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Comparison of the Functional-Link Net and the Generalized Delta Rule Net in Quantitative Structure–Activity Relationship Studies

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The quantitative structure–activity relationships (QSARs) of 37 carboquone derivatives with antileukemic activity and 51 benzodiazepine derivatives with anti-pentylentetrazole activity were studied using two neural computing methods—the functional-link net (FUNCLINK) and the generalized delta rule net with the back propagation of error (GDR). Both methods showed good fitting of the activity values in the two data sets. A great difference appeared, however, in the prediction of the activity values: GDR's predictive ability is much lower than FUNCLINK's. To elucidate the difference of the predictive ability, we examined the contribution of parameters to activity using the QSAR models of carboquone derivatives by plotting the contribution curves. Well-regulated and similar contribution curves resulted for all parameters in both the FUNCLINK and GDR models for the entire data. On the other hand, the contribution curves for the leave-one-out models derived by eliminating one compound from the data set showed that much greater deviations occurred in GDR than in FUNCLINK. The QSAR models of GDR seemed to depend greatly upon each individual compound.

Keywords QSAR; functional-link net; generalized delta rule net; semilinear contribution; leave-one-out prediction; neural network; carboquone; benzodiazepine

Introduction

Neural computing methods for simulating the data processing of neurons and brain have been suggested and widely accepted, such as the generalized delta rule net with the back propagation of error (GDR),[1] Hopfield net,[2,3] and Boltzmann machine.[4] Such methods are characterized by the high ability of pattern recognition, associative memory and other features. Successful applications of the methods to special fields have proved their usability and high performance. Against this background, GDR has been recently introduced into quantitative structure–activity relationship (QSAR) studies,[5–10] since QSAR possesses the feature of pattern recognition. Based on its algorithm, GDR is generally considered as a semilinear approach, and the fitting of activity is usually superior to linear methods such as multiple regression analysis (MRA).[5,6] Based on a quite different algorithm devised by Klassen and Pao,[11] we recently developed a semilinear QSAR method called FUNCLINK (the functional-link net).[12,13] The difference in the two approaches is at that GDR transforms the parameters through a multilayer net by semilinear fitting of the parameters to the activity, while FUNCLINK uses semilinear functions for the same purpose. The QSAR applications have shown that, though a good fitting of the activity is realized by both FUNCLINK and GDR, a great difference results in the leave-one-out prediction—that is, the predictive ability of GDR is much lower than FUNCLINK.[12,13]

In the present study, we compared the QSAR results of FUNCLINK and those of GDR applied to 37 carboquone derivatives with antileukemic activity[14] and to 51 benzodiazepine derivatives with anti-pentylentetrazole activity.[15] QSAR analysis by FUNCLINK showed good results in both reproduction and leave-one-out prediction of the activity. For GDR, however, the leave-one-out prediction was much poorer, though the reproduction of the activity values was superior to that by FUNCLINK. In order to elucidate this difference, the contribution of parameters to activity was investigated by plotting the contribution curves (CCVs) in the QSAR models for carboquone derivatives. In the FUNCLINK and GDR models for the entire set of data, the contribution of each parameter was well regulated and consistent with that in the multiple regression model. CCVs were also drawn for the leave-one-out models calculated by eliminating one compound from the data set. In this case, most of the CCVs by FUNCLINK retained the original pattern well, while GDR showed greater deviations.

Methods

FUNCLINK A published program[11] was used after slight modification.[12] Two steps are necessary for the QSAR analysis of FUNCLINK. In the first step, original parameters are transformed by the functional link. The following six semilinear functions[12] were used for functional linking: x_i^2, $\sin(\pi x_i)$, $\cos(\pi x_i)$, $\log(9x_i+1)$, $4(x_i-0.5)^3+0.5$, and $x_i x_j$. Here, x_i and x_j are the original parameters which are scaled into the range of 0.0 to 1.0. The second step is concerned with QSAR estimation using the functionally linked parameters. In a general way, FUNCLINK makes all possible combinations of the parameters, and then each combination is fed to the network for QSAR estimation in order to select a subset which gives the best fitting of observed activity.

FUNCLINK uses a two layer network—an input layer for the input of parameters, and an output layer for the output of calculated activity values. For QSAR analysis of a data set whose activity data is given by a continuous variate, only one net is needed in the output layer. Each input-net is connected with the output-net. The connections simulate the transmission of the signals. The strength of the connections between different nets is distinct, by which the amount of signals into the output-net is controlled. The value input into the output-net is the sum of the products of all the input values (parameters) and the corresponding strength of connections. The values output from the output-net are transformed by a sigmoidal activation function. Observed activity values are also scaled into the range of 0.0 to 1.0, and used as the reference for the output values. Learning is conducted by iterative correction of the strength values to reduce the error between the output values and the reference values, and is complete when the error is sufficiently small. For the detailed procedure of FUNCLINK, see the literature.[11,12]

Generalized Delta Rule Net A published program was used.[11] A network with one hidden layer was adopted. The first layer was for parameter input. The parameters were scaled into the range of 0.0 to 1.0. The third layer contained one node for output of the calculated values. For the detailed procedure, see ref. 11. The relevant equations used in the program are listed below for reference.

Internal values of the nodes in the second layer:

$$Z_j=\Sigma W_{ji}X_i \quad (1)$$

Sigmoidal activity function:

$$f(Z_j)=1/[1+\exp(-Z_j+\theta)] \quad (2)$$

Output values from the nodes in the second layer:

$$O_j=f(Z_j) \quad (3)$$

Internal value of the node in the third layer:

$$Z_k=\Sigma W_{kj}O_j \quad (4)$$

Output value from the node in the third layer:

$$Y_k=f(Z_k) \quad (5)$$

Correction of weights W_{kj}:

$$\Delta W_{kj}=\eta\delta_k O_j \quad (6)$$

$$\delta_k=(T_k-Y_k)f'(Z_k) \quad (7)$$

Correction of weights W_{ji}:

$$\Delta W_{ji}^{t+1}=\eta\delta_j O_i+\alpha\Delta W_{ji}^{t} \quad (8)$$

$$\delta_j=f'(Z_j)\Sigma\delta_k W_{kj} \quad (9)$$

In these equations, θ is the threshold, η is the constant called "momentum rate," T is the reference activity value, and α is the constant called "learning rate."

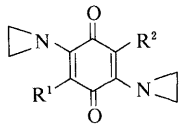
Data Sets for QSAR Estimation The two data sets, 37 2,5-bis(1-aziridinyl)-*p*-benzoquinones (carboquone derivatives) with antileukemic activity[14] and 51 benzodiazepine derivatives with anti-pentylentetrazole activity[15] were cited from the literature. For the carboquone derivatives, we selected the activity data determined as optimal dose on a chronic treatment schedule in mice.

Parameters a) Carboquone Derivatives: Since the QSAR for the data set was investigated by Yoshimoto *et al.* using MRA,[16] we employed the same well-defined physicochemical parameters in our QSAR investigation in order to give an objective comparison of the results. The parameters were the following substituent constants: 1) hydrophobic constant PI_2 for substituent R^2; 2) molar refractivity MR_1 for substituent R^1; 3) $PI_{1,2}$ (PI_1+PI_2); 4) $MR_{1,2}$ (MR_1+MR_2); and 5—6) electronic substituent constants F and R, where F is the sum of field effects, and R is the sum of resonance effects of R^1 and R^2. The values of the parameters are shown in Table I.

b) Benzodiazepine Derivatives: Seven parameters were used in the QSAR analysis. They were all employed by Yoshimoto and his colleagues in MRA of the same data set.[15] The parameters are *MR*-3, *PI*-3, *MR*-7, σ_m-3, *F*-4, *R*-4, and *I*-7. *MR* is the molar refractivity, *PI* is the hydrophobic constant, σ_m is the Hammett electronic constant, *F* and *R* are the field effect and the resonance effect, respectively, and *I*-7 is an indicator variable being 1 for H and 0 for substituents except H. The figure after each parameter (ex. 3 in *MR*-3) indicates the position of the substituent. The values of the parameters are shown in Table II.

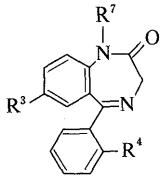
CCV The contribution of parameters to activity in QSAR models by

TABLE I. Structures of 37 Carboquone Derivatives and Their Parameters Used in the QSAR Analysiss



No.	R^1	R^2	$MR_{1,2}$	$PI_{1,2}$	PI_2	MR_1	F	R
1	C_6H_5	C_6H_5	5.08	3.92	1.96	2.54	0.16	−0.16
2	CH_3	$(CH_2)_3C_6H_5$	4.50	3.66	3.16	0.57	−0.08	−0.26
3	C_5H_{11}	C_5H_{11}	4.86	5.00	2.50	2.43	−0.08	−0.26
4	$CH(CH_3)_2$	$CH(CH_3)_2$	3.00	2.60	1.30	1.50	−0.08	−0.26
5	CH_3	$CH_2C_6H_5$	3.57	2.51	2.01	0.57	−0.12	−0.14
6	C_3H_7	C_3H_7	3.00	3.00	1.50	1.50	−0.08	−0.26
7	CH_3	$CH_2OC_6H_5$	3.79	2.16	1.66	0.57	−0.04	−0.13
8	$(CH_2)_2OCON(CH_3)_2$	$(CH_2)_2OCON(CH_3)_2$	6.14	0.72	0.36	3.07	−0.08	−0.26
9	C_2H_5	C_2H_5	2.06	2.00	1.00	1.03	−0.08	−0.26
10	CH_3	$(CH_2)_2OCH_3$	2.28	1.03	0.53	0.57	−0.08	−0.26
11	OCH_3	OCH_3	1.58	−0.04	−0.02	0.79	0.52	−1.02
12	CH_3	$CH(CH_3)_2$	2.07	1.80	1.30	0.57	−0.08	−0.26
13	C_3H_7	$CH(OCH_3)CH_2OCONH_2$	4.24	0.98	−0.52	1.50	−0.04	−0.13
14	CH_3	CH_3	1.14	1.00	0.50	0.57	−0.08	−0.26
15	H	$CH(CH_3)_2$	1.60	1.30	1.30	0.10	−0.04	−0.13
16	CH_3	$CH(OCH_3)CH_2CH_3$	2.75	1.53	1.03	0.57	−0.04	−0.13
17	C_3H_7	$(CH_2)_2OCONH_2$	3.56	1.45	−0.05	1.50	−0.08	−0.26
18	$(CH_2)_2OCH_3$	$(CH_2)_2OCH_3$	3.42	1.03	0.53	1.71	−0.08	−0.26
19	C_2H_5	$CH(OC_2H_5)CH_2OCONH_2$	4.23	0.98	−0.02	1.03	−0.04	−0.13
20	CH_3	$(CH_2)_2OCOCH_3$	2.78	1.23	0.73	0.57	−0.08	−0.26
21	CH_3	$(CH_2)_3$ dimer	1.96	2.00	1.50	0.57	−0.08	−0.26
22	CH_3	C_2H_5	1.60	1.50	1.00	0.57	−0.08	−0.26
23	CH_3	$CH(OCH_2CH_2OCH_3)CH_2OCONH_2$	4.45	0.01	−0.49	0.57	−0.04	−0.13
24	CH_3	$CH_2CH(CH_3)OCONH_2$	3.09	0.75	0.25	0.57	−0.08	−0.26
25	C_2H_5	$CH(OCH_3)CH_2OCONH_2$	3.77	0.48	−0.52	1.03	−0.04	−0.13
26	CH_3	$CH(C_2H_5)CH_2OCONH_2$	3.55	1.25	0.75	0.57	−0.08	−0.26
27	CH_3	$CH(OC_2H_5)CH_2OCONH_2$	3.77	0.48	−0.02	0.57	−0.04	−0.13
28	CH_3	$(CH_2)_3OCONH_2$	3.09	0.95	0.45	0.57	−0.08	−0.26
29	CH_3	$(CH_2)_2OCONH_2$	2.63	0.45	−0.05	0.57	−0.08	−0.26
30	C_2H_5	$(CH_2)_2OCONH_2$	3.09	0.95	−0.05	1.03	−0.08	−0.26
31	CH_3	$(CH_2)_2OH$	1.78	0.34	−0.16	0.57	−0.08	−0.26
32	CH_3	$CH(CH_3)CH_2OCONH_2$	3.09	0.75	0.25	0.57	−0.08	−0.26
33	CH_3	$CH(OCH_3)CH_2OCONH_2$	3.31	−0.02	−0.52	0.57	−0.04	−0.13
34	H	$N(CH_2)_2$	1.66	0.18	0.18	0.10	0.10	−0.92
35	$(CH_2)_2OH$	$(CH_2)_2OH$	2.42	−0.32	−0.16	1.21	−0.08	−0.26
36	CH_3	$N(CH_2)_2$	2.13	0.68	0.18	0.57	0.06	−1.05
37	CH_3	$CH(OCH_3)CH_2OH$	2.47	−0.13	−0.63	0.57	−0.04	−0.13

TABLE II. Structures of 51 Benzodiazepine Derivatives and Their Parameters Used in QSAR Analysis



No.	Substituents	*MR*-3	*PI*-3	*MR*-7	σ_m-3	*F*-4	*R*-4	*I*-7
1	3-Cl-7-iso-C_5H_{11}	0.60	0.71	2.42	0.37	0.00	0.00	0.00
2	3-SC_2H_5	1.84	1.07	0.10	0.15	0.00	0.00	1.00
3	3-SC_4H_9	2.77	2.07	0.10	0.15	0.00	0.00	1.00
4	3-NO_2-7-iso-C_5H_{11}	0.74	−0.28	2.42	0.71	0.00	0.00	0.00
5	3-$N(CH_3)_2$	1.56	0.18	0.10	−0.15	0.00	0.00	1.00
6	3-Cl-4-OCH_3	0.60	0.71	0.10	0.37	0.26	−0.51	1.00
7	3-Cl-7-$(CH_2)_3OH$	0.60	0.71	1.65	0.37	0.00	0.00	0.00
8	3-NO_2-7-$CH_2CONHCH_3$	0.74	−0.28	1.92	0.71	0.00	0.00	0.00
9	3-Cl-7-$(CH_2)_2N(C_2H_5)_2$	0.60	0.71	3.41	0.37	0.00	0.00	0.00
10	3-Cl-7-$CH_2CON(CH_3)_2$	0.60	0.71	2.39	0.37	0.00	0.00	0.00
11	3-Cl-7-$CH_2C_6H_5$	0.60	0.71	3.00	0.37	0.00	0.00	0.00
12	3-Cl-7-$(CH_2)_2N(CH_3)_2$	0.60	0.71	2.48	0.37	0.00	0.00	0.00
13	3-Cl-4-F-7-$(CH_2)_3N(CH_3)_2$	0.60	0.71	2.95	0.37	0.43	−0.34	0.00
14	3-CF_3-7-$CH_2CONHCH_3$	0.50	0.88	1.92	0.43	0.00	0.00	0.00
15	3-SCH_3	1.38	0.61	0.10	0.15	0.00	0.00	1.00
16	3-Cl-7-CH_2CONH_2	0.60	0.71	1.44	0.37	0.00	0.00	0.00
17	3-$SOCH_3$	1.37	−1.58	0.10	0.52	0.00	0.00	1.00
18	3-Cl-4-CH_3	0.60	0.71	0.10	0.37	−0.04	−0.13	1.00
19	3-$N(CH_3)_2$-7-CH_3	1.56	0.18	0.57	−0.15	0.00	0.00	0.00
20	3-Cl-4-F-7-$(CH_2)_2N(C_2H_5)_2$	0.60	0.71	3.41	0.37	0.43	−0.34	0.00
21	3-NO_2-7-$(CH_2)_3N(CH_3)_2$	0.74	−0.28	2.95	−0.15	0.00	0.00	0.00
22	3-NO_2-7-$(CH_2)_2N(CH_3)_2$	0.74	−0.28	2.48	0.71	0.00	0.00	0.00
23	3-Cl-4-Cl	0.60	0.71	0.10	0.37	0.41	−0.15	1.00
24	3-Cl-7-CH_2-cyc-C_3H_5	0.60	0.71	1.82	0.37	0.00	0.00	0.00
25	3-CN	0.63	−0.57	0.10	0.56	0.00	0.00	1.00
26	3-NO_2-4-CF_3	0.74	−0.28	0.10	0.71	0.38	0.19	1.00
27	3-Cl	0.60	0.71	0.10	0.37	0.00	0.00	1.00
28	3-CN-4-F	0.63	−0.57	0.10	0.56	0.43	−0.34	1.00
29	3-Cl-7-C_2H_5	0.60	0.71	1.03	0.37	0.00	0.00	0.00
30	3-SCH_3-7-CH_3	1.38	0.61	0.57	0.15	0.00	0.00	0.00
31	3-Cl-7-CH_2COCH_3	0.60	0.71	1.51	0.37	0.00	0.00	0.00
32	3-Cl-4-Br	0.60	0.71	0.10	0.37	0.44	−0.17	1.00
33	3-NO_2-4-CF_3-7-CH_3	0.74	−0.28	0.57	0.71	0.38	0.19	0.00
34	3-CF_3-7-$(CH_2)_2N(CH_3)_2$	0.50	0.88	2.48	0.43	0.00	0.00	0.00
35	3-Cl-7-$CH_2CH=CH_2$	0.60	0.71	1.45	0.37	0.00	0.00	0.00
36	3,4-Cl_2-7-CH_3	0.60	0.71	0.57	0.37	0.41	−0.15	0.00
37	3-Cl-7-CH_3	0.60	0.71	0.57	0.37	0.00	0.00	0.00
38	3-NO_2-4-Cl-7-CH_3	0.74	−0.28	0.57	0.71	0.41	−0.15	0.00
39	3-CF_3-4-CF_3	0.50	0.88	0.10	0.43	0.38	0.19	1.00
40	3-Br	0.89	0.86	0.10	0.39	0.00	0.00	1.00
41	3-CN-7-CH_3	0.63	−0.57	0.57	0.56	0.00	0.00	0.00
42	3-NO_2	0.74	−0.28	0.10	0.71	0.00	0.00	1.00
43	3-NO_2-7-CH_3	0.74	−0.28	0.57	0.71	0.00	0.00	0.00
44	3-CF_3	0.50	0.88	0.10	0.43	0.00	0.00	1.00
45	3-Cl-4-F-7-CH_3	0.60	0.71	0.57	0.37	0.00	−0.34	0.00
46	3-CF_3-7-$CH_2CH=CH_2$	0.50	0.88	1.45	0.43	0.00	0.00	0.00
47	3-NO_2-4-Cl	0.74	−0.28	0.10	0.71	0.41	−0.15	1.00
48	3-NO_2-7-NH_2	0.74	−0.28	0.54	0.71	0.00	0.00	0.00
49	3-NO_2-4-NO_2	0.74	−0.28	0.10	0.71	0.67	0.16	1.00
50	3-NO_2-4-F	0.74	−0.28	0.10	0.71	0.43	−0.34	1.00
51	3-NO_2-4-F-7-CH_3	0.74	−0.28	0.57	0.71	0.43	−0.34	0.00

FUNCLINK and GDR was investigated by drawing the CCVs of the parameters, since the contribution of parameters in a semilinear QSAR model generally exhibits a semilinear form. A CCV was drawn in the following way. For a parameter in the QSAR model, a number of points over the range of the parameter values were chosen, and the activity values were calculated while all other parameters were kept at their median values. Then, the CCV was drawn by plotting the calculated activity against the parameter values.

The CCVs of the parameters were drawn in the semilinear QSAR model for the whole set of data as well as in the leave-one-out model which was derived for the data sets in which a compound was left out. We call the latter CCVs "leave-one-out CCVs." All such CCVs for the same parameter were drawn on the same axes to see what deviations resulted.

Results and Discussion

QSAR Estimation. a) Carboquone Derivatives a-1) QSAR by FUNCLINK: The correlation of the structure of 37 carboquone derivatives with antileukemic activity as optimal dose on a chronic treatment schedule was analyzed

by MRA[16] and FUNCLINK.[12] The QSAR equations are shown here for comparison with the results from GDR.

FUNCLINK:

$$I_q = 1.894\cos(\pi PI_{1,2}) + 0.757\cos(\pi MR_1) + 2.438\cos(\pi F) - 3.938R \quad (10)$$

$n=37$; $r=0.951$; $s=0.169$; $F=76.4$

leave-one-out: $r=0.935$

MRA:

$$\log 1/C = -0.352PI_2 - 0.290MR_1 - 2.075F - 1.165R + 5.383 \quad (11)$$

$(t=7.58)$ (4.48) (4.02) (4.65) (44.55)

$n=37$; $r=0.894$; $s=0.247$; $F=31.7$

leave-one-out: $r=0.843$

In Eq. 10, Iq is the internal value of the node in the second layer, n is the number of compounds, r is the multiple correlation coefficient, and s is the standard deviation. Three semi-linear parameters, $\cos(\pi PI_{1,2})$, $\cos(\pi MR_1)$, and $\cos(\pi F)$, and a linear parameter, R, were selected in the equation. Since $\cos(x)$ $(0<x<\pi)$ is a decreasing function, it is easily confirmed that the four parameters in Eq. 10 all exhibit negative correlation with the activity, as do those parameters in Eq. 11 derived by MRA. The leave-one-out prediction was also performed to check the predictability of Eqs. 10 and 11. The activity values calculated using Eq. 10 are listed in Table III along with those predicted by the leave-one out prediction.

a-2) QSAR by GDR: The four parameters, $PI_{1,2}$, MR_1, F, and R, selected in the QSAR models by MRA and FUNCLINK were also used for GDR's QSAR estimation. The number of nodes in the second layer, η, and α were examined by a preliminary calculation in order to obtain the best QSAR result. As shown in Table IV, the number of nodes in the second layer varied from 1 to 14, but the correlation coefficients in recognition were not directly improved. When N_{node} was 4, 9, and 11—14, the QSAR models showed good correlation, and the best correlation was derived at $N_{node}=13$. The correlation coefficients by leave-one-out prediction were also calculated and shown in Table IV. No good relationship in correlation coefficients between the recognition and the leave-one-out prediction

TABLE III. Calculated and Predicted Activity Values[a] by FUNCLINK and GDR for Carboquone Derivatives

No.	Obsd.	FUNCLINK		GDR	
		Calcd.	Pred.[b]	Calcd.	Pred.[b]
1	4.140	4.148	4.149	4.159	4.191
2	4.210	4.471	4.537	4.247	4.430
3	4.521	4.202	4.176	4.150	4.164
4	4.589	4.614	4.618	4.588	4.636
5	4.691	4.704	4.709	4.690	4.979
6	4.440	4.475	4.481	4.357	4.319
7	4.709	4.773	4.784	4.849	5.005
8	4.850	5.071	5.298	4.841	5.417
9	5.090	5.074	5.073	5.164	5.175
10	5.419	5.652	5.665	5.725	5.744
11	5.171	5.105	5.209	5.168	6.210
12	5.210	5.313	5.320	5.412	5.430
13	5.069	5.044	5.038	5.080	5.133
14	5.359	5.662	5.678	5.734	5.748
15	5.370	5.259	5.249	5.405	5.346
16	5.330	5.098	5.078	5.213	5.129
17	5.231	5.189	5.186	5.283	5.227
18	5.310	5.295	5.292	5.368	5.351
19	5.239	5.225	5.225	5.266	5.256
20	5.779	5.581	5.572	5.664	5.630
21	5.390	5.201	5.185	5.279	5.096
22	5.370	5.465	5.471	5.561	5.571
23	5.390	5.585	5.597	5.637	5.669
24	5.790	5.732	5.728	5.895	5.908
25	5.221	5.389	5.402	5.406	5.514
26	5.659	5.573	5.568	5.644	5.611
27	5.221	5.507	5.525	5.530	5.564
28	5.931	5.677	5.665	5.747	5.716
29	5.750	5.792	5.794	5.668	5.605
30	5.479	5.575	5.579	5.642	5.653
31	5.790	5.809	5.810	5.801	5.793
32	5.709	5.732	5.733	5.801	5.801
33	5.659	5.587	5.582	5.656	5.638
34	6.189	6.126	6.119	6.206	6.206
35	6.051	5.729	5.697	5.942	5.756
36	6.210	6.164	6.160	6.209	6.209
37	5.750	5.595	5.584	5.871	5.881

a) log $1/C$, C: optimal dose (mol/kg) in a chronic treatment. b) From leave-one-out prediction.

TABLE IV. Effect of the Number of Nodes in the Second Layer of GDR on the Results of QSAR Analysis for Carboquone Derivatives

N_{node}[a]	η[b]	α[c]	r (calc.)[d]	r (pred.)[e]
1	0.6	0.6	0.908	0.827
2	0.6	0.6	0.938	0.844
3	0.6	0.6	0.938	0.840
4	0.6	0.7	0.951	0.855
5	0.6	0.8	0.942	0.840
6	0.6	0.7	0.943	0.834
7	0.6	0.8	0.941	0.856
8	0.6	0.7	0.942	0.832
9	0.6	0.8	0.953	0.834
10	0.6	0.7	0.942	0.859
11	0.6	0.7	0.951	0.856
12	0.6	0.7	0.951	0.852
13	0.6	0.8	0.960	0.849
14	0.6	0.8	0.959	0.856

a) Number of nodes in the second layer. b) Momentum rate. c) Learning rate. d) Correlation coefficient. e) Correlation coefficient for leave-one-out prediction.

TABLE V. Weight Matrices of the QSAR Model by GDR for Carboquone Derivatives

	Layer 1[a]				Layer 3
	1	2	3	4	1
Layer 2					
1	−1.0066	−1.0707	−1.7731	−1.8836	1.8588
2	−1.2315	−1.2014	−1.8843	−1.9647	2.0398
3	−3.5120	0.2854	−4.3936	−4.2715	3.5816
4	−0.7577	−1.2206	−1.6142	−1.9385	1.7994
5	−0.9432	−0.8709	−2.2000	−2.4839	2.1571
6	−0.6539	−0.6902	−0.9023	−1.3727	1.1559
7	−2.7493	−0.0149	−3.8623	−3.8258	3.2833
8	−1.3115	−1.2307	−1.9842	−2.1096	2.0751
9	11.1232	−1.7880	−1.6218	1.0804	−3.3807
10	−1.4125	−0.8052	−2.5821	−2.7787	2.4599
11	−0.8110	−1.0590	−0.8331	−1.2419	1.2193
12	2.6730	4.2088	4.3012	0.4799	−2.3514
13	−0.1032	−0.8545	−0.5893	−1.0891	0.9730

a) The nodes in layer 1 correspond to the following four parameters: 1: $PI_{1,2}$; 2: MR_1; 3: F; and 4: R.

was recognized. We finally selected the QSAR model derived at $N_{node}=13$, $\eta=0.6$, and $\alpha=0.8$ as the best one, whose r is 0.960 in the recognition and 0.849 in the leave-one-out prediction. The weight matrices between the nodes in different layers are listed in Table V. It is very difficult to get information about the contribution of the parameters of activity from this table. The activity values calculated and predicted using GDR are shown in Table III.

b) Benzodiazepine Derivatives b-1) QSAR by FUNCLINK: We used the five parameters included in the multiple regression equation by Yoshimoto *et al.*[16] as the original parameters for the QSAR estimation by FUNCLINK. The five parameters were *MR*-3, *MR*-7, σ_m-3, *F*-4, and *I*-7. After functional linking of the original parameters scaled into the range of 0.0 and 1.0, parameter selection was done to estimate the best QSAR model. Equation 12 was finally derived. The result by MRA[16] is also shown as Eq. 13.

FUNCLINK:

$$Iq=-3.057MR\text{-}3+0.519\cos(\pi MR\text{-}7)+1.036\sigma_m\text{-}3^2 -0.552\cos(\pi F\text{-}4)-0.630I\text{-}7-0.033 \quad (12)$$

$n=51$; $r=0.876$; $s=0.369$; $F=29.5$

leave-one-out: $r=0.842$

MRA:

$$\log 1/C=-0.589MR\text{-}3-0.274MR\text{-}7+1.077\sigma_m\text{-}3+1.481F\text{-}4 \quad (13)$$
$$(t=3.53) \quad (3.55) \quad (3.56) \quad (4.64)$$
$$-0.550I\text{-}7+5.440$$
$$(3.31) \quad (19.40)$$

$n=51$; $r=0.855$; $s=0.397$; $F=24.4$

leave-one-out: $r=0.796$

In Eq. 12, three semilinear parameters, $\cos(\pi MR\text{-}7)$, σ_m-3^2, and $\cos(\pi F\text{-}4)$, as well as two linear ones, *MR*-3 and *I*-7 were selected. As in the QSAR of carboquone derivatives, the contributions of all the parameters in Eqs. 12 and 13 are alike since $\cos(x)$ $(0<x<\pi)$ is a decreasing function and x^2 $(0<x<1)$ is an increasing one. The activity values estimated by Eq. 12 and those by leave-one-out prediction are shown in Table VI.

b-2) QSAR by GDR: The five parameters used in MRA and FUNCLINK were adopted for QSAR analysis by GDR. As done in section a-2), the optimal values of the number of nodes in the second layer, η, and α were examined. The results are shown in Table VII. The correlation coefficient in the recognition was improved when N_{node} was increased to 6; no great improvement was observed thereafter. Compared to the recognition, one can notice that the results of the leave-one-out prediction were rather poor. Except for the first three ones, the lowering of the correlation coefficients from recognition to prediction is 0.3 or more. We selected the QSAR model gained at $\eta=0.6$, $\alpha=0.8$, and $N_{node}=6$ as the best result whose r is 0.887 in recognition and 0.583 in leave-one-out prediction. The weight matrices are shown in Table VIII. It is also very difficult to get information about the contribution of parameters from this table. The activity values calculated and predicted by leave-one-out prediction are shown in Table VI.

By comparing the QSAR results of carboquone derivatives and benzodiazepine derivatives obtained by FUNCLINK with those by GDR, it can be concluded that GDR usually gives a little better fitting of the activity, but the leave-one-out prediction by GDR is poorer than that by FUNCLINK.

Table VI. Calculated and Predicted Activity Values[a] by FUNCLINK and GDR for Benzodiazepine Derivatives

No.	Obsd.	FUNCLINK		GDR	
		Calcd.	Pred.[b]	Calcd.	Pred.[b]
1	4.99	4.729	4.716	4.905	4.903
2	3.57	3.858	3.909	3.454	3.158
3	3.79	3.658	3.647	3.695	3.258
4	4.80	5.103	5.167	4.866	4.862
5	3.84	3.931	3.948	3.764	4.350
6	4.60	5.219	5.274	5.322	5.398
7	4.34	5.013	5.043	5.037	5.075
8	5.29	5.292	5.289	5.122	4.788
9	5.06	4.573	4.531	4.853	4.705
10	5.35	4.738	4.706	4.908	4.853
11	4.64	4.600	4.598	4.868	4.964
12	4.73	4.711	4.710	4.900	4.931
13	4.76	5.254	5.267	5.146	5.899
14	5.06	5.090	5.092	5.117	5.067
15	4.15	4.068	4.059	4.061	3.720
16	5.07	5.096	5.098	5.107	5.087
17	4.08	4.329	4.367	4.199	5.505
18	4.57	4.874	4.906	4.913	5.276
19	4.69	4.164	4.041	4.768	3.874
20	5.38	5.213	5.208	5.114	4.274
21	4.28	4.249	4.247	4.318	4.035
22	4.70	5.083	5.170	4.843	4.760
23	5.85	5.516	5.487	5.738	5.833
24	4.90	4.944	4.946	4.994	4.995
25	5.30	5.116	5.099	5.649	6.231
26	5.70	5.827	5.842	6.163	6.230
27	4.65	4.881	4.908	4.943	4.906
28	5.63	5.777	5.789	5.996	5.802
29	4.90	5.244	5.271	5.320	5.390
30	3.60	4.365	4.536	3.794	4.861
31	5.28	5.069	5.057	5.082	4.966
32	5.77	5.569	5.548	5.832	5.502
33	5.71	6.205	6.265	6.534	6.788
34	4.76	4.887	4.895	5.024	5.008
35	5.35	5.093	5.078	5.103	5.001
36	6.03	5.956	5.942	6.494	7.255
37	5.31	5.360	5.362	5.723	5.961
38	6.92	6.243	6.143	6.570	6.317
39	4.97	5.643	5.705	5.666	6.041
40	5.20	4.606	4.553	5.064	4.031
41	5.44	5.596	5.609	5.987	6.167
42	5.60	5.267	5.228	6.029	6.056
43	5.62	5.737	5.749	5.974	5.951
44	5.48	5.066	5.006	5.133	4.259
45	5.88	5.360	5.293	5.723	5.386
46	5.03	5.282	5.303	5.277	5.153
47	6.30	5.877	5.828	6.197	6.009
48	5.77	5.742	5.741	5.989	5.900
49	5.97	6.096	6.117	6.447	6.508
50	6.00	5.908	5.899	6.220	6.209
51	6.50	6.266	6.233	6.592	6.880

a) log $1/C$, C: ED_{50} (mol/kg). *b*) From leave-one-out prediction.

CCVs The contribution patterns of the parameters to activity were investigated for the QSAR models of carboquone derivatives obtained by FUNCLINK and GDR.

a) FUNCLINK: The CCVs of the four parameters

TABLE VII. Effect of the Number of Nodes in the Second Layer of GDR on the Results of QSAR Analysis for Benzodiazepine Derivatives

N_{node} [a]	η [b]	α [c]	r (calc.) [d]	r (pred.) [e]
1	0.6	0.6	0.705	0.600
2	0.6	0.6	0.835	0.617
3	0.6	0.6	0.849	0.608
4	0.6	0.6	0.864	0.525
5	0.6	0.6	0.855	0.519
6	0.6	0.8	0.887	0.583
7	0.6	0.8	0.879	0.538
8	0.8	0.8	0.864	0.537
9	0.6	0.8	0.875	0.504
10	0.6	0.8	0.865	0.566
11	0.6	0.6	0.860	0.544
12	0.6	0.8	0.861	0.560
13	0.6	0.6	0.864	0.518

a) Number of nodes in the second layer. *b*) Momentum rate. *c*) Learning rate. *d*) Correlation coefficient. *e*) Correlation coefficient for leave-one-out prediction.

TABLE VIII. Weight Matrices of the QSAR Model by GDR for Benzodiazepine Derivatives

	Layer 1 [a]					Layer 3
	1	2	3	4	5	1
Layer 2						
1	−4.0588	0.0270	−5.3435	−0.9899	3.2583	−3.5572
2	2.2155	−5.6553	−3.9618	1.8663	−1.5829	4.8300
3	−0.3436	−5.0460	0.6342	5.0751	−1.1853	1.1608
4	12.1693	0.1761	0.1910	−2.9819	−1.9231	−3.7239
5	−2.3990	−5.6051	6.3713	−2.3504	−1.7429	1.3816
6	0.3195	−0.8682	−1.4978	−0.7196	0.2265	0.1456

a) The nodes in layer 1 correspond to the following five parameters: 1: *MR*-3; 2: *MR*-7; 3: σ_m-3; 4: *F*-4; and 5: *I*-7.

included in Eq. 10 were drawn with the QSAR models for all the 37 data (Fig. 1). Clearly, all four parameters have negative correlation with the activity. The CCV of R which takes a linear form in Eq. 10 is not a linear one in Fig. 1, since the sigmoidal function acted on the output values. The small range of the activity changes with MR_1 means that the contribution of MR_1 to activity is not so great.

The leave-one-out CCVs of the four parameters are shown in Fig. 2. Thirty-seven CCVs for each of the 37 compounds left out of the data set resulted for each parameter. The CCVs in Fig. 1 are also shown here using the open square line. Most of the leave-one-out CCVs showed good agreement with this line, except for two or three which had greater deviation. We then examined these deviating CCVs. For $PI_{1,2}$ or MR_1, the deviation was recognized when compound **11** was eliminated. The F value for compound **11** is 0.52, the maximum value of F in the set. As shown in Table I, the second largest value of F is 0.16, and the third is 0.10. Obviously, the difference of 0.52 from 0.16 is much greater than that of 0.16 from 0.10; therefore, 0.52 of F can be considered an extraordinary value. For F and R, two CCVs are markedly apart from others; these resulted from the elimination of compounds **3** and **11**. The $PI_{1,2}$ value of compound **3** is 5.0, the maximum and discrete value of $PI_{1,2}$. The second and the third largest $PI_{1,2}$ are 3.92 and 3.66, respectively. Therefore, it can be said that the existence of such an "outer discrete value" in the parameters will greatly affect the leave-one-out prediction.

b) GDR: The CCVs of the four parameters in the QSAR model by GDR are also drawn in Fig. 1. Like FUNCLINK, there was negative correlation of all four with the activity. The CCVs of F and R by GDR showed good agreement with those by FUNCLINK.

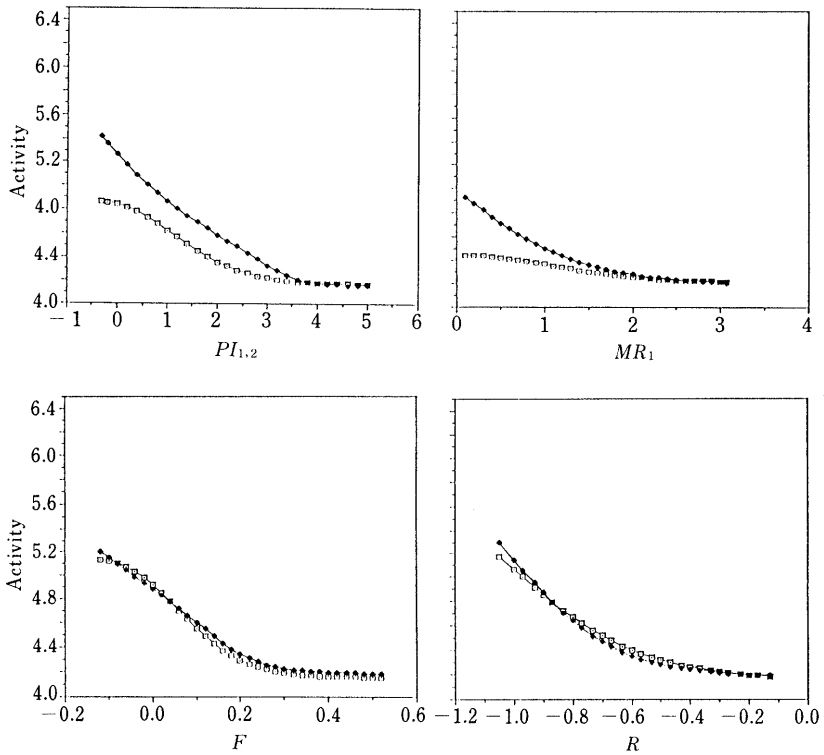


Fig. 1. Contribution Curves for the Parameters in the QSAR Models of Carboquone Derivatives Obtained Using FUNCLINK and GDR
—⊡—, FUNCLINK; —◆—, GDR.

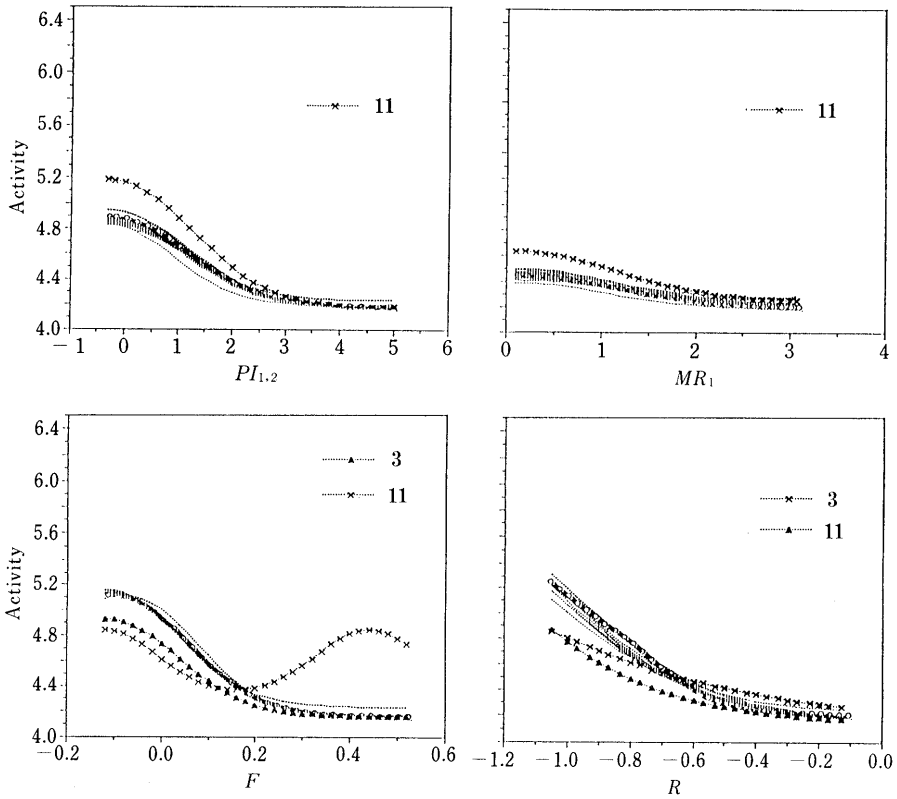


Fig. 2. Leave-one-out Contribution Curves for the Parameters in the FUNCLINK Model

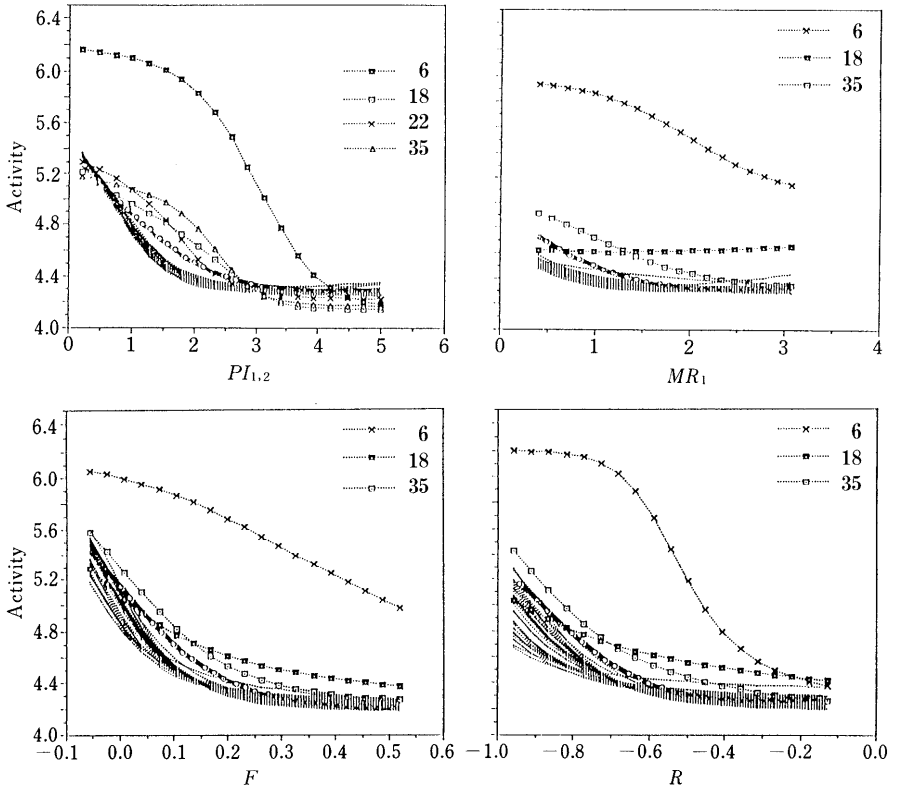


Fig. 3. Leave-one-out Contribution Curves for the Parameters in the GDR Model

The leave-one-out CCVs of the parameters are shown in Fig. 3, along with the four CCVs for the entire data in Fig. 1, which were marked with open squares. Clearly, most of the 37 leave-one-out CCVs behave differently from the CCV with open squares. In addition, four curves for $PI_{1,2}$ and three curves for MR_1, F, and R are noticeably apart away from others; these resulted from the elimination of compounds **6**, **18**, **22**, and **35**. None of them contain outer

discrete parameter values. The reason for the great deviation, therefore, is not the same as in the case of FUNCLINK. In Table I, we find that $PI_{1,2}$ of compound **6** is 3.00, and the two adjacent $PI_{1,2}$ values are 3.66 and 2.60. Therefore, 3.00 may be considered an "inner discrete value" of $PI_{1,2}$. Similary, MR_1 of compounds **18** and **35**, and $PI_{1,2}$ of compound **35** are all such inner discrete values. It seems that the QSAR models of GDR are easily affected by inner discrete values of the parameters in the leave-one-out prediction.

Conclusions

QSAR analyses of the 37 carboquone derivatives with antileukemic activity and of the 51 benzodiazepine derivatives with antipentylentetrazole activity were conducted. The results showed that the QSAR models of GDR usually give excellent fitting of the activity values, but the leave-one-out prediction is unsatisfactory. On the other hand, the QSAR equation modeled by FUNCLINK not only gives good fitting of the activity values, but also good leave-one-out prediction.

The CCVs of the parameters in FUNCLINK and GDR for the entire set of carboquone derivatives showed that the parameters contributed to the activity in a well-regulated nonlinear pattern, and, further, that the contributions of the four parameters were all reverse to the activity like those in MRA. In the leave-one-out CCVs, however, much greater deviations occurred in GDR than FUNCLINK for all four parameters.

In conclusion, the QSAR models of GDR depend upon each individual compound in the data set more than FUNCLINK models. This contributes to the excellent reproduction of the activity, and is also responsible for the poor predictive ability. On the other hand, the models of FUNCLINK usually well reproduce and also well predict the activity, even though they are sometimes greatly affected by outer discrete values of the data.

It seems that the poor predictability caused by the greater dependence on each compound in GDR arises from its characteristic network structure. In the pattern discrimination, for example, a three-layer GDR network can form arbitrarily complex decision regions, and can therefore separate populations of patterns even though such distributions might be intermeshed spatially in pattern space.[17] The GDR network can be expected to give good predictive results only in cases where data used for training the network are extremely precise and include every kind of possible pattern. In such cases, however, no prediction may any longer be needed. Generally speaking, GDR is not considered suitable for QSAR analysis aimed at drug design.

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