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FURTHER ANALYSIS OF THE METABOLIC DATA FROM THE VIEWPOINT OF THE ALMOST-ONE PARAMETER HYPOTHESIS

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According to the first order kinetics, the logarithm of the serum concentration of a drug for the i-th subject, say $X_i(t) = ln\ C_i(t)$, administered at the instant $t = 0$, satisfies a linear equation

(1) $$X_i(t) = X_i(0) - k_i t,$$

if the initial phase of the absorption is neglected, where k_i denotes the rate constant for this subject.

Then taking the mean with respect to i, we obtain the equation for the mean, or the reference subject, namely

(2) $$X.(t) = X.(0) - k.t.$$

Eliminating t, we get the following formula:

(3) $$X_i(t) = a_i + b_i X.(t),$$

where we set

(4) $$a_i = X_i(0) - b_i X.(0), \text{ and } b_i = k_i/k. \quad .$$

Then the variance of $X_i(t)$ is given by

(5) $$V_x(t) = V_a + 2U_{ab}X.(t) + V_b X.^2(t),$$

where V_a, V_b, and U_{ab} denote the variance of a_i, that of b_i, and the covariance of a_i and b_i respectively, or

(6) $$V_x(t) = [s_a - s_b X.(t)]^2 + 2U_{ab}(1 + \rho)X.(t)$$

where s_a, s_b and ρ denote the standard deviation (SD) of a_i, that of b_i, and the correlation coefficient between a_i and b_i respectively. Note that we have

(7) $$\rho = U_{ab}/(V_a V_b)^{1/2}.$$

Now, according to the almost-one parameter hypothesis, ρ is almost equal to $(- 1)$, so that the SD of $X_i(t)$ is given by

(8) $$s_x(t) = s_a - s_b X.(t)$$

approximately.

Since ρ is not exactly equal to minus one, the last formula has a small bias. Let us estimate it.

Now, let us set

(9) $$d = s_a - s_b X.(t)$$

and

(10) $$V_x(t) = d^2 + \varepsilon,$$

and assume that $\varepsilon/d^2 << 1$. Then we have

(11) $$s_x(t) = d + \varepsilon/(2d),$$

and the bias is approximately given by

(12) $$\begin{aligned}\varepsilon/(2d) &= U_{ab}(1 + \rho)X.(t)/d \\ &\doteq - s_a s_b(1 + \rho)/CV_x(t),\end{aligned}$$

where $CV_x(t)$ denotes the coefficient of variation (CV) of $X_i(t)$.

Since $X_i(t)$ is a monotone decreasing function of t, and $s_x(t)$ is a monotone increasing function of t, $CV_x(t)$ is a monotone increasing function of t. Hence the bias is a monotone decreasing function of t, which means that s_b is overestimated, when $X.(t)$ is positive and the bias is neglected.

Naturally, if the sample size is sufficiently large, we may estimate at first V_b in the formula (5) and then we may compute the square root of this estimate. However, the sample size n of available data is usually one dozen or so and the regression estimate of V_b becomes sometimes negative.

The following data (Tables 1 ∿ 4) were obtained to study the bio-availability of commercial products, so that the data are classified according to manufacturers and others.

It is preferable to classify the data according to the magnitude of T_{max} to fit the model (1). However, to make the sample size n larger than 10, two, or three classes are pooled, if necessary.

Two examples are given in the previous papers [1,2], we shall add five more examples. Note that in the following examples the common logarithm is used, except in the last example. Since b_i is dimensionless by definition, the relation $s_b = CV\ of \cdot k_i$ is valid in the common logarithmic scale.

FURTHER ANALYSIS OF THE METABOLIC DATA

1. *Indomethacin.* 25mg per os. Table 1 and Figure 1.

   $T_{max} = 1 \sim 3^{hrs}$. $n = 17$.

   $$s_x(t) = \underset{\pm 0.038}{0.118} - \underset{\pm 0.0344}{0.0705}\, X.(t), \qquad 3 \le t \le 24,$$

   The regression estimate of V_b is negative.

2. *Naldixic acid.* 250mg per os. Table 2 and Figure 2.

   $T_{max} = 1$ or 2^{hrs}. $n = 16$.

   $$s_x(t) = \underset{\pm 0.007}{0.241} - \underset{\pm 0.019}{0.282}\, X.(t), \qquad 3 \le t \le 8,$$

   The regression estimate of V_b is equal to $(0.323)^2$.

3. *Metronidazole.* 250mg per os. Table 3 and Figure 3.

   $T_{max} = 2 \sim 3^{hrs}$. $n = 12$.

   $$s_x(t) = \underset{\pm 0.009}{0.177} - \underset{\pm 0.022}{0.188}\, X.(t), \qquad 6 \le t \le 32,$$

   The regression estimate of V_b is equal to $(0.305)^2$ and the CV obtained from the regression estimates of k_i's is 0.256.

4. *Fulfenamic acid.* 100mg per os. Table 4 [3] and Figure 4.

   $T_{max} = 1.5^{hrs}$. $n = 30$.

   $$s_x(t) = \underset{\pm 0.009}{0.161} - \underset{\pm 0.018}{0.079}\, X.(t), \qquad 2.5 \le t \le 8,$$

   In this case the regression estimate of V_b is negative.

5. *Amikacin.* 200mg intramuscular injection. Table 5 [4] and Figure 5.

   $t = 1 \sim 4^{hrs}$. $n = 12$.

   $$s_x(t) = \underset{\pm 0.009}{0.164} - \underset{\pm 0.011}{0.119}\, X.(t),$$

   We have $\rho(a_i, b_i) = -0.988$. The CV obtained directly from the regression estimates of k_i's is 0.127.

The authors are grateful to Dr. H. Matsuzaki. The original data for the last example were obtained through her.

Subj.	0.5^{hr}	1	2	3	4	6	8	24	Subj.	0.5^{hr}	1	2	3	4	6	8	24
A.1	*1035*	1249	*-1973*	2823	5100	10315	14437	16990	C.1	12676	8508	2218	*1824*	5143	12518	14815	19208
2	2007	-626	*-2817*	635	2798	4698	7620	17696	2	6861	3335	*-660*	1746	2351	9101	9666	16990
3	-2967	*-5196*	-569	2048	4191	10315	10362	20458	3	14089	8729	*-149*	665	5017	9914	11487	16778
4	3116	*-4065*	1707	4157	6778	12218	14089	19586	4	16778	13468	7852	4295	*1180*	4260	8268	18539
5	-183	-599	*-1156*	2111	5143	9431	13188	16198	5	14815	6968	1805	*-1106*	-952	5114	9208	14089
6	1574	*-1232*	-512	2328	5361	8996	11612	15850	6	10044	4295	1118	*-737*	2218	7670	10969	18239
7	4815	2924	1249	*835*	4342	9666	14202	20458	7	16778	13188	10458	*757*	3768	8697	9788	16990
8	-1584	*-2589*	-484	3224	5072	12441	*7122*	14815	8	4056	1163	*605*	2441	3410	7905	12076	14437
9	-2765	*-3434*	1163	4895	8508	10969	*10915*	20458	9	6478	2984	*680*	1765	3862	11487	12518	19208
10	2798	*-4814*	-1517	2218	4473	8996	11487	19586	10	8268	2924	1379	-22	*-1303*	3872	8416	13768
B.1	8069	5317	*315*	2111	5331	10315	14949	18239	D.1	11249	6778	947	*348*	3893	8894	*8097*	18239
2	4855	*1688*	4365	7375	11612	13565	18861	∞	2	∞	15376	9666	5607	*1113*	1373	8794	15086
3	20458	15229	13188	6421	*5452*	6655	7545	12924	3	10362	8633	2774	1249	*17*	4295	9031	17696
4	8996	1215	*-1492*	1146	3768	8996	12441	18239	4	15686	5986	232	*-390*	1046	6198	10362	16576
5	4473	2111	*315*	1851	4486	8069	9706	13979	5	10088	5686	2725	915	*835*	6478	10915	16383
6	3382	1925	*-1106*	1904	4855	12007	12076	19586	6	10362	8601	5498	2048	*1046*	6198	11612	18539
7	8069	*6091*	7033	*4023*	5935	16198	13010	18239	7	*19586*	20458	16198	3778	*757*	5986	9586	15850
8	5272	1463	*835*	4711	5186	11079	14089	15229	8	3645	*2218*	2291	2441	3830	9431	12924	20458
9	13872	*757*	1904	3152	4622	9469	12076	16778	9	4660	3768	*2161*	2269	4486	8069	12366	15686
10	17447	12441	9101	6253	4737	*4157*	7055	14318	10	8729	4895	915	-120	*-1035*	5406	10706	25229

Table 1 $(-X) \times 10^4$ Indomethacin capsule

Subj.	0.5^{hr}	1	2	3	4	5	6.5	8	Subj.	0.5^{hr}	1	2	3	4	5	6.5	8
A.1	3464	*6572*	5488	4176	237	-4486	-9830	-12291	C.1	-5784	*1082*	370	*4800*	1931	-1475	-7620	-10223
2	4878	6474	*9297*	5303	1065	-1904	-3585	-5100	2	-1169	1781	*2753*	2198	1486	-675	-2848	-2487
3	1620	2420	*7126*	4929	1303	1713	-4535	-5031	3	3353	*7124*	6471	4023	1129	-942	-3045	-4353
4	*2894*	980	*3422*	1984	-1457	-8097	-13565	-16990	4	∞	∞	-372	*5079*	3111	-975	-8013	-16990
5	*9309*	7911	5542	1248	-1979	-5498	-7100	∞	5	1781	*4260*	3233	2398	3389	*3446*	-1198	-2495
6	*7452*	6901	*8462*	5544	2601	314	-2090	-2684	6	-18239	-6925	1951	3115	4526	*5041*	402	-3179
7	*8336*	7964	7902	*8238*	3214	-22	-2636	-3279	7	-61	453	*4050*	3359	3541	*4670*	-731	-5560
8	7946	*8091*	5156	849	-2321	-4306	-6162	∞	8	∞	-4962	-3468	-2418	*4993*	4755	1139	-3605
9	7023	*8884*	7284	4014	1052	-1427	-3536	-5638	9	∞	-2441	-545	*1717*	584	*2574*	1443	-5622
10	7211	*8134*	6621	4628	1035	-3197	-6968	-7595	10	*4062*	3438	4639	*8420*	4254	821	48	*170*
B.1	2964	3788	*4002*	2648	*3073*	438	-3851	-5214	D.1	∞	-6799	-3036	-2480	2279	*3391*	-1180	-5817
2	2251	2665	6872	*7121*	5408	2639	660	-325	2	-904	286	3908	5501	*6005*	3122	934	-615
3	1364	2299	4464	*5204*	1752	-2069	-6737	-14559	3	-5031	-3990	-3197	2041	*5697*	4739	2562	667
4	-3134	-3344	*3111*	2804	2548	*3698*	-1818	-1637	4	∞	∞	-10177	-8665	86	*3090*	-1296	-4881
5	-650	418	4630	*5266*	5112	2923	-501	-4449	5	-1325	-580	4198	*4661*	3012	2227	-958	-2306
6	3530	4891	*6556*	6422	5623	3892	-1481	-6253	6	-5003	-1494	2598	*4211*	4195	*4925*	3749	2502
7	871	5814	*6662*	5533	4396	2345	-1605	-2291	7	-443	1335	2049	4423	*6292*	5263	3854	2204
8	286	*7000*	6823	3126	1590	-273	-283	-1481	8	-3298	*4153*	3806	2400	-458	-2620	-5784	-8697
9	741	5806	*6760*	5691	2767	1116	-1018	-2211	9	-2676	2360	*5373*	4288	2266	366	-1593	-3028
10	-2041	-1355	-2041	*7543*	5579	1556	-3161	-4609	10	-2749	-1361	-921	4943	*5871*	4118	492	199

Table 2 $X \times 10^4$ Naldixic acid tablet

Subj.	0.75 hr	1.5	2.5	4.0	6.0	8.0
A.1	8028	10966	8109	2577	-223	-6021
2	10626	8965	4955	1584	-6021	-3468
3	10500	10821	7050	6149	1931	-2676
4	9652	9777	6920	2833	-2366	-3768
5	-2076	4425	11937	7520	3483	-915
6	5786	9217	11059	7505	1335	-6576
7	8831	9504	7427	3181	-1249	-5086
8	5775	9253	9196	5011	-132	-5528
9	11679	9238	6284	3636	-915	-2366
10	6618	6222	6972	4150	-1192	-3979
11	11926	10298	7931	4249	934	-555
12	8401	9586	7218	5490	828	-3279
13	9232	9850	7474	3636	828	-3468
14	7388	11565	8363	4914	294	-2291
15	9754	7076	6712	7832	2014	-1612
C.1	4166	7126	8519	5694	3243	-362
2	8904	6767	6875	2765	899	-2757
3	5694	7789	5944	6435	4757	-410
4	5198	9969	8357	4014	-1367	-4815
5	10781	9528	7945	4116	-44	-4437
6	-3279	253	1847	7152	7404	1492
7	-4089	9112	8500	5105	531	-4089
8	5105	11504	9315	6325	1732	-2676
9	8000	10382	8537	4742	2227	-1135
10	∞	3579	5611	8062	1875	-4318
11	-10969	6776	10103	6513	2227	-605
12	-13979	9227	10103	8704	3838	-1249
13	-1871	-5376	7466	6702	2577	-132
14	11183	9304	6160	1987	-2147	∞
15	-1675	11297	8370	4728	531	-2147
E.1	∞	4983	9562	7372	4548	2577
2	∞	6222	9633	5717	-177	-2366
3	7612	7284	6785	5809	3483	492
4	-757	8129	8351	5366	-315	-4089
5	11884	9680	7505	5527	969	-1938
6	∞	334	9952	8585	4728	1847
7	-5086	7846	8621	5263	755	-1192
8	∞	-6778	1584	5999	7084	2095
9	8762	8904	5999	3711	531	-2147
10	-15229	∞	∞	6415	7642	1492
11	-15229	-5528	11661	7760	3160	-2076
12	10261	11106	9703	6053	2788	-2076
13	3766	8142	8162	5132	1644	-862
14	8531	8102	5635	2553	-1024	-7447
15	10615	10752	8287	5172	531	-1938

Table 3a $X \times 10^4$ Fulfenamic acid capsule

FURTHER ANALYSIS OF THE METABOLIC DATA

Subj.	*0.75*^{hr}	*1.5*	*2.5*	*4.0*	*6.0*	*8.0*
B.1	2201	*9671*	9058	5366	374	-2007
2	*10554*	8482	5658	2014	-3979	-10000
3	*9823*	9731	7267	5119	1644	-3010
4	3927	*8000*	6571	1335	-4815	∞
5	8055	*10434*	8055	4409	294	-2076
6	3838	5340	*5775*	4330	*4378*	-362
7	∞	*10453*	8325	4900	1967	-3188
8	-7447	-1549	5658	*7752*	5740	-555
9	6656	*11183*	7853	4518	128	-5376
10	*8716*	7917	7059	4216	-1079	-4437
11	-12218	*7896*	7738	4579	-1487	-7959
12	8837	*10137*	9063	6551	755	-4949
13	7551	*9345*	7396	4065	-555	-4815
14	7853	*9523*	6749	3032	-2218	-3872
15	*10000*	8388	5563	1644	-862	-7212
D.1	-5229	7604	*7973*	6628	3324	-1135
2	-3188	*7110*	6656	4983	374	-4559
3	9800	*10013*	7723	5403	128	-3768
4	7832	*8814*	6085	2601	-2007	-5086
5	*9987*	9106	7308	5694	1206	-3565
6	8299	*8814*	8261	6031	1303	-5528
7	∞	8681	*8698*	6191	1673	-2007
8	∞	8235	*11345*	8470	3820	-555
9	9571	*10069*	7642	5514	864	-2007
10	-10458	43	6571	*7767*	3927	531
11	-9208	-2147	*9566*	8871	5775	1644
12	-7447	6964	*10719*	8476	4232	-88
13	7566	*10035*	8585	3838	755	-410
14	*11326*	9605	7193	4183	294	-1024
15	-5528	-809	*9841*	8727	4314	1038

Table 3b

Subj.	1^{hr}	2	3	4	6	8	24	32
AA.1	*7401*	7123	7075	6558	5702	4732	-577	-3634
2	6154	*6958*	6645	6328	5281	*5457*	2158	634
3	*6940*	6639	*7439*	6253	5561	4701	397	-1966
4	6711	*6897*	5938	6060	5378	4893	822	-1639
5	4102	7127	*7139*	6607	4904	4473	815	-2505
AB.1	7577	7589	*7790*	6178	*6195*	5399	819	-1653
2	5709	*8218*	7751	*7928*	6536	5467	-559	-3427
3	6522	*7874*	6641	5965	5721	*6142*	1516	-1155
4	*8135*	7256	6882	6532	6307	3583	-2744	-6203
5	5765	*6315*	5540	5187	4845	3425	-2474	-6712
BA.1	-6847	3683	*7960*	7797	5970	*6234*	655	-3772
2	1492	5856	*6977*	6845	6313	6137	2907	958
3	-6273	-875	*7798*	7423	6998	5541	2527	1152
4	776	5793	6352	*6503*	4789	4323	532	-2513
5	-4217	*8311*	8055	7445	6500	5945	1450	-1572
BB.1	∞	54	4947	*6631*	6515	5860	1646	-545
2	-7228	-2877	2183	4610	*7883*	6846	725	-1672
3	∞	-1292	4423	4803	*7316*	6431	1510	-1189
4	∞	3394	3917	*4498*	3612	2749	-3072	-9477
5	∞	-3311	5681	*6993*	5594	4917	-2387	-7383

Subj.	1^{hr}	2	3	4	6	8	24	32
CA.1	-4467	-2019	-899	-335	*906*	408	*2835*	348
2	∞	∞	-4194	-2510	-2455	-1583	*2182*	497
3	∞	-20809	-3760	938	1585	*2007*	687	-967
4	-12358	6390	*6639*	6271	5343	4983	707	-1467
5	-9948	3550	5971	*6910*	5828	5931	3150	1235
CB.1	-3925	4169	*4705*	4241	3639	*3929*	1788	-218
2	∞	∞	-6625	-3152	-354	*95*	-1280	*312*
3	-17471	-9014	-3966	-3231	-377	*2637*	1295	-1383
4	∞	-9031	-4387	-3189	-1746	*50*	-9727	-14389
5	∞	∞	∞	∞	-52	*3754*	1240	-5941
DA.1	∞	3678	6188	*6272*	5556	4954	-597	-2339
2	∞	∞	∞	∞	-11427	-8687	*1862*	66
3	∞	732	*7842*	7398	5649	*5944*	2776	588
4	403	3549	5123	*6789*	5911	5355	699	-1729
5	∞	∞	∞	∞	∞	∞	∞	∞
DB.1	∞	-1414	2942	*7147*	4612	*5851*	986	-1523
2	∞	∞	∞	-9289	-3799	*2663*	-745	-4045
3	∞	∞	-8289	-5035	4437	*7235*	2799	1179
4	∞	∞	∞	∞	-8887	-3671	*-3331*	-7945
5	*-3221*	-7889	∞	∞	-2208	*2337*	-1496	-7506

Table 4. $X \times 10^4$ Metronidazole sugar-coated pill

FURTHER ANALYSIS OF THE METABOLIC DATA

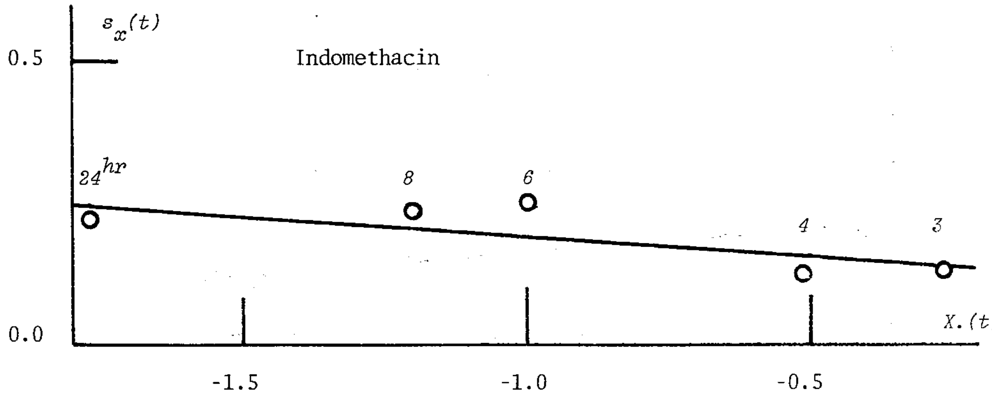

Fig. 1

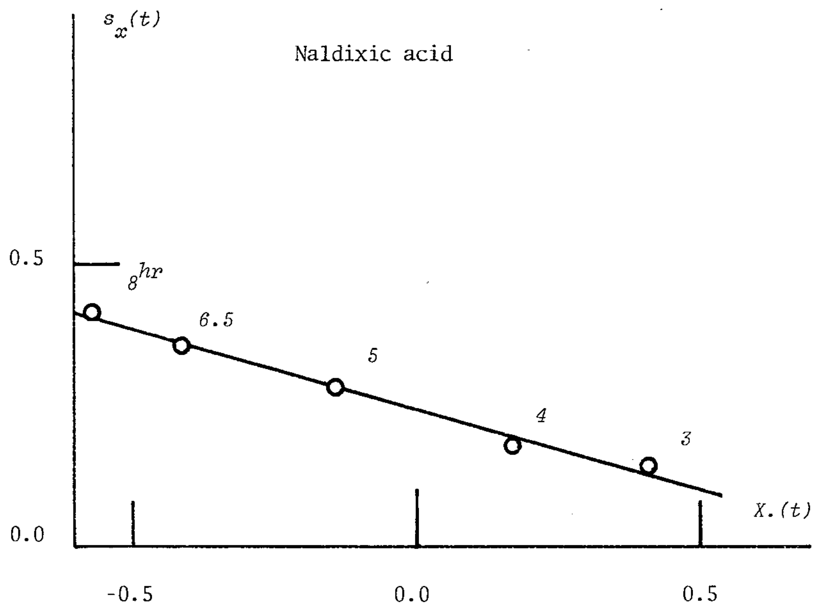

Fig. 2

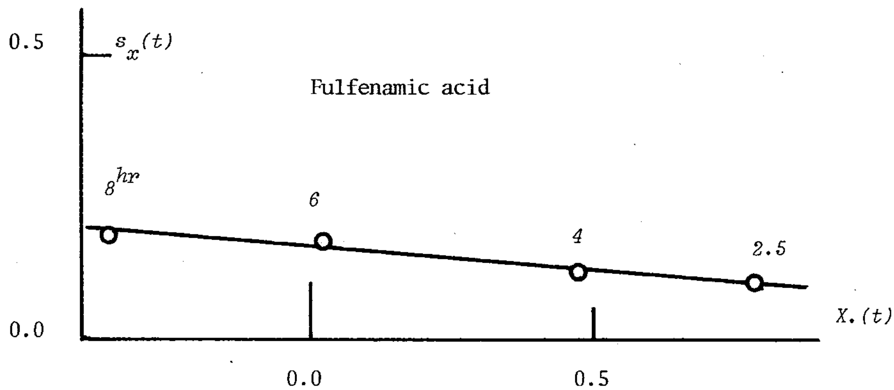
0.5
$s_x(t)$
Fulfenamic acid
8^{hr}
6
4
2.5
0.0
$X.(t)$
0.0
0.5

Fig. 3

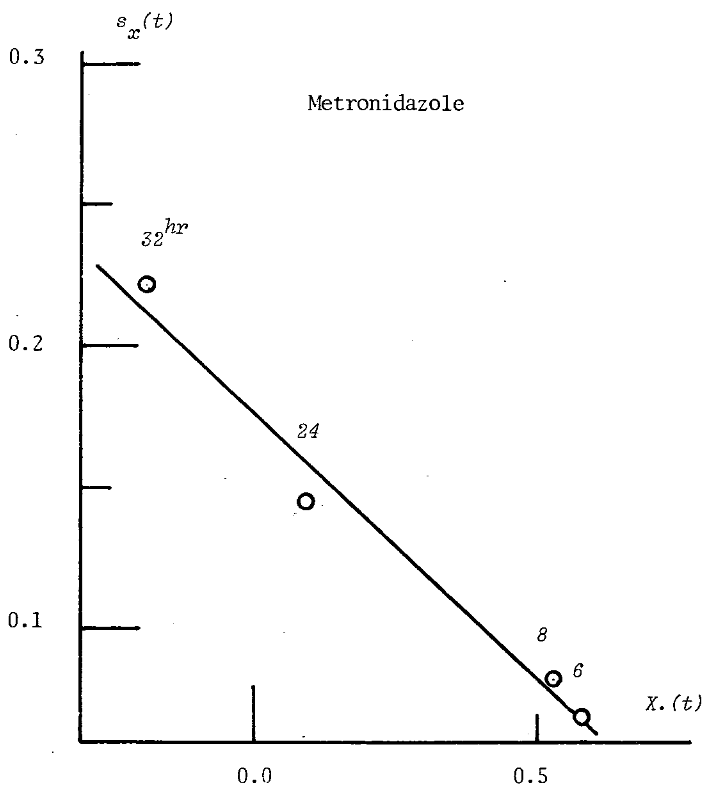
$s_x(t)$
0.3
Metronidazole
32^{hr}
0.2
24
0.1
8
6
$X.(t)$
0.0
0.5

Fig. 4

	$C^{\mu g/ml}$								
Subj.	0.5^{hrs}	1	2	3	4	$10^4 k_i$	$10^3 X_i(0)$	$10^4 a_i$	$10^4 b_i$
i = 1	12.6	11.8	8.7	6.0	3.9	3693	2869	2461	9123
2	10.1	11.6	8.2	5.1	3.2	4338	2921	-1602	10717
3	13.1	12.7	8.6	5.8	3.9	3936	2937	1413	9723
4	13.0	11.8	8.0	4.7	3.4	4265	2896	-1335	10535
5	12.6	12.1	9.2	6.5	4.3	3451	2873	4220	8525
6	11.1	11.2	8.1	5.3	3.5	3914	2835	555	9668
7	11.7	10.4	7.2	4.5	3.2	4006	2747	-983	9896
8	9.5	10.7	7.5	4.7	3.1	4184	2812	-1599	10335
9	10.2	9.8	6.0	3.3	1.9	5519	2857	-10633	13635
10	12.2	12.2	8.6	5.7	3.9	3833	2897	1744	9468
11	9.2	12.1	9.1	6.5	4.2	3511	2880	3860	8673
12	11.2	13.0	9.4	5.9	4.1	3928	2980	1899	9702
					mean	4048	2875	0	10000

Table 5 Amikacin

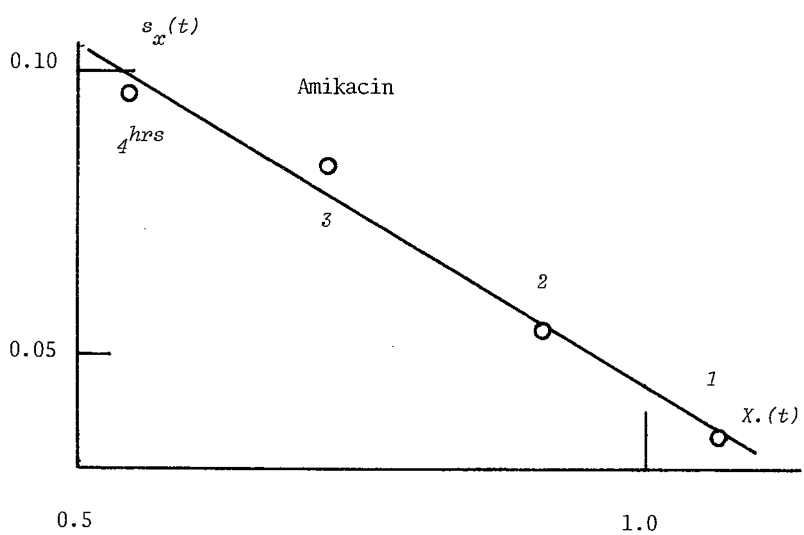

Fig. 5

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