

Chapter 16

Variability Analysis

In some clinical studies, the spread of the data may be more relevant than the average of the data. E.g., when we assess how a drug reaches various organs, variability of drug concentrations is important, as in some cases too little and in other cases dangerously high levels get through. Also, variabilities in drug response may be important. For example, the spread of glucose levels of a slow-release-insulin is important.

One Sample Variability Analysis

For testing whether the standard deviation (or variance) of a sample is significantly different from the standard deviation (or variance) to be expected the chi-square test with multiple degrees of freedom is adequate. The test statistic, the chi-square-value (χ^2 -value) is calculated according to

$$\chi^2 = \frac{(n-1)s^2}{\sigma^2} \text{ for } n-1 \text{ degrees of freedom}$$

(n =sample size, s =standard deviation, s^2 =variance sample, σ =expected standard deviation, σ^2 =expected variance).

For example, the aminoglycoside compound gentamicin has a small therapeutic index. The standard deviation of 50 measurements is used as a criterion for variability. Adequate variability is accepted if the standard deviation is less than 7 $\mu\text{g/l}$. In our sample a standard deviation of 9 $\mu\text{g/l}$ is observed.

The test procedure is given.

$$\chi^2 = (50-1)9^2 / 7^2 = 81$$

The chi-square table (page 32) shows that, for $50-1=49$ degrees of freedom, we will find a p -value < 0.01 . This sample's standard deviation is significantly larger than that required. This means that the variability in plasma gentamicin concentrations is larger than acceptable.

Two Sample Variability Test

F-tests can be applied to test if the variabilities of two samples are significantly different from one another. The division sum of the samples' variances (larger variance/smaller variance) is used for the analysis. For example, two formulas of gentamicin produce the following standard deviations of plasma concentrations.

	Patients (n)	Standard deviation (SD) ($\mu\text{g/l}$)
Formula-A	10	3.0
Formula-B	15	2.0

$$\begin{aligned}
 \text{F-value} &= \text{SD}_A^2 / \text{SD}_B^2 \\
 &= 3.0^2 / 2.0^2 \\
 &= 9 / 4 = 2.25
 \end{aligned}$$

with degrees of freedom (dfs) for

$$\text{formula-A of } 10 - 1 = 9$$

$$\text{formula-B of } 15 - 1 = 14.$$

The F-table on the next page shows that an F-value of at least 3.01 is required not to reject the null - hypothesis. Our F-value is 2.25 and, so, the p-value is > 0.05 . No significant difference between the two formulas can be demonstrated. This F-test is given on the next page.

df of denominator	2-tailed P-value	1-tailed P-value	Degrees of freedom (df) of the numerator												
			1	2	3	4	5	6	7	8	9	10	15	25	500
1	0.05	0.025	647.8	799.5	864.2	899.6	921.8	937.1	948.2	956.6	963.3	968.6	984.9	998.1	1017.0
1	0.10	0.05	161.4	199.5	215.7	224.6	230.2	234.0	236.8	238.9	240.5	241.9	245.9	249.3	254.1
2	0.05	0.025	38.51	39.00	39.17	39.25	39.30	39.33	39.36	39.37	39.39	39.40	39.43	39.46	39.50
2	0.10	0.05	18.51	19.00	19.16	19.25	19.13	19.33	19.35	19.37	19.38	19.40	19.43	19.46	19.49
3	0.05	0.025	17.44	16.04	15.44	15.10	14.88	14.73	14.62	14.54	14.47	14.42	14.25	14.12	13.99
3	0.10	0.05	10.13	9.55	9.28	9.12	9.01	8.94	8.89	8.85	8.81	8.79	8.70	8.63	8.53
4	0.05	0.025	12.22	10.65	9.98	9.60	9.36	9.20	9.07	8.98	8.90	8.84	8.66	8.50	8.27
4	0.10	0.05	7.71	6.94	6.59	6.39	6.26	6.16	6.09	6.04	6.00	5.96	5.86	5.77	5.64
5	0.05	0.025	10.01	8.43	7.76	7.39	7.15	6.98	6.85	6.76	6.68	6.62	6.43	6.27	6.03
5	0.10	0.05	6.61	5.79	5.41	5.19	5.05	4.95	4.88	4.82	4.77	4.74	4.62	4.52	4.37
6	0.05	0.025	8.81	7.26	6.60	6.23	5.99	5.82	5.70	5.60	5.52	5.46	5.27	5.11	4.86
6	0.10	0.05	5.99	5.14	4.76	4.53	4.39	4.28	4.21	4.15	4.10	4.06	3.94	3.83	3.68
7	0.05	0.025	8.07	6.54	5.89	5.52	5.29	5.12	4.99	4.90	4.82	4.76	4.57	4.40	4.16
7	0.10	0.05	5.59	4.74	4.35	4.12	3.97	3.87	3.79	3.73	3.68	3.64	3.51	3.40	3.24
8	0.05	0.025	7.57	6.06	5.42	5.05	4.82	4.65	4.53	4.43	4.36	4.30	4.10	3.94	3.68
8	0.10	0.05	5.32	4.46	4.07	3.84	3.69	3.58	3.50	3.44	3.39	3.35	3.22	3.11	2.94
9	0.05	0.025	7.21	5.71	5.08	4.72	4.48	4.32	4.20	4.10	4.03	3.96	3.77	3.60	3.35
9	0.10	0.05	5.12	4.26	3.86	3.63	3.48	3.37	3.29	3.23	3.18	3.14	3.01	2.89	2.72
10	0.05	0.025	6.94	5.46	4.83	4.47	4.24	4.07	3.95	3.85	3.78	3.72	3.52	3.35	3.09
10	0.10	0.05	4.96	4.10	3.71	3.48	3.33	3.22	3.14	3.07	3.02	2.98	2.85	2.73	2.55
15	0.05	0.025	6.20	4.77	4.15	3.80	3.58	3.41	3.29	3.20	3.12	3.06	2.86	2.69	2.41
15	0.10	0.05	4.54	3.68	3.29	3.06	2.90	2.79	2.71	2.64	2.59	2.54	2.40	2.28	2.08
20	0.05	0.025	5.87	4.46	3.86	3.51	3.29	3.13	3.01	2.91	2.84	2.77	2.57	2.40	2.10
20	0.10	0.05	4.35	3.49	3.10	2.87	2.71	2.60	2.51	2.45	2.39	2.35	2.20	2.07	1.86
30	0.05	0.025	5.57	4.18	3.59	3.25	3.03	2.87	2.75	2.65	2.57	2.51	2.31	2.12	1.81
30	0.10	0.05	4.17	3.32	2.92	2.69	2.53	2.42	2.33	2.27	2.21	2.16	2.01	1.88	1.64
50	0.05	0.025	5.34	3.97	3.39	3.05	2.83	2.67	2.55	2.46	2.38	2.32	2.11	1.92	1.57
50	0.10	0.05	4.03	3.18	2.79	2.56	2.40	2.29	2.20	2.13	2.07	2.03	1.87	1.73	1.46
100	0.05	0.025	5.18	3.83	3.25	2.92	2.70	2.54	2.42	2.32	2.24	2.18	1.97	1.77	1.38
100	0.10	0.05	3.94	3.09	2.70	2.46	2.31	2.19	2.10	2.03	1.97	1.93	1.77	1.62	1.31
1000	0.05	0.025	5.04	3.70	3.13	2.80	2.58	2.42	2.30	2.20	2.13	2.06	1.85	1.64	1.16
1000	0.10	0.05	3.85	3.00	2.61	2.38	2.22	2.11	2.02	1.95	1.89	1.84	1.68	1.52	1.13