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ASYMPTOTIC PROPERTIES OF MSAE ESTIMATES IN MULTISTAGE MODEL

Preliminary Results

by

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1. INTRODUCTION

For carcinogenesis risk assessment studies the multistage model proposed by Armitage and Doll (1954) is the most frequently used. In this model the mechanism of carcinogenesis is expressed as a series of k mutations at the cellular level. The model has been often used to compute virtually safe dose VSD by extrapolating the curve to dose levels below the experimental doses, Portier and Hoel (1983). The VSD represents the dose s that would yeld an incremental response ε in life time tumor incidence over the spontaneous background incidence level. Usually ε is some small value between 10^{-8} and 10^{-4}. However, they pointed out that the variability due to binomial sampling or the improper assumptions concerning the functional form of dose-response model can result in error in the estimation of VSD for small bioassays.

André, Peres and Narula (1991) show that the least squares estimates of the parameters of a multistage dose- response model may be unduly affected by outliers. They proposed to estimate the parameters of the model by minimizing the sum of absolute errors MSAE as these estimates are more resistant to outliers than the least squares estimates. André, Peres and Narula (1991, 1992) proposed algorithms to compute the MSAE estimates for the model. Althought it is possible to compute the MSAE estimates of parameters of the model and VSD, yet not much is known about the statistical properties of the MSAE estimators of the parameters and VSD. At the present it is not clear how to determine the asymptotic distribution or small sample properties of the MSAE estimates of the parameters of the model or VSD.

Our objective is to investigate small and medium sample properties of the MSAE estimators of the parameters and VSD for the multistage dose-response model. In most applications of the multistage model to chemical carcinogenesis, the estimated number of chemically affected stages has been at most two, Guess, Crump and Peto (1977). The risk analysis for ionizing radiation have considered at most two stages, Land (1990). Therefore, we restrict our attention to at most two affected stages. In particular we consider the following two models :

(i) the linear model

$$y_i = 1 - \exp(-\beta_0 - \beta_1 d_i) + e_i, \quad i = 1,\cdots,n$$

(ii) the linear-quadratic model

$$y_i = 1 - \exp(-\beta_0 - \beta_1 d_i - \beta_2 d_i^2) + e_i, \quad i = 1,\cdots,n$$

where y_i denotes the value of the response variable corresponding to dose d_i, β_0, β_1, and β_2 are unknown parameters and e_i denotes unobservable random errors. The rest of the paper is organized as follows: In Section 2, we describe the simulation study. In Section 3, we report the results of the study. We conclude the paper with a few remarks in Section 4..

2. SIMULATION STUDY

In our simulation study we use a set of two stages models. The linear model is uniquely defined by two increasing dose-response points. By standardizing the dose scale to set the maximun tolerated dose MTD - the highest dose that will produce no acute toxicity - to one, we define four linear models given in Table 1. We also define four models for the linear-quadratic model the way it is described in Portier and Hoel (1983). The models are summarized in Table 2.

Table 1- Fixed values for the linear models parameters

response at dose zero	response at dose 1(MTD)	β_0	β_1	s
0.005	0.30	0.0050125	0.35166	2.86×10^{-6}
0.005	0.90	0.0050125	2.29760	4.37×10^{-7}
0.200	0.30	0.22314	0.13353	9.36×10^{-6}
0.200	0.90	0.22314	2.07940	6.01×10^{-7}

Table 2- Fixed values for the linear-quadratic models parameters

response at dose zero	response at dose 1(MTD)	β_0	β_1	β_2	s
0.005	0.30	0.0050125	0.27836	0.07330	3.01×10^{-6}
0.005	0.90	0.0050125	0.07373	2.22380	1.36×10^{-5}
0.200	0.30	0.22314	0.12462	0.00891	1.00×10^{-5}
0.200	0.90	0.22314	0.22202	1.85740	5.63×10^{-6}

Suppose that we have n doses d_i and there are N animals at each dose. Let p_i denote the true response at dose d_i, i.e., the response given by the true model at d_i, $i = 1,\dots,n$. At each dose d_i, we generate a response y_i from the binomial distribution with parameters N and p_i. After fitting the dose-response model to the data, we can evaluate the VSD $\hat{s}$ for a given risk ε as follows:

$$\hat{s} = \begin{cases} [-\ln(\exp(-\hat{\beta}_0) - \varepsilon) - \hat{\beta}_0]/\hat{\beta}_1, & \text{if } \hat{\beta}_0 \geq 0, \hat{\beta}_1 > 0, \hat{\beta}_2 = 0 \\ [-\hat{\beta}_1 + \{\hat{\beta}_1^2 - 4\hat{\beta}_2(\ln(\exp(-\hat{\beta}_0) - \varepsilon) + \hat{\beta}_0\}^{1/2}]/(2\hat{\beta}_2), & \text{if } \hat{\beta}_0 \geq 0, \hat{\beta}_1 \geq 0 \text{ and } \hat{\beta}_2 > 0 \end{cases}$$

Repeating this procedure R times, we can generate a randon sample of size R of MSAE estimates of the parameters and VSD.

In the study we consider the number of doses n equal to five and nine. The smallest dose equal to zero and the highest dose MTD equal to one. The remaining doses were equally spaced between 0 and 1. For each model and number of doses, we set the number of animals N at each dose equal to 50 (small sample) and 200 (medium sample). Thus for each model, we have four experimental conditions corresponding to four different combinations of n and N. For each design in Tables 1 and 2, we generated R=800 replicates of experiment. The safe dose estimates are calculated for ε equal to 10^{-6}.

3.RESULTS

The results of the simulation study can be summarized as follows.

3.1 The linear model

For the four linear models, the results are summarized in Tables 3 to 10. For each model a table gives the mean, the standard deviation, a 90% confidence interval based on the simulated distribution for the parameters and VSD, the Kolmogorov-Smirnov K-S statistic, the critical value for the Lillifors test for normality and the mean absolute error.

From these tables, we conclude that:

(i) the MSAE estimators are unbiased.

(ii) the standard deviation and mean of absolute errors decrease as N increases.

(iii) the hypothesis that the sampling distribution for $\hat{\beta}_0$ is normal is always rejected. However the value of the K-S statistic decreases as n increases (for fixed N) and as N increases (for fixed n). The value of K-S statistic is close to the critical value for β_0 = 0.2 suggesting that the distribution of $\hat{\beta}_0$ must be close to normal distribution for n and N values considered in the study.

(iv) the hypothesis that the sampling distribution of $\hat{\beta}_1$ is normal is not rejected in several situations. When the hypothesis is rejected, the observed value of the K-S statistic is very close to the critical value.

(v) the hypothesis that the sampling distribution of $\hat{s}$ is normal is accepted only for the model

$$Y = 1 - \exp(-0\ 00501 - 2.2976\ d)$$

for n = 5 and 9 and N = 200.

3.2 The linear-quadratic model

For the four linear-quadratic models, the results are summarized in Tables 11 to 18.From the tables we conclude :

(i) the MSAE estimators are asymptotically unbiased.

(ii)the standard deviations and the mean of absolute errors decrease as N increases.

(iii) the value of K-S statistics decreases as N increases.

4. REMARKS

The results presented in Section 3 suggested that, for the linear model, the estimators distributions will turn to be normal for values of N not very far from 200. For the linear-quadratic model, we will´ probably need greater values of N. Similar results were observed by Portier and Hoel (1983) also in the study of Maximun Likelihood estimators distribution. They showed analytically that the asymptotic distribution of VSD estimator is normal. However, when the model is linear-quadratic, the distribution obtained in the simulation is bimodal even for large bioassays whith as many as 100000 animals.

We are conducting more simulations runs with large values of N to prove the results mentioned above.

Table 3- Means, Standard Deviations and Mean Absolute Errors for the model:

$$Y = 1 - \exp(-0.0050125 - 0.35166d)$$

n	N	estimador	mean	standard deviation	MAE
5	50	$\hat{\beta}_0$	0.00844	0.01633	0.00976
		$\hat{\beta}_1$	0.35009	0.07227	0.05733
		$\hat{s}$	3.05×10^{-6}	1.09×10^{-6}	5.58×10^{-7}
5	200	$\hat{\beta}_0$	0.00619	0.00754	0.00515
		$\hat{\beta}_1$	0.34828	0.03540	0.02753
		$\hat{s}$	2.92×10^{-6}	3.22×10^{-6}	2.41×10
9	50	$\hat{\beta}_0$	0.00864	0.01377	0.00931
		$\hat{\beta}_1$	0.34483	0.05664	0.04559
		$\hat{s}$	3.01×10^{-6}	5.85×10^{-7}	4.28×10^{-7}
9	200	$\hat{\beta}_0$	0.00616	0.00712	0.00516
		$\hat{\beta}_1$	0.34737	0.02758	0.02191
		$\hat{s}$	2.92×10^{-6}	2.53×10^{-7}	1.94×10^{-7}

Table 4- Means, Standard Deviations and Mean Absolute Errors for the model:

$$Y = 1 - \exp(-0.0050125 - 2.2976d)$$

n	N	estimador	mean	standard deviation	MAE
5	50	$\hat{\beta}_0$	0.00491	0.01002	0.00766
		$\hat{\beta}_1$	2.32750	0.26731	0.20745
		$\hat{s}$	4.37×10^{-7}	4.89×10^{-8}	3.90×10^{-8}
5	200	$\hat{\beta}_0$	0.00530	0.00533	0.00381
		$\hat{\beta}_1$	2.30310	0.13071	0.10393
		$\hat{s}$	4.37×10^{-7}	2.51×10^{-8}	2.00×10^{-8}
9	50	$\hat{\beta}_0$	0.00843	0.01560	0.00982
		$\hat{\beta}_1$	2.28750	0.18669	0.14380
		$\hat{s}$	4.43×10^{-7}	3.81×10^{-8}	2.90×10^{-8}
9	200	$\hat{\beta}_0$	0.00555	0.00706	0.00461
		$\hat{\beta}_1$	2.28340	0.09162	0.07415
		$\hat{s}$	4.41×10^{-7}	1.86×10^{-8}	1.49×10^{-8}

Table 5- Means, Standard Deviations and Mean Absolute Errors for the model:

$$Y = 1 - \exp(-0.22314 - 0.13353d)$$

n	N	estimador	mean	standard deviation	MAE
5	50	$\hat{\beta}_0$	0.16701	0.04466	0.06089
		$\hat{\beta}_1$	0.26188	0.07356	0.12976
		$\hat{s}$	4.96×10^{-6}	2.00×10^{-6}	4.59×10^{-6}
5	200	$\hat{\beta}_0$	0.20883	0.03091	0.02444
		$\hat{\beta}_1$	0.16108	0.05483	0.04070
		$\hat{s}$	8.43×10^{-6}	3.08×10^{-6}	2.32×10^{-6}
9	50	$\hat{\beta}_0$	0.18046	0.04344	0.05410
		$\hat{\beta}_1$	0.22562	0.09340	0.06745
		$\hat{s}$	7.49×10^{-6}	1.76×10^{-6}	5.05×10^{-6}
9	200	$\hat{\beta}_0$	0.21849	0.02644	0.01935
		$\hat{\beta}_1$	0.14233	0.04461	0.03557
		$\hat{s}$	9.74×10^{-6}	3.53×10^{-6}	2.64×10^{-6}

Table 6-Means, Standard Deviations and Mean Absolute Errors for the model:

$$Y = 1 - \exp(-0.22314 - 2.0794d)$$

n	N	estimador	mean	standard deviation	MAE
5	50	$\hat{\beta}_0$	0.22487	0.07698	0.06016
		$\hat{\beta}_1$	2.11970	0.34094	0.26456
		$\hat{s}$	6.11×10^{-7}	1.29×10^{-7}	1.00×10^{-7}
5	200	$\hat{\beta}_0$	0.22410	0.03529	0.02789
		$\hat{\beta}_1$	2.08200	0.15670	0.12433
		$\hat{s}$	6.06×10^{-7}	5.90×10^{-8}	4.63×10^{-8}
9	50	$\hat{\beta}_0$	0.21885	0.06868	0.05440
		$\hat{\beta}_1$	2.10255	0.25165	0.20017
		$\hat{s}$	6.05×10^{-7}	1.10×10^{-7}	8.24×10^{-8}
9	200	$\hat{\beta}_0$	0.22052	0.03408	0.02708
		$\hat{\beta}_1$	2.08100	0.11876	0.09381
		$\hat{s}$	6.02×10^{-7}	4.98×10^{-8}	3.89×10^{-8}

Table 7- K-S Statistics and 90% Confidence Intervals for the Parameters in the model:

$$Y = 1 - \exp(-0.0050125 - 0.35166d)$$

n	N	estimador	K-S statistic	Confidence Interval
5	50	$\hat{\beta}_0$	0.303	[0.0000 ; 0.0408]
		$\hat{\beta}_1$	0.026	[0.2324 ; 0.4648]
		$\hat{s}$	0.167	[2.16×10^{-6} ; 4.45×10^{-6}]
5	200	$\hat{\beta}_0$	0.206	[0.0000 ; 0.0202]
		$\hat{\beta}_1$	0.401	[0.2863 ; 0.4045]
		$\hat{s}$	0.089	[2.49×10^{-6} ; 3.56×10^{-6}]
9	50	$\hat{\beta}_0$	0.265	[0.0000 ; 0.0373]
		$\hat{\beta}_1$	0.022	[0.2500 ; 0.4372]
		$\hat{s}$	0.101	[2.29×10^{-6} ; 4.14×10^{-6}]
9	200	$\hat{\beta}_0$	0.193	[0.0000 ; 0.0194]
		$\hat{\beta}_1$	0.020	[0.3036 ; 0.3907]
		$\hat{s}$	0.060	[2.56×10^{-6} ;3.34×10^{-6}]

critical values : 1%:0.036; 5%:0.031; 10%:0.028

Table 8- K-S Statistics and 90% Confidence Intervals for the Parameters in the model:

$$Y = 1 - \exp(-0.0050125 - 2.2976d)$$

n	N	estimador	K-S statistic	Confidence Interval
5	50	$\hat{\beta}_0$	0.441	[0.0000 ; 0.0205]
		$\hat{\beta}_1$	0.063	[1.9381 ; 2.8148]
		$\hat{s}$	0.087	[3.55×10^{-7} ; 5.22×10^{-7}]
5	200	$\hat{\beta}_0$	0.200	[0.0000 ; 0.0151]
		$\hat{\beta}_1$	0.029	[2.0969 ; 2.5322]
		$\hat{s}$	0.018	[3.97×10^{-7} ; 4.79×10^{-7}]
9	50	$\hat{\beta}_0$	0.309	[0.0000 ; 0.0392]
		$\hat{\beta}_1$	0.057	[1.9908 ; 2.6172]
		$\hat{s}$	0.067	[3.82×10^{-7} ; 5.12×10^{-7}]
9	200	$\hat{\beta}_0$	0.216	[0.0000 ; 0.0172]
		$\hat{\beta}_1$	0.038	[2.1428 ; 2.4436]
		$\hat{s}$	0.023	[4.10×10^{-7} ;4.70×10^{-7}]

critical values : 1%:0.036; 5%:0.031; 10%:0.028

Table 9- K-S Statistics and 90% Confidence Intervals for the Parameters in the model:

$$Y = 1 - \exp(-0.22314 - 0.13353d)$$

n	N	estimador	K-S statistic	Confidence Interval
5	50	$\hat{\beta}_0$	0.058	[0.09980; 0.24559]
		$\hat{\beta}_1$	0.057	[0.16139; 0.39370]
		$\hat{s}$	0.130	[2.89×10^{-6}; 7.63×10^{-6}]
5	200	$\hat{\beta}_0$	0.071	[0.16793 ; 0.25088]
		$\hat{\beta}_1$	0.083	[0.09721; 0.23437]
		$\hat{s}$	0.094	[5.12×10^{-6} ; 1.32×10^{-5}]
9	50	$\hat{\beta}_0$	0.062	[0.10695; 0.24370]
		$\hat{\beta}_1$	0.090	[0.09997; 0.39481]
		$\hat{s}$	0.370	[2.91×10^{-6} ; 1.22×10^{-5}]
9	200	$\hat{\beta}_0$	0.059	[0.17922; 0.25678]
		$\hat{\beta}_1$	0.051	[0.07920; 0.21973]
		$\hat{s}$	0.100	[5.47×10^{-6};1.60×10^{-5}]

critical values : 1%:0.036; 5%:0.031; 10%:0.028

Table 10- K-S Statistics and 90% Confidence Intervals for the Parameters in the model:

$$Y = 1 - \exp(-0.22314 - 2.0794d)$$

n	N	estimador	K-S statistic	Confidence Interval
5	50	$\hat{\beta}_0$	0.094	[0.10559; 0.35710]
		$\hat{\beta}_1$	0.048	[1.6277 ;2.70516]
		$\hat{s}$	0.057	[4.30×10^{-7}; 8.57×10^{-7}]
5	200	$\hat{\beta}_0$	0.047	[0.16843 ; 0.28742]
		$\hat{\beta}_1$	0.031	[1.82980; 2.35720]
		$\hat{s}$	0.044	[5.11×10^{-7} ; 7.10×10^{-7}]
9	50	$\hat{\beta}_0$	0.053	[0.11565; 0.33271]
		$\hat{\beta}_1$	0.021	[1.69730; 2.55230]
		$\hat{s}$	0.067	[4.56×10^{-7} ; 7.94×10^{-7}]
9	200	$\hat{\beta}_0$	0.038	[0.16706; 0.27808]
		$\hat{\beta}_1$	0.021	[1.88410; 2.28080]
		$\hat{s}$	0.034	[5.23×10^{-7};6.91×10^{-7}]

critical values : 1%:0.036; 5%:0.031; 10%:0.028

Table 11- Means, Standard Deviations and Mean Absolute Errors of the Estimators for the model:

$$Y = 1 - \exp(-0.0050125 - 0.27836d - 0.07330d^2)$$

n	N	estimador	mean	standard deviation	MAE
5	50	$\hat{\beta}_0$	0.00919	0.01769	0.01061
		$\hat{\beta}_1$	0.22077	0.12399	0.10618
		$\hat{\beta}_2$	0.14554	0.15907	0.13324
		$\hat{s}$	1.60×10^{-4}	4.83×10^{-4}	1.56×10^{-4}
5	200	$\hat{\beta}_0$	0.00563	0.00613	0.00428
		$\hat{\beta}_1$	0.26085	0.08025	0.06360
		$\hat{\beta}_2$	0.09466	0.10229	0.08287
		$\hat{s}$	9.00×10^{-6}	8.09×10^{-5}	5.87×10^{-6}
9	50	$\hat{\beta}_0$	0.00837	0.01355	0.00934
		$\hat{\beta}_1$	0.22439	0.11141	0.09530
		$\hat{\beta}_2$	0.13637	0.14315	0.11820
		$\hat{s}$	8.86×10^{-5}	3.49×10^{-4}	8.54×10^{-5}
9	200	$\hat{\beta}_0$	0.00624	0.00694	0.00467
		$\hat{\beta}_1$	0.26009	0.06703	0.05439
		$\hat{\beta}_2$	0.09388	0.08591	0.07178
		$\hat{s}$	6.31×10^{-6}	5.79×10^{-5}	3.10×10^{-6}

Table 12- Means, Standard Deviations and Mean Absolute Errors of the Estimators for the model:

$$Y = 1 - \exp(-0.0050125 - 0.07373d - 2.2238d^2)$$

n	N	estimador	mean	standard deviation	MAE
5	50	$\hat{\beta}_0$	0.00394	0.00898	0.00702
		$\hat{\beta}_1$	0.18041	0.23901	0.17778
		$\hat{\beta}_2$	2.07483	0.45581	0.37687
		$\hat{s}$	2.94×10^{-4}	3.21×10^{-4}	2.89×10^{-4}
5	200	$\hat{\beta}_0$	0.00411	0.00451	0.00349
		$\hat{\beta}_1$	0.13199	0.16844	0.11972
		$\hat{\beta}_2$	2.15431	0.27973	0.23401
		$\hat{s}$	2.33×10^{-4}	3.03×10^{-4}	2.27×10^{-4}
9	50	$\hat{\beta}_0$	0.00387	0.00837	0.00662
		$\hat{\beta}_1$	0.11809	0.16515	0.12026
		$\hat{\beta}_2$	2.15125	0.33935	0.25983
		$\hat{s}$	2.98×10^{-4}	3.17×10^{-4}	2.91×10^{-4}
9	200	$\hat{\beta}_0$	0.00439	0.00471	0.00379
		$\hat{\beta}_1$	0.08932	0.09855	0.07931
		$\hat{\beta}_2$	2.18506	0.18224	0.14647
		$\hat{s}$	2.24×10^{-4}	2.97×10^{-4}	2.16×10^{-4}

Table 13- Means, Standard Deviations and Mean Absolute Errors of the Estimators for the model:

$$Y = 1 - \exp(-0.22314 - 0.12462d - 0.00891d^2)$$

n	N	estimador	mean	standard deviation	MAE
5	50	$\hat{\beta}_0$	0.17249	0.04549	0.05664
		$\hat{\beta}_1$	0.14918	0.13128	0.11960
		$\hat{\beta}_2$	0.13060	0.13966	0.12294
		$\hat{s}$	6.44×10^{-4}	9.68×10^{-4}	6.40×10^{-4}
5	200	$\hat{\beta}_0$	0.21592	0.02852	0.02272
		$\hat{\beta}_1$	0.10269	0.07832	0.06457
		$\hat{\beta}_2$	0.06284	0.07614	0.06241
		$\hat{s}$	6.41×10^{-4}	1.19×10^{-3}	6.34×10^{-4}
9	50	$\hat{\beta}_0$	0.18970	0.03733	0.04019
		$\hat{\beta}_1$	0.13459	0.11362	0.09872
		$\hat{\beta}_2$	0.10163	0.11446	0.10064
		$\hat{s}$	6.54×10^{-4}	1.05×10^{-3}	6.49×10^{-4}
9	200	$\hat{\beta}_0$	0.22239	0.02257	0.01822
		$\hat{\beta}_1$	0.09657	0.06462	0.05577
		$\hat{\beta}_2$	0.04866	0.06348	0.06922
		$\hat{s}$	5.66×10^{-4}	1.17×10^{-3}	5.58×10^{-4}

Table 14- Means, Standard Deviations and Mean Absolute Errors of the Estimators for the model:

$$Y = 1 - \exp(-0.22314 - 0.22202d - 1.85740d^2)$$

n	N	estimador	mean	standard deviation	MAE
5	50	$\hat{\beta}_0$	0.21662	0.06937	0.05515
		$\hat{\beta}_1$	0.38303	0.43288	0.34348
		$\hat{\beta}_2$	1.67027	0.64192	0.52638
		$\hat{s}$	2.60×10^{-4}	3.62×10^{-4}	2.57×10^{-4}
5	200	$\hat{\beta}_0$	0.22245	0.03299	0.02631
		$\hat{\beta}_1$	0.24922	0.24374	0.19783
		$\hat{\beta}_2$	1.83222	0.37042	0.29773
		$\hat{s}$	2.06×10^{-4}	3.31×10^{-4}	2.03×10^{-4}
9	50	$\hat{\beta}_0$	0.21313	0.05572	0.04462
		$\hat{\beta}_1$	0.30458	0.34337	0.27235
		$\hat{\beta}_2$	1.76024	0.49580	0.39577
		$\hat{s}$	2.72×10^{-4}	3.66×10^{-4}	2.70×10^{-4}
9	200	$\hat{\beta}_0$	0.22123	0.03196	0.02528
		$\hat{\beta}_1$	0.23367	0.21274	0.17498
		$\hat{\beta}_2$	1.83865	0.28660	0.23346
		$\hat{s}$	1.78×10^{-4}	3.15×10^{-4}	1.74×10^{-4}

Table 15- K-S Statistics and 90% Confidence Interval for the Parameters in the model:

$$Y = 1 - \exp(-0.0050125 - 0.27836d - 0.07330d^2)$$

n	N	estimador	K-S Statistic	Confidence Interval
5	50	$\hat{\beta}_0$	0.319	[0.0000 ; 0.0417]
		$\hat{\beta}_1$	0.091	[0.0000 ; 0.4001]
		$\hat{\beta}_2$	0.202	[0.0000 ; 0.4423]
		$\hat{s}$	0.488	$[2.50\times10^{-6} ; 1.55\times10^{-3}]$
5	200	$\hat{\beta}_0$	0.194	[0.0000 ; 0.0156]
		$\hat{\beta}_1$	0.095	[0.1088 ; 0.3678]
		$\hat{\beta}_2$	0.177	[0.0000 ; 0.3025]
		$\hat{s}$	0.467	$[2.73\times10^{-6} ; 9.33\times10^{-6}]$
9	50	$\hat{\beta}_0$	0.286	[0.0000 ; 0.0383]
		$\hat{\beta}_1$	0.086	[0.0007 ; 0.3771]
		$\hat{\beta}_2$	0.170	[0.0000 ; 0.4135]
		$\hat{s}$	0.490	$[2.65\times10^{-6} ; 9.30\times10^{-4}]$
9	200	$\hat{\beta}_0$	0.184	[0.0000 ; 0.0201]
		$\hat{\beta}_1$	0.074	[0.1390 ; 0.3509]
		$\hat{\beta}_2$	0.137	[0.0000 ; 0.2528]
		$\hat{s}$	0.473	$[2.86\times10^{-6} ; 7.32\times10^{-6}]$

critical values : 1%:0.036 ; 5%:0.031 ; 10%:0.028

Table 16- K-S Statistics and 90% Confidence Interval for the Parameters in the model:

$$Y = 1 - \exp(-0.0050125 - 0.07373d - 2.22380d^2)$$

n	N	estimador	K-S Statistic	Confidence Interval
5	50	$\hat{\beta}_0$	0.459	[0.0000 ; 0.0202]
		$\hat{\beta}_1$	0.225	[0.0000 ; 0.7000
		$\hat{\beta}_2$	0.050	[1.2861 ; 2.7358]
		$\hat{s}$	0.320	[1.44×10^{-6} ; 7.03×10^{-4}]
5	200	$\hat{\beta}_0$	0.209	[0.0000 ; 0.0149]
		$\hat{\beta}_1$	0.217	[0.0000 ; 0.4264]
		$\hat{\beta}_2$	0.074	[1.6215 ; 2.5422]
		$\hat{s}$	0.350	[2.35×10^{-6} ; 6.74×10^{-4}]
9	50	$\hat{\beta}_0$	0.399	[0.0000 ; 0.0202]
		$\hat{\beta}_1$	0.237	[0.0000 ; 0.4703]
		$\hat{\beta}_2$	0.064	[1.5159 ; 2.6248]
		$\hat{s}$	0.299	[2.13×10^{-6} ; 6.94×10^{-4}]
9	200	$\hat{\beta}_0$	0.176	[0.0000 ; 0.0141]
		$\hat{\beta}_1$	0.182	[0.0000 ; 0.2731]
		$\hat{\beta}_2$	0.058	[1.8596 ; 2.4564]
		$\hat{s}$	0.342	[3.66×10^{-6} ; 6.72×10^{-4}]

critical values : 1%:0.036 ; 5%:0.031 ; 10%:0.028

Table 17- K-S Statistics and 90% Confidence Interval for the Parameters in the model:

$$Y = 1 - \exp(-0.22314 - 0.12462d - 0.00891d^2)$$

n	N	estimador	K-S Statistic	Confidence Interval
5	50	$\hat{\beta}_0$	0.070	[0.1054 ; 0.2484]
		$\hat{\beta}_1$	0.177	[0.0000 ; 0.3536]
		$\hat{\beta}_2$	0.244	[0.0000 ; 0.3714]
		$\hat{s}$	0.404	[3.25×10^{-6};2.33×10^{-3}
5	200	$\hat{\beta}_0$	0.038	[0.1690 ; 0.2593]
		$\hat{\beta}_1$	0.125	[0.0000 ; 0.2146]
		$\hat{\beta}_2$	0.260	[0.0000 ; 0.2056]
		$\hat{s}$	0.436	[5.63×10^{-6};3.11×10^{-3}
9	50	$\hat{\beta}_0$	0.047	[0.1283 ; 0.2485]
		$\hat{\beta}_1$	0.157	[0.0000 ; 0.3119]
		$\hat{\beta}_2$	0.233	[0.0000 ; 0.3023]
		$\hat{s}$	0.411	[3.72×10^{-6} ;2.58×10^{-3}]
9	200	$\hat{\beta}_0$	0.030	[0.1859 ; 0.2592]
		$\hat{\beta}_1$	0.117	[0.0000 ; 0.1948]
		$\hat{\beta}_2$	0.267	[0.0000 ; 0.1699]
		$\hat{s}$	0.455	[6.24×10^{-6};3.21×10^{-3}]

critical values : 1%:0.036 ; 5%:0.031 ; 10%:0.028

Table 18- K-S Statistics and 90% Confidence Interval for the Parameters in the model:

$$Y = 1 - \exp(-0.22314 - 0.22202d - 1.8574d^2)$$

n	N	estimador	K-S Statistic	Confidence Interval
5	50	$\hat{\beta}_0$	0.096	[0.1054 ; 0.3326]
		$\hat{\beta}_1$	0.188	[0.0000 ; 1.2517]
		$\hat{\beta}_2$	0.033	[0.5400 ; 2.6439]
		$\hat{s}$	0.370	[9.53×10^{-7};8.72×10^{-4}
5	200	$\hat{\beta}_0$	0.046	[0.1684 ; 0.2744]
		$\hat{\beta}_1$	0.153	[0.0000 ; 0.6884]
		$\hat{\beta}_2$	0.052	[1.8432 ; 2.3674]
		$\hat{s}$	0.403	[1.77×10^{-6};7.99×10^{-4}
9	50	$\hat{\beta}_0$	0.048	[0.1273 ; 0.3011]
		$\hat{\beta}_1$	0.188	[0.0000 ; 0.9654]
		$\hat{\beta}_2$	0.078	[0.8818 ; 2.4670]
		$\hat{s}$	0.370	[1.22×10^{-6} ;8.39×10^{-4}]
9	200	$\hat{\beta}_0$	0.043	[0.1684 ; 0.2739]
		$\hat{\beta}_1$	0.136	[0.0000 ; 0.6118]
		$\hat{\beta}_2$	0.060	[1.3433 ; 2.2449]
		$\hat{s}$	0.407	[1.93×10^{-6};7.98×10^{-4}]

critical values : 1%:0.036 ; 5%:0.031 ; 10%:0.028

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