探索提高三维定量构效关系模型预测能力的方法

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摘 要: 为了解决使用三维定量构效关系(three-dimensional quantitative structure-activity relationship, 3D-QSAR)模型预测新化合物生物活性效果不理想的问题,建立了 2 种新的一致性模型. 模型一是由多元线性回归(multiple linear regression,MLR)方法构建的加权一致性模型(weighted consensus modeling,WCM),该模型为每个子模型添加了各自的权重系数. 模型二通过计算多个子模型预测值的平均值来构建平均一致性模型(average consensus modeling,ACM). 研究结果表明,当交叉验证相关系数 $0.5 < q^2 \leqslant 0.8$ 时,一致性模型可以提高预测能力,而在 $q^2 > 0.8$ 时不能提高 3D-QSAR 模型的预测能力. 该方法可为提高模型预测能力和设计新型高活性抑制剂提供帮助.

关键词: 三维定量构效关系; 一致性模型; 加权一致性模型; 平均一致性模型
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Preliminary Exploration of Improving Predictive Capability of Three Dimensional Quantitative Structure Activity Relationship Models

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Abstract: To solve the problem that the three-dimensional quantitative structure-activity relationship (3D-QSAR) model is not ideal when using the model to predict the biological activity of the new compounds, two new consensus models were established to improve the prediction ability of the model. A different weight to each submodule (named weighted consensus model, WCM) was added to one of the consensus models. In order to construct WCM, multiple linear regression (MLR) methods were used to calculate different weight coefficients for each submodule. Another consensus model was constructed from the average of the predicted values for each sub-model obtained in the literature (named average consensus model, ACM). Results show that the consensus model can improve the prediction ability when $0.5 < q^2 \leqslant 0.8$, but it can't improve the 3D-QSAR model's prediction ability when $q^2 > 0.8$. This result can help to improve the prediction of the model and the design of new high activity inhibitors.

Key words: 3D-QSAR; consensus model; weighted consensus modeling; average consensus modeling

三维定量构效关系(three-dimensional quantitative structure-activity relationship, 3D-QSAR)是一种可用于描述分子生物活性与其结构之间定量关系的方法,该方法可以预测药物分子和生物大分子之间的相互作用[1-2],并评估抑制剂对受体分子的抑制效果. 比较分子场分析(comparative molecular field analysis,CoMFA)方法与比较分子相似因子分析(comparative molecular similarity induces analysis,

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CoMSIA)方法是2种常用的3D-QSAR方法. 3D-QSAR模型广泛应用于生物学、医学、化学、环境科学等众多领域,研究内容包括分子的生物活性[3-5]、化合物毒性、药代动力学参数和抑制剂的抑制机理等[6-7]. 使用3D-QSAR方法研究人类免疫缺陷病毒(human immunodeficiency virus, HIV)抑制剂的技术目前已经比较成熟[8],但是仍需提高模型的预测准确性.

现有的提高模型的预测准确性方法之一是建立一致性模型. 一致性模型与单个模型相比具有许多优点,如一致性模型比单一模型更稳定、具有更强的泛化能力. 一致性模型可以更充分地描述整个数据集中的分子特征,并从整个数据集中获得更全面的分子结构信息. 2013 年,Helguera 等[3]发表了关于预测人类单胺氧化酶抑制活性和选择性的一致性模型的文章,首先,使用包括 Dragon、MOE 和 TOPS-MODE 模型在内的多种 3D-QSAR 模型,计算了 21 组数据并按顺序进行编号,然后将几个数据集组合成一个一致性模型,再验证这个新模型对预测能力是否有提升. 这一研究证明一致性模型在一定程度上确实可以提高模型的预测能力.

1 原理与方法

1.1 一致性模型

本文使用多元线性回归和均值计算这2种经典统计方法,分别建立一致性模型,然后比较这2种一致性模型的预测能力. 这个实验的过程如图1所示.

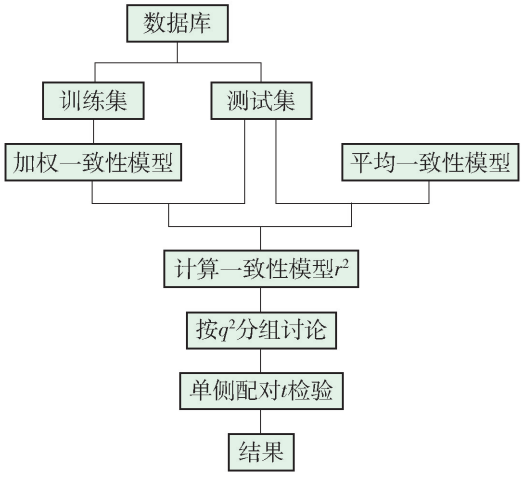


图1 实验流程图

Fig. 1 Experiment flowchart

模型一是由多元线性回归(multiple linear regression, MLR)方法构建的加权一致性模型(weighted consensus modeling, WCM),这一模型为每个子模型添加了各自的权重系数. 多元线性回归是研究一组独立变量如何直接影响因变量的方法,其最大的优势是可以根据2个变量之间的线性关系清晰地分析它们的物理意义[9]. 模型二是通过计算多个子模型预测值的平均值来构建平均一致性模型(average consensus modeling, ACM). 最后使用配对 t 检验来验证 ACM 和 WCM 的预测能力是否比单个模型更高.

1.2 数据库的构建

为了构建数据库,本课题组查阅了数百篇文献,并从2006—2013年发表的80篇文章中收集了3D-QSAR模型的数据作为原始实验数据[1,8,10-86]. 本文使用 IC_{50}(最大抑制浓度的50%)的负对数,即 pIC_{50} 作为化合物分子生物活性的指标.

1.3 一致性模型的构建

下面以 Lu 等[11]的论文为例详细介绍模型构建的方法. 在其论文中共构建了48个化合物分子,其中随机挑选12个作为测试集化合物,在其编号后加角标 t 表示,其余化合物作为训练集. 训练集用来构建一致性模型,测试集用来验证一致性模型. 这些化合物的相关数据见表1. 表中 $pIC_{50,CoMFA}$ 和 $pIC_{50,CoMSIA}$ 分别是从文献中获得的用 CoMFA、CoMSIA 两种模型计算得到的化合物活性的 pIC_{50} 预测值.

表1 文献中化合物的 pIC_{50} 实验值和单一模型预测值

Table 1 pIC_{50} experimental value and predicted value by single model of compounds in the literature

化合物编号	实验值	$pIC_{50,CoMFA}$	$pIC_{50,CoMSIA}$
1	7.30	7.26	7.23
2	5.79	5.73	5.73
3^t	6.10	6.90	6.91
4	6.39	6.42	6.40
5	6.30	6.43	6.31
6^t	5.97	6.56	6.02
7	5.93	5.92	5.87
8	6.14	6.20	6.11
9	6.43	6.45	6.44
10^t	6.60	6.92	7.08

续表 1

化合物编号	实验值	$pIC_{50,CoMFA}$	$pIC_{50,CoMSIA}$
11	7.16	6.98	7.18
12	5.64	5.71	5.77
13	7.08	7.13	7.21
14	7.51	7.52	7.39
15[t]	7.26	7.09	7.25
16	7.59	7.62	7.58
17	7.19	7.17	7.20
18	7.50	7.60	7.51
19[t]	7.42	7.11	7.53
20	7.46	7.40	7.51
21	6.94	6.90	6.84
22	6.67	7.13	6.98
23[t]	7.68	7.46	7.52
24	7.11	7.00	7.00
25	7.36	7.33	7.31
26	7.62	7.51	7.53
27[t]	7.08	7.64	7.46
28	7.60	7.48	7.44
29	7.47	7.50	7.46
30	7.92	8.08	8.00
31[t]	7.37	7.45	7.18
32	7.39	7.33	7.33
33	6.17	6.08	6.20
34	7.30	7.22	7.34
35[t]	8.05	8.01	7.84
36	7.83	7.86	7.83
37	7.42	7.32	7.47
38	8.05	8.01	7.99
39[t]	8.09	8.14	8.13
40	8.09	8.06	8.12
41	8.22	8.15	8.25
42	8.25	8.27	8.32
43[t]	8.01	7.94	7.94
44	8.24	8.25	8.17
45	8.14	8.14	8.22
46	7.84	7.83	7.85
47[t]	8.24	8.41	8.24
48	8.17	8.22	8.10

注："t"为测试集化合物.

构建一致性模型要将表 1 中训练集的 $pIC_{50,CoMFA}$、$pIC_{50,CoMSIA}$和实验值输入到 SPSS 软件，用多元线性回归分析方法，把 $pIC_{50,CoMFA}$ 和 $pIC_{50,CoMSIA}$ 作为自变量，实验值作为因变量. 非标准化系数 B 即 WCM 方程的各项系数，由此得到 WCM 方程. 另一个一致性模型是 ACM 的构建方法，即使用 SPSS 软件转换菜单中的计算变量来求取 $pIC_{50,CoMFA}$ 和 $pIC_{50,CoMSIA}$ 的平均值，即 ACM 的 $pIC_{50,A}$ 预测值.

1.4　模型的评价方法

从文献中引入 2 个参数 q^2 和 r^2，q^2 是交叉验证相关系数，r^2 是非交叉验证相关系数. q^2 值和 r^2 值分别由公式

$$q^2 = 1 - \frac{\sum (y_{pred} - y_{obs})^2}{\sum (y_{pred} - y_{mean})^2} \quad (1)$$

$$r^2 = 1 - \frac{\sum (y_{obs} - y_{pred})^2}{\sum (y_{obs} - y_{mean})^2} \quad (2)$$

得出. 式中：y_{obs} 表示测试集中化合物的 pIC_{50} 的实验值；y_{pred} 是测试集中化合物的 pIC_{50} 的预测值；y_{mean} 表示测试集所有分子 pIC_{50} 值的均值.

将测试集中化合物的单一模型预测值 $pIC_{50,CoMFA}$ 和 $pIC_{50,CoMSIA}$ 代入一致性模型方程，便可得到 $pIC_{50,W}$ 或 $pIC_{50,A}$（$pIC_{50,W}$ 和 $pIC_{50,A}$ 分别是使用 WCM 和 ACM 计算的测试集化合物的 pIC_{50} 预测值）. 选择 SPSS 软件分析菜单中的回归线性，把 $pIC_{50,W}$ 或 $pIC_{50,A}$ 作为自变量，实验值作为因变量，点击确定进行计算得到 r^2_{pred}. 生物统计学领域认为，一个有效的模型应同时符合[10]

$$q^2 > 0.5 \quad (3)$$

$$r^2 > 0.6 \quad (4)$$

不满足这 2 个条件的值应该被剔除.

2　结果与讨论

2.1　模型构建

以 Lu 等[11]的工作为例，用多元线性回归方法计算 WCM 各项系数，由此得到 WCM 方程

$$pIC_{50,W} = 0.604pIC_{50,CoMFA} + 0.367pIC_{50,CoMSIA} + 0.131 \quad (5)$$

使用 ACM 方法构建的一致性方程，即

$$pIC_{50,A} = \frac{1}{2}(pIC_{50,CoMFA} + pIC_{50,CoMSIA}) \quad (6)$$

由一致性方程得到 $pIC_{50,W}$ 和 $pIC_{50,A}$ 预测值，汇总至表 2 中.

表 2 WCM 和 ACM 计算得到的 pIC_{50} 预测值

Table 2 Predicted value of pIC_{50} calculated by WCM and ACM

化合物编号	$pIC_{50,W}$	$pIC_{50,A}$
3[t]	6.91	6.91
6[t]	6.14	6.30
10[t]	7.05	7.00
15[t]	7.22	7.17
19[t]	7.44	7.32
23[t]	7.51	7.49
27[t]	7.50	7.55
31[t]	7.24	7.32
35[t]	7.88	7.93
39[t]	8.14	8.14
43[t]	7.95	7.94
47[t]	8.28	8.33

注:“t”为测试集化合物.

2.2 一致性模型 r^2_{pred} 的直观分析

2.2.1 WCM

以文献[11]为例,计算得到的 WCM 的 r^2_{pred} 值为 0.867,高于文献中给出的 CoMFA 模型的 r^2_{pred} (0.810)和 CoMSIA 模型的 r^2_{pred}(0.860),说明使用 WCM 可以提高预测能力. 图 2 是使用 WCM 计算出的 80 篇文章中预测值 r^2_{pred}.

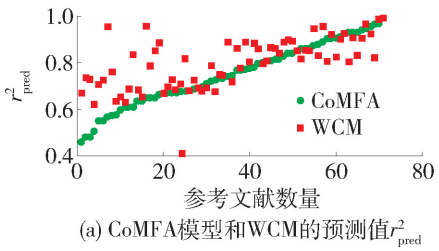
由图 2(a)可以看出,当 CoMFA 模型的 $r^2_{pred}<0.850$ 时,大部分 WCM 的 r^2_{pred} 比单一模型高;当单一模型的 $r^2_{pred}>0.850$ 时,大部分 WCM 的 r^2_{pred} 比单一模型低. 由图 2(b)可以看出,当 CoMSIA 模型的 $r^2_{pred}<0.750$ 时,大部分 WCM 的 r^2_{pred} 比单一模型高;当单一模型的 r^2_{pred} 满足 $0.750<r^2_{pred}<0.800$ 时,WCM 的部分 r^2_{pred} 大于单一模型;当单一模型的 $r^2_{pred}>0.800$ 时,大部分 WCM 方法的 r^2_{pred} 低于单一模型. 所以 WCM 方法只能提高部分模型的预测能力.

2.2.2 ACM

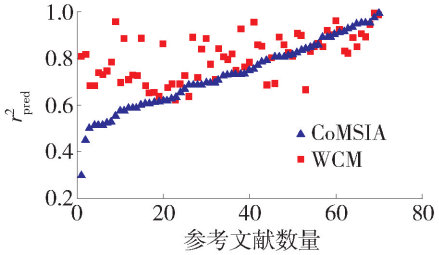
以文献[11]为例,ACM 的 r^2_{pred} 值为 0.874,大于 CoMFA 模型 r^2_{pred} 值(0.810)和 CoMSIA 模型 r^2_{pred} 值(0.860),说明使用 ACM 的预测能力更高.

将 CoMFA 和 CoMSIA 模型测试集中化合物分子的 pIC_{50} 预测值代入公式(6),计算这些化合物预测值的平均值 $pIC_{50,A}$,后续的验证步骤与 WCM 相同. 图 3 是使用 ACM 计算出的 80 篇文章中的预测值 r^2_{pred}.

由图 3(a)可以看出,在 CoMFA 模型的 $r^2_{pred}<0.850$ 时,大部分 ACM 的 r^2_{pred} 比单一模型高;在单一模型的 $r^2_{pred}>0.850$ 时,ACM 的 r^2_{pred} 大部分没有明显提高. 由图 3(b)可以看出,在 CoMSIA 模型的 $r^2_{pred}<0.750$ 时,本文所用的 ACM 的 r^2_{pred} 比单一模型高;在单一模型的 $r^2_{pred}>0.750$ 时一部分 ACM 的 r^2_{pred} 低于单一模型. 所以 ACM 方法只能提高部分模型的预测能力.



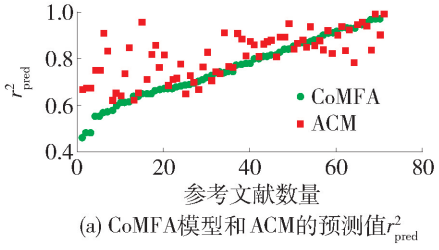
(a) CoMFA模型和WCM的预测值r^2_{pred}



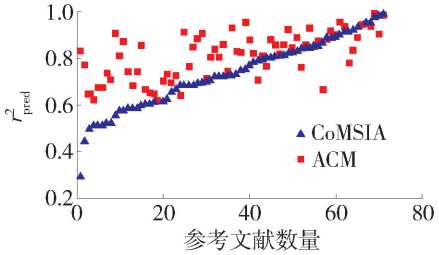
(b) CoMSIA模型和WCM的预测值r^2_{pred}

图 2 CoMFA 模型、CoMSIA 模型及 WCM 的预测值 r^2_{pred}

Fig. 2 r^2_{pred} of CoMFA, CoMSIA model and WCM



(a) CoMFA模型和ACM的预测值r^2_{pred}



(b) CoMSIA模型和ACM的预测值r^2_{pred}

图 3 CoMFA 模型、CoMSIA 模型及 ACM 的预测值 r^2_{pred}

Fig. 3 r^2_{pred} of CoMFA, CoMSIA model and ACM

2.3 单侧配对 t 检验

2.3.1 WCM

进一步将 79 篇文献中的 q^2 和 r^2_{pred} 两个值按照 q^2 的大小分成以下 4 组:$0.5<q^2\leqslant0.6$, $0.6<q^2\leqslant$

0.7, $0.7 < q^2 \leqslant 0.8$ 和 $q^2 > 0.8$. 然后对 WCM 的 r^2_{pred} 和文献中的 CoMFA 或 CoMSIA 的 r^2_{pred} 值进行配对 t 检验.

用配对 t 检验验证 WCM 相对于 CoMFA 模型预测能力的提高效果,比较的结果见表 3. 由表 3 可以看出,当 $0.5 < q^2 \leqslant 0.6$ 时,t 的绝对值为 2.588,大于 t 界值 1.729(自由度 df = 19),差异具有统计学意义. 因为 WCM 的 r^2_{pred} 均值(0.777)大于 CoMFA 的 r^2_{pred} 均值(0.715),所以 WCM 可以提高 3D-QSAR 模型的预测能力. 当 $0.6 < q^2 \leqslant 0.7$ 和 $0.7 < q^2 \leqslant 0.8$ 时,差异具有统计学意义,且 WCM 的 r^2_{pred} 均值更高,所以结论与第一组相同,即 WCM 可以提高 3D-QSAR 模型的预测能力. 但是当 $q^2 > 0.8$ 时,t 的绝对值为 0.974,比 t 界值表中的统计值 1.895(df = 7)小,差异不具有统计学意义. 从整体上分析,结果见表 3 最后一行,t 值的绝对值大于 t 界值,差异具有统计学意义,且 WCM 的 r^2_{pred} 均值(0.820)大于 CoMFA 的 r^2_{pred} 均值(0.757),这说明 WCM 提高了模型的预测能力.

用配对 t 检验验证 WCM 相对于 CoMSIA 模型预测能力的提高效果,比较的结果见表 4,其结果与 CoMFA 模型相同.

表 3　WCM 与 CoMFA 模型的比较结果

Table 3　Comparison of WCM and CoMFA models

q^2	样本数	t 值	t 界值[a]	统计学意义	CoMFA $\bar{r}^2_{pred}$[b]	WCM $\bar{r}^2_{pred}$[c]
0.5 ~ 0.6	20	−2.588	1.729	有	0.715	0.777
0.6 ~ 0.7	23	−2.341	1.717	有	0.753	0.796
0.7 ~ 0.8	19	−1.904	1.734	有	0.773	0.819
> 0.8	8	−0.974	1.895	无	0.840	0.871
> 0.5	70	−4.120	1.667	有	0.757	0.820

注:a 表示 t 界值的显著水平为 95%,下同;b 表示使用 CoMFA 模型计算出的 r^2_{pred} 的均值,记为 CoMFA $\bar{r}^2_{pred}$,下同;c 表示使用 WCM 模型计算出的 r^2_{pred} 的均值,记为 WCM $\bar{r}^2_{pred}$,下同.

表 4　WCM 与 CoMSIA 模型的比较结果

Table 4　Comparison of WCM and CoMSIA models

q^2	样本数	t 值	t 界值	统计学意义	CoMSIA $\bar{r}^2_{pred}$[a]	WCM $\bar{r}^2_{pred}$
0.5 ~ 0.6	16	−3.090	1.753	有	0.655	0.772
0.6 ~ 0.7	23	−3.324	1.717	有	0.686	0.784
0.7 ~ 0.8	22	−2.143	1.721	有	0.780	0.811
> 0.8	8	−0.152	1.895	无	0.911	0.916
> 0.5	69	−4.729	1.667	有	0.735	0.806

注:a 表示使用 CoMSIA 模型计算出的 r^2_{pred} 的均值,记为 CoMSIA $\bar{r}^2_{pred}$,下同.

2.3.2　ACM

用配对 t 检验验证 ACM 相对于 CoMFA 模型预测能力的提高效果,比较的结果见表 5. 当 $0.5 < q^2 \leqslant 0.6$ 时,t 的绝对值为 3.263,大于 t 界值 1.729(df = 19),认为差异具有统计学意义. 因为 ACM 的 r^2_{pred} 均值(0.787)大于 CoMFA 的 r^2_{pred} 均值(0.715),证明 ACM 可以提高 3D-QSAR 模型的预测能力. 当 $0.6 < q^2 \leqslant 0.7$ 和 $0.7 < q^2 \leqslant 0.8$ 时差异具有统计学意义,且 ACM 的 r^2_{pred} 均值更高,所以结论与第一组相同. 但是当 $q^2 > 0.8$ 时,t 的绝对值为 0.835,比 t 界值表中的统计值 1.895(df = 7)小,差异不具有统计学意义. 从整体上分析,结果见表 5 最后一行,t 值的绝对值大于 t 界值,认为差异具有统计学意义,而且 ACM 的 r^2_{pred} 均值(0.815)大于 CoMFA 的 r^2_{pred} 均值(0.764),可以说明 ACM 提高了模型的预测能力.

使用相同方法验证 ACM 相对于 CoMSIA 模型预测能力的提高效果,验证结果见表 6,结论与 CoMFA 模型相同.

表 5 ACM 与 CoMFA 模型的比较结果

Table 5 Comparison of ACM and CoMFA models

q^2	样本数	t 值	t 界值	统计学意义	CoMFA $\bar{r}^2_{pred}$	ACM $\bar{r}^2_{pred}$ [a]
0.5 ~ 0.6	20	-3.263	1.729	有	0.715	0.787
0.6 ~ 0.7	21	-2.499	1.725	有	0.764	0.814
0.7 ~ 0.8	21	-1.997	1.725	有	0.781	0.823
>0.8	8	-0.835	1.895	无	0.840	0.869
>0.5	70	-4.543	1.667	有	0.764	0.815

注:a 表示使用 ACM 模型计算出的 r^2_{pred} 的均值,记为 ACM $\bar{r}^2_{pred}$,下同.

表 6 ACM 与 CoMSIA 模型的比较结果

Table 6 Comparison of ACM and CoMSIA models

q^2	样本数	t 值	t 界值	统计学意义	CoMSIA $\bar{r}^2_{pred}$	ACM $\bar{r}^2_{pred}$
0.5 ~ 0.6	15	-2.956	1.761	有	0.657	0.769
0.6 ~ 0.7	23	-4.629	1.717	有	0.686	0.799
0.7 ~ 0.8	22	-2.232	1.721	有	0.796	0.836
>0.8	9	-1.158	1.860	无	0.891	0.919
>0.5	69	-5.684	1.667	有	0.743	0.818

3 结论

1) 配对 t 检验的结果表明:当使用 WCM 方法时,在 $0.5 < q^2 \leqslant 0.8$ 的条件下,WCM 提高了模型的预测能力;当 $q^2 > 0.8$ 时,此方法不能提高 3D-QSAR 模型的预测能力. 但是从整体上分析,可以认为 WCM 提高了模型的预测能力.

2) 当使用 ACM 方法时,配对 t 检验的结果与 WCM 配对 t 检验的结果相同.

3) 在 $q^2 \leqslant 0.8$ 时,建立一致性模型可以提高原始模型的预测能力,而在 $q^2 > 0.8$ 时不能提高 3D-QSAR 模型的预测能力. 这说明本实验建立的 WCM 和 ACM 模型在一定条件下可以有效提高化合物活性的预测能力. 这一结果可以为提高模型预测能力的研究和新型高活性抑制剂的设计提供帮助.

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