

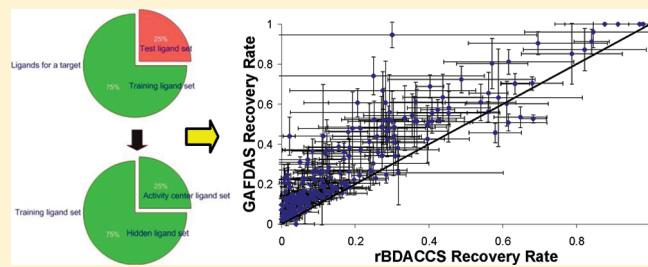
# G-Protein Coupled Receptors Virtual Screening Using Genetic Algorithm Focused Chemical Space

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Supporting Information

**ABSTRACT:** Exploiting the ever growing set of activity data for compounds against biological targets represents both a challenge and an opportunity for ligand-based virtual screening (LBVS). Because G-protein coupled receptors (GPCRs) represent a rich set of potential drug targets, we sought to develop an appropriate method to examine large sets of GPCR ligand information for both screening collection enhancement and hit expansion. To this end, we have implemented a modified version of BDACCS that removes highly correlated descriptors (rBDACCS). To test the hypothesis that a smaller, focused descriptor set would improve performance, we have extended rBDACCS by using a genetic algorithm (GA) to choose target-specific descriptors appropriate for selecting the set of 100 compounds most likely to be active from a decoy database. We have called this method GA-focused descriptor active space (GAFDAS). We compared the performance of rBDACCS and GAFDAS using a collection of activity data for 252 GPCR/ligand sets versus two decoy databases. While both methods appear effective in LBVS, overall GAFDAS performs better than rBDACCS in the early selection of compounds against both decoy databases.



## ■ INTRODUCTION

G-protein coupled receptors (GPCRs) represent one of the richest drug target families, as more than 40 GPCRs are bona fide drug targets.<sup>2</sup> There are estimated to be 799 GPCRs, though most drug discovery research has been focused on the nonolfactory receptors.<sup>2</sup> Finding new ligands for GPCRs remains a high priority in drug discovery. We sought to develop, implement, and test a ligand-based virtual screening (LBVS) method that would be useful for high-throughput screening (HTS) hit expansion as well as screening collection enhancement to exploit the growing collection of GPCR ligand data. The desired method would need to be able to be applied rapidly and automatically to large sets of ligands, amenable to variations in the size of the active molecule pool, insensitive to 3D conformations of active and/or decoy molecules, perform well in the early recovery of actives, and straightforward to implement for large numbers of active ligand collections.

Methods that use positions in active compound “descriptor space” seemed appropriate as starting points for our effort.<sup>3–10</sup> Recent studies have suggested that distances in *n*-dimensional chemical spaces defined by simple two-dimensional (2D) descriptors can be used successfully in LBVS. Starting with a simple high-dimensional descriptor-based Euclidian distance function<sup>3</sup> that showed the utility of this approach, Vogt et al.<sup>1</sup> later demonstrated that a bayesian interpretation of the distance function was better for LBVS.

In this work we have implemented BDACCS<sup>1</sup> to generate and test models for 252 GPCRs and their ligands with the exception that we first reduced the descriptor pool by removing descriptors that were more than 90% correlated with other descriptors

(rBDACCS). We have extended the BDACCS approach by using a genetic algorithm (GA) to select descriptors most appropriate for early identification of actives. We call this method GA-focused descriptor active space (GAFDAS). In comparing these two methods, we focused on performance in the top 100 ranked molecules in order to simulate real-world scenarios for complementing medicinal chemistry discovery efforts through external compound acquisition. These methods could also be part of a broad set of computational approaches to identify potentially useful compounds for corporate collection expansion. We have performed these studies using two decoy databases. First, our GPCR ligand database collection of active ligand molecules (CALM, which is comprised of GPCR-annotated molecules from Wombat<sup>11</sup> and other GPCR molecules retrieved from the literature) uses all actives except those from the target of interest and second ZINC7<sup>12</sup> as an example of a diverse general decoy database. We have evaluated each method using different metrics of performance and have used bootstrapping to estimate the ranges of performance of the methods. We demonstrate that while rBDACCS performs well across most GPCRs, GAFDAS outperforms rBDACCS in early performance.

## ■ METHODS

**Molecular Descriptors.** Descriptor values were calculated using the Molecular Operating Environment (MOE).<sup>13</sup> A set

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**Table 1.** Descriptors Used in the Study

physical properties	adjacency and distance matrix descriptors
density	balabanJ
FCharge	BCUT_SLOGP_0
logS	BCUT_SLOGP_1
reactive	BCUT_SLOGP_2
SlogP	BCUT_SLOGP_3
subdivided surface areas	BCUT_SMR_0
SlogP_VSA1	BCUT_SMR_1
SlogP_VSA4	BCUT_SMR_2
SlogP_VSA5	BCUT_SMR_3
SlogP_VSA6	petitjean
SlogP_VSA7	GCUT_PEOE_0
SlogP_VSA8	GCUT_PEOE_1
SMR_VSA1	GCUT_PEOE_2
SMR_VSA3	GCUT_SLOGP_0
SMR_VSA6	GCUT_SLOGP_1
SMR_VSA7	GCUT_SLOGP_2
atom and bond counts	GCUT_SMR_0
a_ICM	GCUT_SMR_1
a_nB	GCUT_SMR_2
a_nF	GCUT_SMR_3
a_nP	petitjeanSC
a_nS	radius
a_nCl	VDistEq
a_nBr	weinerPath
a_nI	pharmacophore feature descriptors
b_ar	a_base
b_rotN	vsa_acid
b_triple	vsa_base
chiral_u	vsa_hyd
lipViolation	vsa_other
nmol	vsa_pol
opr_leadlike	
oprViolation	
rings	
VAdjEq	

of 134 1D and 2D molecular descriptors was chosen for analysis. All 134 descriptors were calculated for the CALM data set, and a descriptor correlation analysis was undertaken for all pairs of descriptors. While there could be minor changes in performance of the final method based on the order of the descriptor removal, descriptor dimensionality was reduced by randomly removing one member of each pair of descriptors having a Pearson correlation coefficient greater than 0.9.

The rationale for selecting the Pearson correlation coefficient ( $R$ ) cutoff of 0.9 in the descriptor reduction exercise was to attempt to reduce the search space for the GA without losing important information. Using a Pearson  $R$  value of 0.9 provides that more than 80% of the information content of the descriptor pair would be maintained by keeping one of the pair of descriptors thus maintaining a reasonable compromise between descriptor reduction and information retention. We have listed the set of 63 descriptors resulting from this exercise in Table 1.

**Decoy Data Sets.** CALM. An internally generated set of target annotated GPCR ligands extracted from WOMBAT v2007.2<sup>11</sup> and other literature sources containing 50 852 unique molecules.

This data set spans a large part of known GPCR targets and contains a wide variety of ligands for each target.

ZINC. To represent a large virtual screening decoy database, we used the ZINC7 drug-like single representation, which contains 2 066 906 molecules.<sup>12</sup>

**External Validation Sets.** During the time of this work, the next version of Wombat<sup>11</sup> (version 2008.1) was released and revealed 80 targets with at least 5 ligands not present in the training sets. We used these ligand sets to further test the performance of each of the corresponding resultant models.

**Ligand Sets.** From CALM, 252 GPCR targets (161 human, 21 mouse, 70 rat) each having a minimum of 20 ligands were chosen as active ligand sets for model generation and evaluation. The activity classes and the number of molecules active against the receptors are listed in the Supporting Information.

**rBDACCS**<sup>1,3</sup>. BDACCS takes into account the descriptor value distribution of the decoy database in which the actives were hidden. The likelihood of a compound belonging to an activity class and to the decoy database was approximated based on the Bayesian principle, and the ratio of these two likelihoods provides a measure of the ‘odds’ of a compound belonging to either an active class or the decoy database. Minimizing the distance ( $d_{BDACCS}$ ) is equivalent to increasing the odds that the compound belongs to the activity class.

$$d_{BDACCS}(j) \propto \sum_{i=1}^n \frac{(\chi_{ij} - \mu_i)^2}{2\sigma_i^2} - \frac{(\chi_{ij} - \nu_i)^2}{2\tau_i^2} \quad (1)$$

Where  $n$  is the number of descriptors,  $\chi_{ij}$  is descriptor value for descriptor  $i$  of compound  $j$ ,  $\mu_i$  is the mean descriptor value of descriptor  $i$  for the actives,  $\nu_i$  is the mean for descriptor  $i$  value for the decoy molecules,  $\sigma_i$  is the standard deviation of descriptor  $i$  values for the actives, and  $\tau_i$  is the standard deviation of descriptor values for the decoy molecules. eq 1 was used as a measure of distance from the center of active compounds to the test compound in descriptor space. Using this distance can rank test compounds by their proximity to the center of actives.

**GAFDAS.** In this work, we extend the rBDACCS<sup>1</sup> approach by selecting descriptors specific to an active set of molecules using the GA, described below. The fitness function used in optimizing the GA was the hit rate in the top ranked 100 molecules.

**GA.** The GA used in this work was developed internally at Arena Pharmaceuticals. A GA is a computer program that mimics the process of evolution by manipulating a collection of data structures called chromosomes. Each of these chromosomes encodes a possible solution, i.e., a selection of descriptors, and may be assigned a fitness score based on the relative merit of that descriptor selection. A steady state with no duplicate operator-based GA<sup>14,15</sup> was used to search possible descriptor selections. We used normalized rank-based linear selection<sup>14</sup> with a selection pressure of 1.1 to select operator parents. A parent was selected stochastically by spinning a roulette wheel,<sup>14,16</sup> where each chromosome had a slice of the wheel that was proportional to its scaled fitness score. An island model was employed where 2 subpopulations of 100 chromosomes evolved independently.<sup>14</sup> The 63 descriptors were encoded as binary values in a chromosome of length 63. The GA started with every chromosome in each island created with random binary values. When a bit is turned on, the corresponding descriptor is included in the calculation of the activity center and the BDACCS distance function as in eq 1. The GA then iterated over each island applying a total of 1000 genetic operators. The genetic operators



**Figure 1.** Data set split for active ligands of a target.

available were crossover, mutation, and migration. In any iteration, a genetic operator was selected using roulette wheel selection<sup>14,16</sup> with weights of 45 for the two-point crossover and the mutation operators and 5 for the migration operator (this meant that migrations were applied 5.3% of the time and that crossover and mutation were each applied 47.4% of the time).<sup>14</sup> Each genetic operator required one or two parents chosen using roulette wheel parent selection. The operators produced one or two children which replaced the worst individuals in the island.

**Performance Metrics.** Six measures of LBVS performance were used in this study. All calculations of *t*-test statistics were performed in Excel 2003:

- (1) Hit rate is the number of active compounds in the top 100 ranked compounds.
- (2) Recovery rate is the fraction of active compounds found out of total possible in top 100 ranked compounds.
- (3) Enrichment factor is  $N_{\text{active}}/N_{\text{random}}$  in the top 100 ranked molecules.
- (4) AUCROC<sub>0.2</sub> is the area under the receiver operator characteristic curve at 0.2% of the database. The AUC for the top portion of the ROC curve up to the false positive rate cutoff of 0.002 (corresponding to the top 100 inactives being retrieved from the ranked molecules within the ~50 k CALM decoy; in the evaluation with ZINC we also used a subset of 50 k molecules) was normalized to lie between 0 and 1 by dividing by perfect VS performance in the top 100 compounds which is  $0.002^*1 = 0.002$ . Random performance for AUCROC<sub>0.2</sub> is  $0.002^*0.002/2 = 2 \times 10^{-6}$ .
- (5) BEDROC<sup>17</sup> score was calculated with an  $\alpha$  value of 1151.3, which corresponds to the top 0.2% of the ranking accounting for 90% of the score.
- (6) AUCROC is the area under the receiver operator characteristic curve.<sup>18</sup>

**Ligand Set Preparation.** For each target model, the ligands for the given target were extracted from CALM and used as the

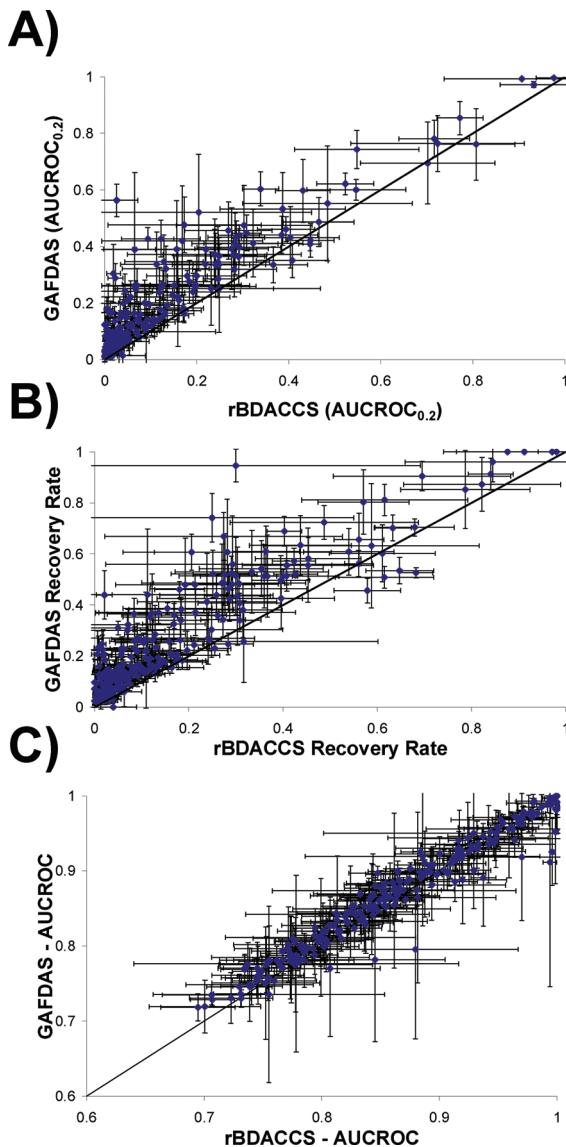
known actives. As shown in Figure 1, a random selection of 25% of the ligand collection was set aside as the test set. From the remaining 75% of the collection, a random subselection of two groups was made: 25% was used to define the activity center, and the remaining 75% was merged back into the decoy database and used for descriptor selection using the genetic algorithm. For rBDACCS-based model development, identical data sets were used, but no training step was necessary. Five bootstrapping (sampling with replacement) runs of the preceding procedure were performed to evaluate variations in the performance of the methods.

**Timings and Memory Requirements.** The GA optimization and evaluation of the models were carried out on a Linux cluster of 20 nodes. Each node contained two AMD Operon 2 GHz processors and 2–8 GB memory. In-house software was written to distribute the computation among nodes and to automate the generation and evaluation of the models across all the targets. For a training ligand set of size 110, it took 3 min to generate one GA-optimized model. Memory requirements were approximately 1 GB per 1 million database molecules. We found that timing and memory usage scaled linearly with database size.

## RESULTS AND DISCUSSION

**Virtual Screening Performance using CALM as the Decoy Database.** As discussed by Jain and Nicholls,<sup>19,20</sup> the choice of the decoy or the decoy data set can significantly impact the results of virtual screening (VS). In the first analysis of rBDACCS and GAFDAS, we used the entirety of the GPCR ligand collection CALM as the decoy database. The CALM data set is a ‘mimetic’ data set in the Nicholls<sup>20</sup> parlance. The molecules are more likely to be closely located in descriptor space than in a general collection, and as such, selecting active molecules from inactive compounds is more challenging. In addition, some GPCRs share a common ligand (i.e., there are several receptors for both serotonin and dopamine), so the potential exists for active molecules to be present in the decoy data set marked as inactive simply because no data has been reported for the molecules against the given target. Thus, the determined performance of the methods may underestimate the true performance. The experiment evaluated the ability of each method to distinguish ligands of a given target versus those of fellow GPCR targets. The performance of a VS method can also vary widely among different targets; errors can be significant when a small number of targets are considered.<sup>20</sup> Including a broad range of GPCR targets to compare the performance of GAFDAS with rBDACCS should allow us to be able to draw conclusions with high confidence as well as to evaluate the variance of method performance among GPCR targets.

The CALM data set contains 252 GPCR targets which have at least 20 associated ligands; 161 of these targets are unique human receptors, and 91 of the targets are alternative species orthologues of included human receptors or are unique nonhuman receptors. The list of GPCRs and ligand counts for the CALM collection is in Table 1, Supporting Information. Each receptor and its associated ligands are treated as an independent data set. We used CALM as the set of targets against which we would build models using rBDACCS and GAFDAS. During model development and testing, each target ligand collection was removed from the CALM collection, and three subsets were prepared as described in the Methods and Figure 1. For all of the figures comparing performance of the methods using various metrics,



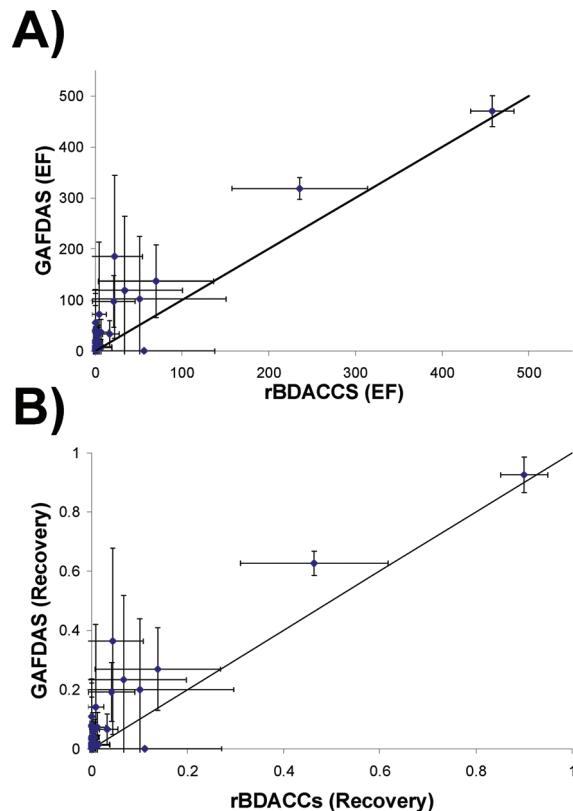
**Figure 2.** Comparison of GAFDAS and rBDACCS performance for all 252 receptor models against the CALM decoy database using AU-CROC<sub>0.2</sub> (A), recovery rate (B), and AUCROC (C). Data are plotted as mean  $\pm$  95% confidence interval.

the mean data  $\pm$  95% confidence interval was graphed with GAFDAS performance plotted on the *y*-axis and rBDACCS performance on the *x*-axis; the line of unity is also plotted. If the bulk of the data lies on the left side of the line of unity, then GAFDAS performed better. If the bulk of the data lies to the right of the line of unity, then rBDACCS performed better. If the data is centered around the line of unity, then the methods have roughly equivalent performance.

In this exercise, in the vast majority of cases, both methods performed better than random, and the ability to generate productive models for each method was good. GAFDAS produced models that identified active molecules in all but one case, and rBDACCS failed in only five cases. Figure 2A shows a comparison of rBDACCS and GAFDAS for the AUCROC<sub>0.2</sub> metric  $\pm$  95% confidence interval. Two observations are immediately apparent from the figure. First, both methods perform much better than random (random performance =  $2 \times 10^{-6}$  for AUCROC<sub>0.2</sub>)

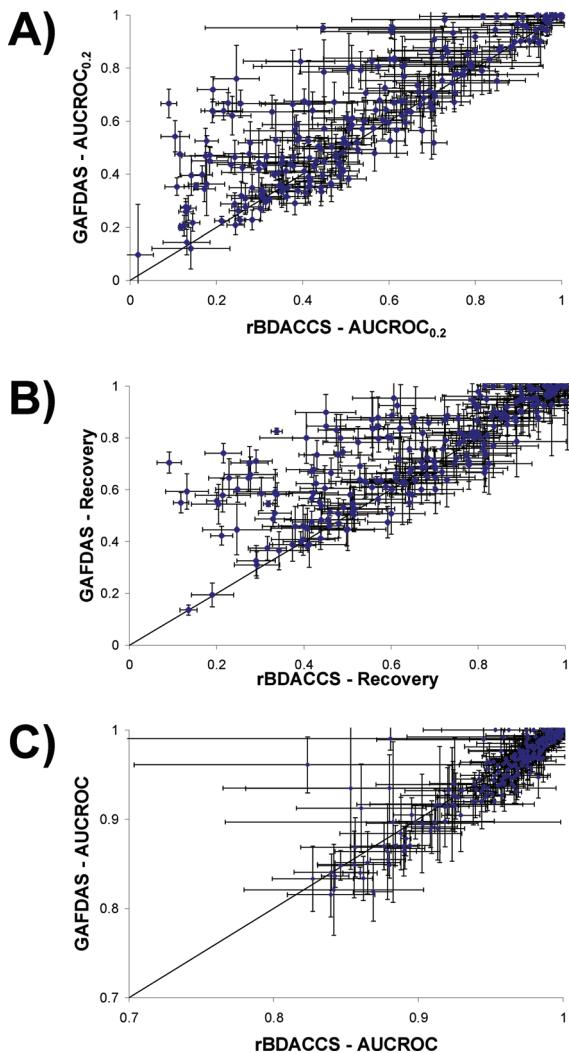
**Table 2. Summary Performance**

metric	GAFDAS		rBDACCS		
	mean	SD	mean	SD	P(t)
CALM					
hit rate (top 100)	0.12	0.09	0.07	0.07	<<0.0001
recovery rate	0.27	0.23	0.17	0.21	<<0.0001
enrichment factor (top 100)	123.74	121.21	81.33	108.27	<<0.0001
AUC-0.2	0.18	0.20	0.11	0.18	<<0.0001
BEDROC	0.23	0.18	0.14	0.17	<<0.0001
ZINC					
hit rate (top 100)	0.49	0.29	0.44	0.30	<<0.0001
recovery rate	0.76	0.19	0.68	0.24	<<0.0001
enrichment factor (top 100)	306.40	125.68	271.06	127.84	<<0.0001
AUC-0.2	0.62	0.24	0.54	0.26	<<0.0001
BEDROC	0.81	0.15	0.72	0.22	<<0.0001
AUCROC	0.96	0.04	0.96	0.04	<0.02
AUCROC	0.87	0.08	0.86	0.08	<<0.0001



**Figure 3.** Comparison of GAFDAS and rBDACCS performance for 80 receptor models having data not present in the original experiment against the CALM decoy database using enrichment (A) and recovery rate (B). Data are plotted as mean  $\pm$  95% confidence interval.

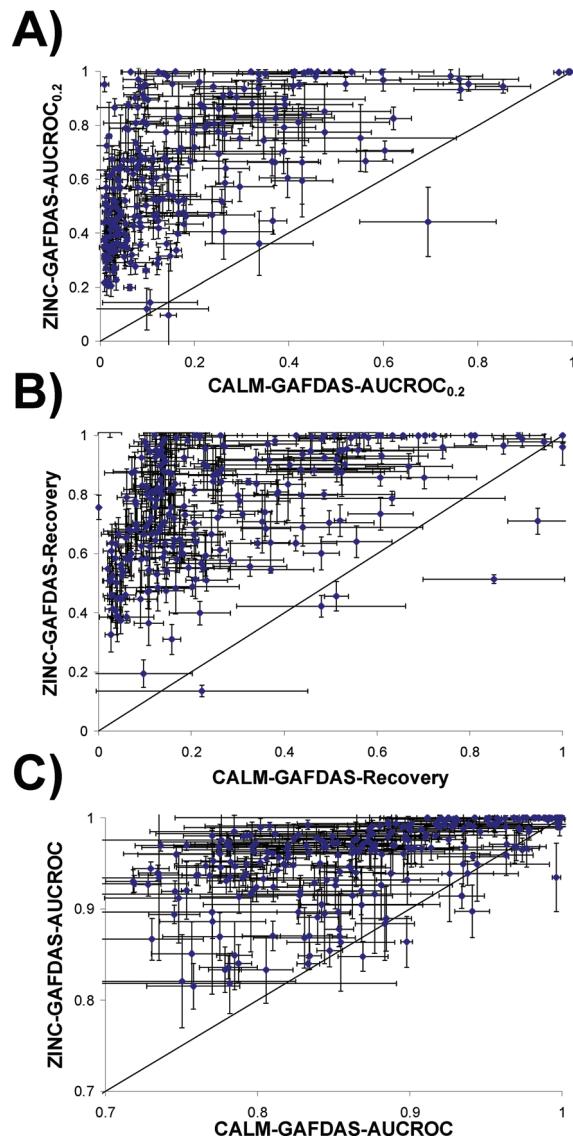
with mean performance ranges from 0.0089 to 0.995 with a mean of 0.181 for GAFDAS and a range from 0.0017 to 0.976 with a mean of 0.114 for rBDACCS. Second, for the most part, GAFDAS outperformed rBDACCS as seen by the shift of the majority of the data that points toward the *y*-axis as compared to the line of unity in the graph. The mean performance of the GAFDAS-based



**Figure 4.** Comparison of GAFDAS and rBDACCS performance for all 252 receptor models against the ZINC decoy database using AUCROC<sub>0.2</sub> (A), recovery rate (B), and AUCROC (C). Data are plotted as mean  $\pm$  95% confidence interval.

models outperformed the mean performance of the rBDACCS-based models in 242 cases. rBDACCS-based models outperformed GAFDAS-based models in only 10 cases. Overall, the mean performance of GAFDAS was statistically superior to rBDACCS for AUCROC<sub>0.2</sub> as shown in Table 2.

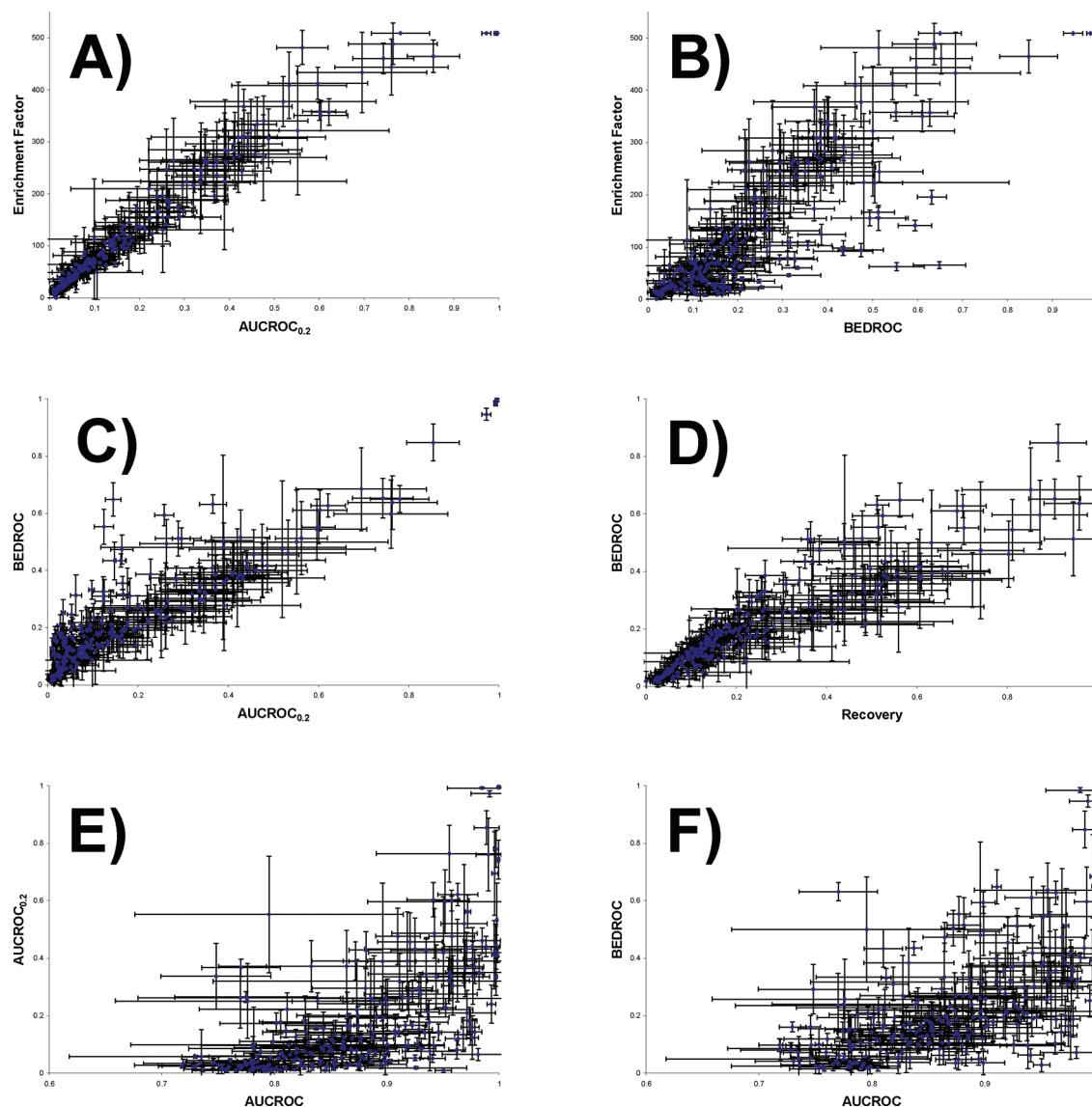
Figure 2B shows a comparison of rBDACCS and GAFDAS in the ability to recover active molecules from the CALM decoy database. Again, for the most part, both rBDACCS and GAFDAS performed much better than the random rate (which in this case varied from 0.002 to 0.014 because of the difference in size of the active molecule sets). GAFDAS recovery rates ranged from 0 to 1.0 with a mean of 0.271. rBDACCS recovery rates ranged from 0 to 0.98 with a mean of 0.173. GAFDAS on the whole outperformed rBDACCS as observed in the shift of the body of the data toward the y-axis from the line of unity in Figure 2B. For 247 data sets, the GAFDAS mean recovery rate was better than rBDACCS. rBDACCS had superior mean recovery rates for only five data sets. Again, for the recovery metric, GAFDAS-based models were statistically superior to rBDACCS models as shown in Table 2.



**Figure 5.** Comparison of decoy database performance for all 252 receptor models built with GAFDAS against ZINC and CALM using AUCROC<sub>0.2</sub> (A), recovery rate (B), and AUCROC (C). Data are plotted as mean  $\pm$  95% confidence interval.

Figure 2C shows a comparison of rBDACCS and GAFDAS using the full AUCROC metric. Again, both methods perform much better than the random rate of 0.5; with AUCROC values ranging from 0.69 to 0.99 with a mean of 0.863 for rBDACCS and from 0.72 to 0.99 with a mean of 0.869 for GAFDAS. Analysis of this metric also showed that GAFDAS statistically outperformed rBDACCS.

**Validation with External Data.** For the models generated above, an external validation test was carried out with new ligand data sets extracted from Wombat<sup>11</sup> that were not present in our first evaluation of these methods. In this experiment, 80 receptors having at least 5 new ligands were employed; each tested with the original 5 sets of bootstrapping models created using rBDACCS and GAFDAS. In the validation experiment, the external test set was merged with the same decoy database for the specific receptor as in the optimization process. Enrichment factors and recovery rates were calculated from the 100 top-ranked molecules. GAFDAS was able



**Figure 6.** Comparison of metrics using the GAFDAS method and CALM as the decoy database: (A) Enrichment factor vs AUCROC<sub>0.2</sub>; (B) Enrichment factor vs BEDROC; (C) BEDROC vs AUCROC<sub>0.2</sub>; (D) BEDROC vs recovery; (E) AUCROC<sub>0.2</sub> vs AUCROC; (F) BEDROC vs AUCROC. BEDROC  $\alpha$  parameter set to 1151.3. Data are plotted as mean  $\pm$  95% confidence interval.

to recover active molecules from the decoy database in 30 of 80 data sets. rBDACCS was able to recover active molecules in 19 of 80 data sets. In addition, neither method was able to return active molecules in every iteration of the bootstrapping exercise, thus increasing the perceived performance errors. However, when active molecules were retrieved, performance as measured by enrichment factor and recovery rate was better than those expected at random. GAFDAS performance ranged from 1.64 to 470 with a mean of 23.8 for enrichment factor and 0.003 to 0.925 with a mean of 0.047 for recovery rate compared to rBDACCS with enrichment factor ranging from 0.68 to 457 with a mean of 12.5 and recovery rate ranging from 0.001 to 0.9 with a mean of 0.025. As shown by the *y*-axis shift in Figure 3, GAFDAS in general outperformed rBDACCS.

**Virtual Screening Performance using ZINC as the Decoy Database.** To measure performance of the two methods against a universal decoy database, we chose ZINC7.<sup>12</sup> Again, we used bootstrapping to model overall performance of the methods and

analyzed several metrics that measured both early and overall performance for rBDACCS and GAFDAS for the 252 GPCR receptor/ligand data sets. To allow direct comparison with the CALM results for each bootstrap run, we randomly selected decoy data sets of 50 000 molecules from the ZINC collection and measured performance in that background.

Figure 4A shows a comparison of rBDACCS and GAFDAS using AUCROC<sub>0.2</sub>. As with the CALM decoy data set, both rBDACCS and GAFDAS performed much better than random, with performance values ranging from 0.097 to 0.99 with a mean of 0.619 for GAFDAS and from 0.018 to 0.975 with a mean of 0.542 for rBDACCS. Mean performance for both methods was higher using ZINC rather than CALM as the decoy database, illustrating the challenge that the CALM data set represented. The CALM molecules were all known ligands of a GPCR target and would be expected to have higher similarities to one another than a collection of commercially available compounds. Neither GAFDAS nor rBDACCS had any data sets with zero recovery. As

observed with the CALM decoy database, GAFDAS generally outperformed rBDACCS as shown by the shift of the body of data toward the *y*-axis. GAFDAS had a higher mean performance than rBDACCS for 171 data sets. rBDACCS had a higher mean performance than GAFDAS for 73 data sets. The two methods had equal mean performance for eight data sets. The mean performance for GAFDAS was statistically superior to rBDACCS using AUCROC<sub>0.2</sub> as a metric, as shown in Table 2.

Figure 4B shows a comparison of rBDACCS and GAFDAS using the recovery metric. Overall performance for GAFDAS and rBDACCS was higher against the ZINC decoy database as compared with CALM (Table 2). GAFDAS and rBDACCS both had performance superior to random, with mean recovery values ranging from 0.135 to 1.0 for GAFDAS and from 0.09 to 1.0 for rBDACCS. As with the CALM decoy database, GAFDAS generally outperformed rBDACCS as shown by the shift of the body of data toward the *y*-axis. Mean performance for GAFDAS outperformed rBDACCS for 175 data sets. rBDACCS outperformed GAFDAS for 58 data sets. The two methods had equal mean performance for 19 data sets. The mean performance for GAFDAS was statistically superior to rBDACCS using recovery as a metric as shown in Table 2.

Figure 4C shows a comparison of rBDACCS and GAFDAS using the full AUCROC metric. Overall performance for GAFDAS and rBDACCS was higher against the ZINC decoy database than against the CALM database, and both methods performed better than the random level of 0.5. GAFDAS performance ranged from 0.82 to 0.99 with a mean of 0.956, and rBDACCS performance ranged from 0.82 to 0.99 with a mean of 0.958. GAFDAS mean performance was greater for 96 data sets, rBDACCS mean performance was greater for 150 data sets, and the methods had equal mean performance for 6 data sets. Overall performance was statistically higher for rBDACCS compared to GAFDAS. This is the sole example where the mean performance of rBDACCS outperforms GAFDAS, however, given that the mean absolute difference in performance is approximately 0.01 AUC units, this difference may not be meaningful.

**Virtual Screening Performance Comparing Decoy Databases.** Nichols suggested that the performance of a given computational method would be highly dependent on the composition of the decoy database.<sup>20</sup> In our study, observed performance for the two methods was highly dependent on the decoy database. With few exceptions, as shown in Figure 5, both rBDACCS and GAFDAS performed better against the universal database ZINC than the mimetic-like database CALM, regardless of the performance metric used. The mean recovery rate for rBDACCS was 0.679 with ZINC as the decoy database but was only 0.173 against CALM. Accordingly, the mean GAFDAS recovery rate was 0.759 against ZINC and 0.271 against CALM. The mean AUCROC<sub>0.2</sub> for rBDACCS was 0.542 against ZINC and 0.114 against CALM. For GAFDAS it was 0.619 against ZINC and 0.181 against CALM. Using the full AUCROC curve, the performance differences between the two decoy databases were less extreme but still consistent. rBDACCS had a mean AUCROC value of 0.958 against the ZINC database and 0.863 against CALM. GAFDAS had similar changes in apparent performance using AUCROC with a mean value of 0.956 versus ZINC and 0.869 against CALM. There was no discernible trend in the degree of improvement in apparent performance between models against the two decoy databases except that as general rule, performance was much better against ZINC than CALM.

**Evaluating Metrics of Performance.** In analyzing our results we used six different performance metrics: hit rate, recovery rate,

enrichment factor, AUCROC<sub>0.2</sub>, BEDROC, and AUCROC. Each of the metrics selected for evaluating early performance (hit rate, recovery rate, enrichment factor, AUCROC<sub>0.2</sub>, and BEDROC) lead us to the same conclusion that GAFDAS outperformed rBDACCS. Furthermore, as shown in Figure 6 for GAFDAS against CALM as the decoy database, all of the early performance metrics are highly correlated. From a practical point of view, answering the question of whether it is better to perform the extra step of descriptor selection when attempting to bias compounds toward a given chemical space, all of the metrics focused on early performance would have lead us to the same affirmative conclusion.

## CONCLUSIONS

In this study we have created chemical space-based activity models for the ligands of 252 GPCRs. We have extended the BDACCS<sup>1</sup> methodology two-fold. First, we removed covariant descriptors (rBDACCS). Second, we used a GA to select descriptors most appropriate for each GPCR/ligand collection (GAFDAS). Using a bootstrapping approach to simulate variance in the performance of the methods, we have measured the ability of each method to enrich the top 100 compounds for active molecules against both a mimetic-like decoy and a universal decoy database. The 100 compound threshold was chosen to try to simulate real-world performance in complementing medicinal chemistry lead exploration approaches or expanding corporate collections. We show that both methods perform well in virtual screening and that GAFDAS outperforms rBDACCS in ranking active molecules in the top 100 regardless of the decoy database used or whether the data was part of the original collection or not. We also demonstrate that the makeup of the decoy database plays a large roll in the overall performance of the method; retrieving active compounds from the universal decoy database was much easier than from the mimetic-like database. We have shown that the extension of rBDACCS by selecting descriptors provides a meaningful improvement of the method to support the selection of GPCR-focused compound sets from existing compound collections for screening or corporate collection expansion.

## ASSOCIATED CONTENT

**S Supporting Information.** The activity classes and the number of molecules active against the receptors used in this study are listed. This Information is available free of charge via the Internet at <http://pubs.acs.org/>.

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