longrightarrow \infty$ then $\hat{\theta}_n$ is consistent, that is $\hat{\theta}_n \longrightarrow^P \theta$

6.4 Kolmogorov-Smirnov test

The objective of the Kolmogorov-Smirnov test is to test whether a sample of a random variable belongs to a predefined distribution. The null hypothesis must therefore specify both the type of distribution function and its parameters (the null hypothesis states that the sample belongs to the distribution specified). The alternative hypothesis is that the assumed probability distribution function does not match the underlying one. The idea behind the Kolmogorov-Smirnov test is quite simple: the maximum difference between the assumed cumulative pdf and the random sample to be investigated is used to decide whether the random sample belongs to the distribution or not.

$$H_0 : F(x) = F^*(x) versus H_1 : F(x) \neq F^*(x)$$

where $F(x)$ is the unknown distribution of the random sample, $F * (x)$ is a completely specified hypothesized distribution function.
The test statistic is

$$T = sup_x |F^*(x) - S(x)|$$

where S(x) is the empirical distribution function based on the random sample. The hypothesis regarding the distributional form is rejected if the test statistic, T, is greater than the critical value obtained from a table.

6.5 Likelihood Ratio Test

The likelihood ratio test (LRT) is a statistical test of the goodness-of-fit between two models. A relatively more complex model is compared to a simpler model to see if it fits a particular dataset significantly better. The LRT is only valid if used to compare hierarchically nested models. That is, the more complex model must differ from the simple model only by the addition of one or more parameters. Adding additional parameters will always result in a higher likelihood score. However, there comes a point when adding additional parameters is no longer justified in terms of significant improvement in fit of a model to a particular dataset. The LRT provides one objective criterion for selecting among possible models. The LRT begins with a comparison of the likelihood scores of the two models:

$$H_0 : \theta \in \Theta_0 versus H_1 : \theta \notin \Theta_0$$

The likelihood ratio statistic is

$$\lambda = 2 * ln(\mathcal{L}(\hat{\theta}) - \mathcal{L}(\hat{\theta}_0))$$

where $\hat{\theta}$ is MLE and $\hat{\theta}_0$ is the MLE when θ is restricted to lie in Θ_0. This LRT statistic approximately follows a chi-square distribution. To determine if the difference in likelihood scores among the two models is statistically significant, we next must consider the degrees of freedom. In the LRT, degrees of freedom is equal to the number of additional parameters in the more complex model. Using this information we can then determine the critical value of the test statistic from standard statistical tables. Let be r the dimension of Θ and q the dimension of Θ_0, the $p - value$ for the test is $\mathcal{P}(\chi^2_{r-q} > \lambda)$.

7 Appendix B

7.1 FEF

7.1.1 Table Single Model Parameters

	[Beta]	[mu]	[sigma2]	[AIC1]
[1,]	39.062624	13.0347225	4.875880e+01	1095.1111
[2,]	38.509874	2.0000000	0.000000e+00	573.7698
[3,]	11.880683	4.5499695	3.862719e+00	1990.2017
[4,]	10.088239	2.8087864	1.285473e+00	2986.7135
[5,]	41.746190	1.0000000	0.000000e+00	1339.5263
[6,]	14.270501	1.4897776	1.412534e-01	1972.4921
[7,]	80.203210	0.9999774	6.797027e-12	964.6248
[8,]	18.277497	16.9142854	4.260597e+01	619.5444
[9,]	51.256247	1.9933752	1.306169e-06	499.1577
[10,]	41.695355	0.9970054	2.981541e-07	1163.8121
[11,]	58.994392	3.0000000	0.000000e+00	825.8489
[12,]	52.149339	2.0000000	0.000000e+00	1449.9618
[13,]	48.022097	8.3929515	1.022317e+02	1076.6798
[14,]	25.964210	10.8206077	5.403232e+01	716.1899
[15,]	15.784871	18.7089556	6.122811e+01	1354.3673
[16,]	19.568485	13.4720522	1.183412e+02	659.7940
[17,]	44.491678	4.7634015	2.416910e+00	952.0969
[18,]	64.303464	0.9999996	3.964176e-15	600.4982
[19,]	23.229100	13.0481308	1.134024e+02	918.5775
[20,]	46.695716	1.0000000	0.000000e+00	799.3718
[21,]	61.476264	10.8711940	2.288113e+01	1230.3036
[22,]	66.663929	5.3079070	3.926950e+00	748.1119
[23,]	83.781881	13.7444353	2.342257e+01	630.6179
[24,]	62.287660	2.0000000	0.000000e+00	704.7687
[25,]	53.400991	1.9995470	6.468826e-09	841.2774
[26,]	25.727960	5.2510480	5.173978e+00	1242.9454
[27,]	12.626594	4.5956722	5.565605e+00	1203.9505
[28,]	28.331412	2.0000000	0.000000e+00	723.8683
[29,]	24.609877	0.9999835	4.860356e-12	926.6361
[30,]	28.067006	1.0000000	0.000000e+00	1156.0944
[31,]	22.217185	4.6751731	2.543645e+00	1088.8175
[32,]	38.018648	1.0000000	0.000000e+00	728.3061
[33,]	23.728661	3.0000000	0.000000e+00	745.9241
[34,]	24.750514	1.0000000	0.000000e+00	1731.6387
[35,]	58.496745	0.9998031	1.202825e-09	644.8517
[36,]	37.184239	2.0000000	0.000000e+00	1510.2096
[37,]	107.907354	2.0000000	0.000000e+00	896.3578
[38,]	40.736143	4.7688067	3.237915e+00	3841.4170
[39,]	54.269191	1.0000000	0.000000e+00	1993.5001
[40,]	25.076871	3.8136660	1.454863e+00	4604.1729
[41,]	3.490961	3.9902576	1.298844e+00	2826.9347
[42,]	21.828436	2.9541726	6.559869e-01	1520.7607
[43,]	20.790653	1.0000000	0.000000e+00	2108.1077
[44,]	18.495728	1.9999168	3.640647e-10	907.0343
[45,]	50.262091	2.0000000	0.000000e+00	706.8473
[46,]	92.052472	3.8352836	9.818312e+00	2182.5778

7.1.2 Table Dual Model Parameters

	[mu]	[sigma2]	[lambda0]	[lambda1]	[p]	[AIC2]
[1,]	13.5083000	5.311701e+01	2.825114e-02	0.017821942	0.154113872	1099.0357
[2,]	1.9999980	0.000000e+00	4.573641e-02	0.009672969	0.205499694	566.9869
[3,]	5.5160695	5.353270e+00	1.684912e-01	0.045365778	0.309136171	1973.8901
[4,]	3.3012966	1.940270e+00	1.514881e-01	0.046434316	0.200510486	2967.2054
[5,]	1.9043631	7.265421e-01	7.050211e-02	0.017034321	0.564926505	1333.1381
[6,]	1.5099486	1.437391e-01	4.741900e-02	0.081384893	0.776957507	1975.5994
[7,]	0.9999997	1.184162e-18	1.245627e-02	0.014427789	0.000000000	968.6246
[8,]	16.9142795	4.260595e+01	5.633855e-02	0.054712062	1.000000000	623.5444
[9,]	2.0000000	0.000000e+00	1.968439e-02	0.019387101	0.244450370	503.1436
[10,]	2.2378945	1.700582e+00	3.995973e-01	0.016998157	0.713715623	1143.0756
[11,]	10.0283578	7.256514e+01	3.265431e-02	0.014796480	0.550865440	834.2688
[12,]	5.0547359	9.289091e+00	5.501381e-02	0.010220937	0.382195053	1433.4914
[13,]	2.0000000	0.000000e+00	1.837726e-02	0.001497171	0.000000000	1069.2880
[14,]	10.8205748	5.403188e+01	2.134022e-01	0.038514547	1.000000000	720.1899
[15,]	19.4382177	6.542693e+01	1.194626e-01	0.058814743	0.774447936	1358.2650
[16,]	13.4720448	1.183414e+02	1.977609e-01	0.051102539	1.000000000	663.7940
[17,]	4.7634042	2.416945e+00	8.878085e-06	0.022476096	1.000000000	956.0969
[18,]	1.0000000	0.000000e+00	1.358898e-02	0.005952781	0.000000000	603.4319
[19,]	13.0481071	1.134022e+02	2.045422e+00	0.043049414	1.000000000	922.5775
[20,]	1.0000000	0.000000e+00	2.944950e-02	0.014487605	0.355156052	802.3161
[21,]	21.4259860	9.986689e+01	1.235042e-01	0.011846944	0.561169794	1223.7910
[22,]	5.3079097	3.926978e+00	1.500062e-02	0.020509056	0.000000000	752.1119
[23,]	13.7444337	2.342252e+01	5.647105e-02	0.011935755	1.000000000	634.6179
[24,]	1.9998953	5.724611e-10	3.243456e-02	0.014516921	0.836844386	708.5717
[25,]	2.0000000	0.000000e+00	4.289480e-01	0.015617084	0.824380728	827.2849
[26,]	5.2510286	5.173849e+00	4.809048e-02	0.038868175	1.000000000	1246.9454
[27,]	4.8500946	6.216481e+00	2.074269e-02	0.086869644	0.976548577	1205.3775
[28,]	7.2405246	1.934100e+01	1.227334e-01	0.013076429	0.189286916	702.9093
[29,]	2.4474205	1.545160e+00	3.353323e-01	0.027474571	0.618622545	911.0308

```
[30,]  1.0000000 0.000000e+00 2.169344e-02 0.078763539 0.848022588 1121.9367
[31,] 11.4878056 2.180916e+01 1.370141e+00 0.025845220 0.386561497 1066.9355
[32,]  0.9999966 0.000000e+00 1.529014e-01 0.015696313 0.544566360  705.2735
[33,]  3.0000000 0.000000e+00 1.516455e-01 0.027432886 0.539176499  732.7623
[34,]  3.3488477 2.608960e+00 1.587819e-01 0.018019337 0.327339084 1656.1400
[35,]  1.2222284 6.732080e-01 1.243056e-02 0.033369190 0.437759150  648.6631
[36,]  3.6126590 3.696596e+00 6.848503e-02 0.020501069 0.581068395 1512.7316
[37,]  2.0000000 0.000000e+00 1.914640e-01 0.009977697 0.648098530   844.7044
[38,]  5.7870663 5.877436e+00 3.779609e-02 0.010687826 0.197597756 3815.2400
[39,]  1.8303412 5.932640e-01 2.837406e-01 0.012551909 0.655351185 1917.1887
[40,]  4.5567310 2.360976e+00 1.008225e-01 0.027785668 0.552920414 4578.5782
[41,]  3.9902546 1.298846e+00 2.864559e-01 0.286453298 0.725187531 2830.9347
[42,]  3.7145452 1.639459e+00 8.167457e-02 0.018864240 0.216460075 1501.1527
[43,]  2.6785860 1.196889e+00 9.443124e-02 0.025184352 0.082694558 2046.4898
[44,]  2.1431243 2.202974e-01 1.208502e-01 0.025526204 0.326135564  896.3173
[45,]  2.0000000 0.000000e+00 8.037639e-02 0.008606348 0.341781222  673.1877
[46,]  1.0000005 9.999999e-01 1.053572e-02 0.016244909 0.001000148 2188.3951
```

7.1.3 P-value LRT

```
 [1] 9.629912e-01 4.555275e-03 3.885094e-05 7.857360e-06 5.549352e-03 6.399451e-01 9.999335e-01
 [8] 1.000000e+00 9.929410e-01 4.251454e-06 0.000000e+00 3.588345e-05 3.359719e-03 1.000000e+00
[15] 9.501509e-01 1.000000e+00 1.000000e+00 5.867612e-01 1.000000e+00 5.898613e-01 5.214713e-03
[22] 1.000000e+00 1.000000e+00 9.061913e-01 1.238731e-04 1.000000e+00 2.762345e-01 3.803733e-06
[29] 5.530529e-05 5.178125e-09 2.397778e-06 1.348746e-06 1.876527e-04 0.000000e+00 9.100522e-01
[36] 4.775986e-01 0.000000e+00 2.799991e-07 0.000000e+00 3.746130e-07 1.000000e+00 7.474538e-06
[43] 5.662137e-15 6.371580e-04 6.642542e-09 1.000000e+00
```

7.1.4 AIC.diff

```
[1]   3.924578  -6.782939 -16.311556 -19.508120  -6.388148   3.107254   3.999867   4.000000
 [9]   3.985832 -20.736499   8.419889 -16.470469  -7.391796   4.000000   3.897731   4.000000
[17]   4.000000   2.933725   4.000000   2.944264  -6.512543   4.000000   4.000000   3.802990
[25] -13.992506   4.000000   1.426989 -20.959055 -15.605284 -34.157646 -21.881936 -23.032670
[33] -13.161836 -75.498690   3.811493   2.522031 -51.653382 -26.176959 -76.311345 -25.594745
[41]   4.000000 -19.608017 -61.617883 -10.716986 -33.659542   5.817275
```

7.2 MD

7.2.1 Table Single Model Parameters

```
para
          [,1]       [,2]         [,3]      [,4]
 [1,] 45.02995  3.0000000 0.000000e+00  803.9060
 [3,] 50.26410  2.9995055 6.636818e-09  762.3000
 [4,] 87.05906  1.9994438 6.757432e-09  618.3203
 [5,] 51.98072  9.7939384 1.235673e+02  734.8279
 [6,] 32.71627  0.9999924 5.355286e-13  883.1592
 [7,] 52.56861  6.3284458 2.118841e+01  691.3976
 [8,] 62.91160 13.3484033 1.464151e+02 1067.3172
 [9,] 46.77800 11.4751479 2.810922e+01 1568.9805
[10,] 35.42325 12.7832858 6.567710e+01  882.5781
[11,] 30.49971  5.0940281 1.545615e+01 1165.4986
[12,] 57.22854  5.9659030 3.477637e+01  745.7010
[13,] 85.19840  6.3554463 7.309088e+01  725.1996
[14,] 33.37644 15.3798551 3.238749e+01 1114.0493
[15,] 31.58283 17.5637251 5.623039e+01 1086.0713
[16,] 51.49936  5.1322195 1.911403e+01  577.8589
[17,] 44.08407 27.7730740 7.349038e+01  769.0687
[18,] 48.03822  0.9999995 8.165745e-15  733.8073
[19,] 35.63179  5.7398857 8.153185e+00 1055.7285
[20,] 23.75266 13.0273355 3.213531e+00  429.4320
[21,] 44.80009 12.6265777 7.665927e+01  751.5885
```

7.2.2 Table Dual Model Parameters

```
            [,1]         [,2]         [,3]         [,4]       [,5]      [,6]
 [1,]  5.9473537 1.383339e+01   0.02377980   0.02377971 0.88618735  809.5323
 [3,]  3.0000000 0.000000e+00   0.01739834   0.05346827 0.10777727  765.5956
 [4,]  1.9999477 6.104028e-11   0.01125320   3.15437137 0.02052455  620.3576
 [5,]  2.9998081 2.427304e-09   0.01701458   0.06829477 0.00000000  730.4675
 [6,]  0.9999764 2.631542e-11   0.06028010   0.01760765 0.42843999  879.3471
 [7,]  6.3284465 2.118841e+01   0.02118186   0.01902276 1.00000000  695.3976
 [8,] 13.3484040 1.464151e+02   0.01361083   0.01589532 1.00000000 1071.3172
 [9,] 13.9887099 4.206088e+01   0.03784151   0.01165287 0.30036238 1564.8445
[10,] 14.4773237 7.840279e+01   0.02103454   0.04456930 0.55018045  885.8563
[11,] 11.2993622 5.229718e+01   0.19190659   0.02726907 0.60658268 1166.8562
[12,] 22.4333701 1.419375e+02   0.89147867   0.01297792 0.52203606  743.2605
[13,]  0.9999995 7.519541e-15   0.01104315   0.04433577 0.00000000  725.7728
[14,] 15.3798274 3.238717e+01   0.00000000   0.02996122 1.00000000 1118.0493
[15,] 18.4294940 6.312570e+01   0.02505904   0.04204949 0.56986798 1089.8423
[16,] 16.3947949 8.271649e+01   0.30087491   0.01431054 0.55462704  576.1210
[17,] 31.2710860 9.993065e+01   0.06570523   0.01908100 0.68210503  772.1741
[18,]  1.0000000 0.000000e+00   0.00756635   0.02120206 0.96508006  737.3415
[19,]  7.2888430 1.253721e+01   0.01153576   0.04810870 0.79823284 1047.2214
[20,] 13.0273356 3.213534e+00   0.08424686   0.04210054 1.00000000  433.4320
[21,] 17.0912019 1.244419e+02   0.03311890   0.00565785 0.06919773  747.8970
```

7.2.3 P-value LRT

```
pv
 [1] 1.000000000 0.703113899 0.374798659 0.015295182 0.020120268 1.000000000
 [7] 1.000000000 0.017112280 0.697042004 0.266815287 0.039945769 0.180248291
 [12]1.000000000 0.891832908 0.056759329 0.639376195 0.792220954 0.001923610
 [18]1.000000000 0.021370494
```

7.2.4 AIC.diff

```
 [1] 5.626276  3.295527  2.037267 -4.360435 -3.812055  4.000000  4.000000
 [8] -4.135918 3.278181  1.357603 -2.440465  0.573160  4.000000  3.771047
 [15]-1.737871 3.105475  3.534170 -8.507103  4.000000 -3.691488
```

7.3 SC

7.3.1 Table Single Model Parameters

```
45.02995   3.0000000 0.000000e+00   803.9060
50.26410   2.9995055 6.636818e-09   762.3000
87.05906   1.9994438 6.757432e-09   618.3203
51.98072   9.7939384 1.235673e+02   734.8279
32.71627    0.9999924 5.355286e-13   883.1592
52.56861   6.3284458 2.118841e+01   691.3976
62.91160 13.3484033 1.464151e+02 1067.3172
46.77800 11.4751479 2.810922e+01 1568.9805
35.42325 12.7832858 6.567710e+01   882.5781
30.49971   5.0940281 1.545615e+01 1165.4986
57.22854   5.9659030 3.477637e+01   745.7010
85.19840   6.3554463 7.309088e+01   725.1996
33.37644 15.3798551 3.238749e+01 1114.0493
31.58283 17.5637251 5.623039e+01 1086.0713
51.49936   5.1322195 1.911403e+01   577.8589
44.08407 27.7730740 7.349038e+01   769.0687
48.03822   0.9999995 8.165745e-15   733.8073
35.63179   5.7398857 8.153185e+00 1055.7285
23.75266 13.0273355 3.213531e+00   429.4320
44.80009 12.6265777 7.665927e+01   751.5885
```

7.3.2 Table Dual Model Parameters

```
 5.9473537 1.383339e+01 0.02377980 0.02377971 0.88618735  809.5323
 3.0000000 0.000000e+00 0.01739834 0.05346827 0.10777727  765.5956
 1.9999477 6.104028e-11 0.01125320 3.15437137 0.02052455  620.3576
 2.9998081 2.427304e-09 0.01701458 0.06829477 0.00000000  730.4675
 0.9999764 2.631542e-11 0.06028010 0.01760765 0.42843999  879.3471
 6.3284465 2.118841e+01 0.02118186 0.01902276 1.00000000  695.3976
13.3484040 1.464151e+02 0.01361083 0.01589532 1.00000000 1071.3172
13.9887099 4.206088e+01 0.03784151 0.01165287 0.30036238 1564.8445
14.4773237 7.840279e+01 0.02103454 0.04456930 0.55018045  885.8563
11.2993622 5.229718e+01 0.19190659 0.02726907 0.60658268 1166.8562
22.4333701 1.419375e+02 0.89147867 0.01297792 0.52203606  743.2605
 0.9999995 7.519541e-15 0.01104315 0.04433577 0.00000000  725.7728
15.3798274 3.238717e+01 0.00000000 0.02996122 1.00000000 1118.0493
18.4294940 6.312570e+01 0.02505904 0.04204949 0.56986798 1089.8423
16.3947949 8.271649e+01 0.30087491 0.01431054 0.55462704  576.1210
31.2710860 9.993065e+01 0.06570523 0.01908100 0.68210503  772.1741
 1.0000000 0.000000e+00 0.00756635 0.02120206 0.96508006  737.3415
 7.2888430 1.253721e+01 0.01153576 0.04810870 0.79823284 1047.2214
13.0273356 3.213534e+00 0.08424686 0.04210054 1.00000000  433.4320
17.0912019 1.244419e+02 0.03311890 0.00565785 0.06919773  747.8970
```

7.3.3 P-value LRT

```
1.000000000 0.703113899 0.374798659 0.015295182 0.020120268 1.000000000
1.000000000 0.017112280 0.697042004 0.266815287 0.039945769 0.180248291
1.000000000 0.891832908 0.056759329 0.639376195 0.792220954 0.001923610
1.000000000 0.021370494
```

7.3.4 AIC.diff

```
5.626276   3.295527   2.037267 -4.360435 -3.812055  4.000000  4.000000
-4.135918  3.278181 1.357603 -2.440465  0.573160  4.000000  3.771047
-1.737871  3.105475  3.534170 -8.507103 4.000000 -3.691488
```

8 Appendix C: Reference

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