Sensitivity Analysis and Other Improvements to Tailored Combinatorial Library Design

Eric Martin*,† and Alex Wong‡

Chiron Corporation, 4560 Horton Street, Emeryville, California 94608, and Alex Wong Consulting, 4517A 8th Street, San Francisco, California 94114

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"Tailoring" combinatorial libraries was developed several years ago as a very general and intuitive method to design diverse compound collections while controlling the profile of other pharmaceutically relevant properties. The candidate substituents were assigned to "categorical bins" according to their properties, and successive steps of D-optimal design were performed to generate diverse substituent sets consistent with required membership quotas from each bin. This serial algorithm was expedient to implement from existing D-optimal design codes, but was order-dependent and did not generally locate the very best possible design. A new "parallel" Fedorov search algorithm has now been implemented that can find the most diverse property-tailored design. An ambiguous mass penalty has been added, whereby most duplicate masses can be eliminated with little loss of library diversity. Sensitivity analysis has also been added to quantitatively explore the diversity trade-offs due to increasing or decreasing each specific kind of bias.

INTRODUCTION

Combinatorial library design attempts to choose the best set of substituents for a combinatorial synthetic scheme, from all available candidates, to maximize the chances of finding a useful compound such as a drug lead. Initial efforts focused primarily on maximizing diversity, perhaps allowing some bias by the inclusion of a fixed set of pharmacophoric substituents. Calculating a property space, specifying any fixed substituents, and sampling the remaining candidates by D-optimal design provided a means to obtain maximally diverse libraries.[1] Such libraries were designed, synthesized, and screened, and potent ligands were identified,[2,3] but experience revealed that many hits were too flexible, insoluble, lipophilic, or of too high molecular weight to qualify as attractive drug leads. Comparison to random selection showed that maximizing diversity was systematically biasing the libraries away from the preferred ranges for many of these properties. Methods are thus needed to control the profile of pharmaceutically relevant properties, while still maintaining high diversity. [4−9] "Tailored" library design was developed several years ago to address this need.[4,10,11] The entire combinatorial library design process is illustrated in Figure 1. Suitable reagents were identified from a database of commercially available compounds. Structural properties were calculated for each candidate substituent. From these, a "property space" was computed in which proximity reflected similarity. The candidate substituents were assigned to categorical "bins". Bins are overlapping subsets of the candidates that share a common pharmaceutically relevant property such as being polar, rigid, or pharmacophoric, having low molecular weight, or being expensive. The user could then specify a profile of "bin quotas" for the design, requiring that so many substituents must be polar, so many must be rigid, only so many can be expensive, etc. Successive steps of D-optimal design were then performed to generate diverse libraries that were constrained to match the desired profile of quotas for these relevant properties. The "Tailor" program, which performs this last sampling step, is the subject of this paper.

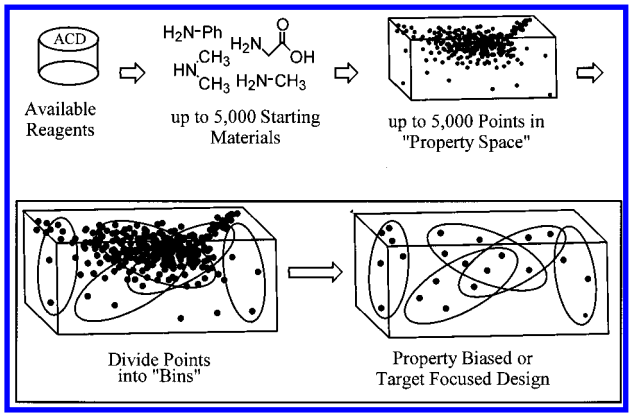

Figure 1. Overview of library design process. This paper pertains to the last step enclosed in the box.

Tailoring libraries by serial steps of D-optimal design could be conveniently implemented simply by wrapping a Tcl script around an existing D-optimal design code. The D-optimal design program was repeatedly called, using the previous design at each step as a fixed set to be augmented from the next bin as the candidate set. This implementation was expedient, but it was an order-dependent algorithm that did not generally locate the best possible design. A new "parallel" Fedorov search algorithm has now been developed, which is able to find the most diverse design consistent with a given property profile.

Mass spectroscopy (MS) is increasingly used to identify the active component in a mixture, so it is convenient to have as few mass duplicates in a mixture as possible. Tailoring with bins is a very general and intuitive mechanism

* Corresponding author. Phone: (510) 923-3306. E-mail: martine@chiron.com.
† Chiron Corporation.
‡ Alex Wong Consulting.

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to incorporate most kinds of pharmaceutical bias, but it cannot be used to minimize the number of ambiguous MWs. A small duplicate mass penalty has now been added to the diversity score. It is found that most ambiguous masses can be eliminated with little loss of diversity.

Maximizing diversity and incorporating pharmaceutical bias are opposing goals. Although tailoring with bin quotas is a powerful and convenient way to constrain the property profile of a combinatorial library, one must always be cognizant of the compromise between bias and diversity. How many compounds can be required to come from each bin without sacrificing too much diversity? Sensitivity analysis is a general method to quantify how sensitive an objective function is to small changes in each of its input parameters. It has been implemented here to show how much the diversity increases or decreases with changes in the quotas for each bin, thus quantitatively exploring the trade-offs between bias and diversity. For a given property profile, it graphically shows which bin quotas are limiting the library's overall diversity and which could be increased with very little diversity loss.

METHODS

D-optimal Design. D-optimal design works by choosing a "design" set of substituents from a larger "candidate" set, by maximizing the determinant of the "information matrix", $|X'X|$, for a "design matrix", X. The rows of X are the substituents in the design, and the columns are the "model terms", i.e., the property space dimensions and/or higher order terms such as their squares or cross-terms. This minimizes the determinant of the inverse, which is the prediction error for a regression model.[12] Roughly speaking, maximizing the determinant requires large diagonal elements, which are variances, so the selected points are well spread out and therefore not redundant. It requires small off-diagonals, which are covariances, so collinearities are minimized and all the dimensions are well-sampled. D-optimal design programs typically allow a fixed initial set of points to be specified. A numerical optimization procedure then searches the candidates to find the points that will augment the fixed set to produce the most diverse overall design of the desired size.

Original "Serially Tailored" D-optimal Design Algorithm. In the original "serial" implementation of the Tailor program, the design algorithm incorporated a slightly modified version of the public domain FORTRAN D-optimal design program, DOPT.for, which was obtained from the Carnegie Mellon University StatLib web site.[13,14] Property space coordinates were separately calculated for all candidate substituents using the previously described program MAKESPACE.[4] Principal components analysis was performed on the property space, and enough cross-terms were added to saturate the design model, making the number of property space dimensions equal to the total desired number of substituents. The candidates' structures and pharmaceutically important computed properties were stored in a Daylight Thor database.[11] Since a bin is just a collection of candidate substituents, it was implemented as a Daylight "hitlists", i.e., an ascii ".tdt" file. The user could create predefined bins using scripts written in Merlin Control Language or create new ad hoc bins interactively using xvmerlin.[15] Additional bins came from any other sources, such as docking programs, that could output a file of smiles. Figure 2 shows Tailor's Tcl/Tk graphical user interface through which the user then specified the bin names and "quotas", i.e., the minimum number of members from each bin. The quotas were chosen on the basis of intuition and trial-and-error, attempting to mimic the property profiles of known drugs without sacrificing too much diversity. Tailor called DOPT to find the most diverse design of size quota 1 points, considering only members of bin 1 as the candidate set, and using only the first quota 1 dimensions in the model. This intermediate result was then kept as a fixed set, which was augmented with quota 2 members from bin 2, adding quota 2 more dimensions to the model. This procedure was repeated, sequentially, in one pass, until the entire design had been assembled as illustrated in Figure 3. The algorithm is clearly order-dependent and is therefore unlikely to find the most diverse possible design that satisfies the bin quota profile. Furthermore, dimensions of property space can only be included to equal the total number of points to be selected at each stage in the procedure, so the entire property space is not considered until the last sequential step. Nevertheless, by specifying the most elite, restrictive bins early in the design, and allowing the most general bins to compensate near the end, it was hoped that a nearly optimal design might be found.

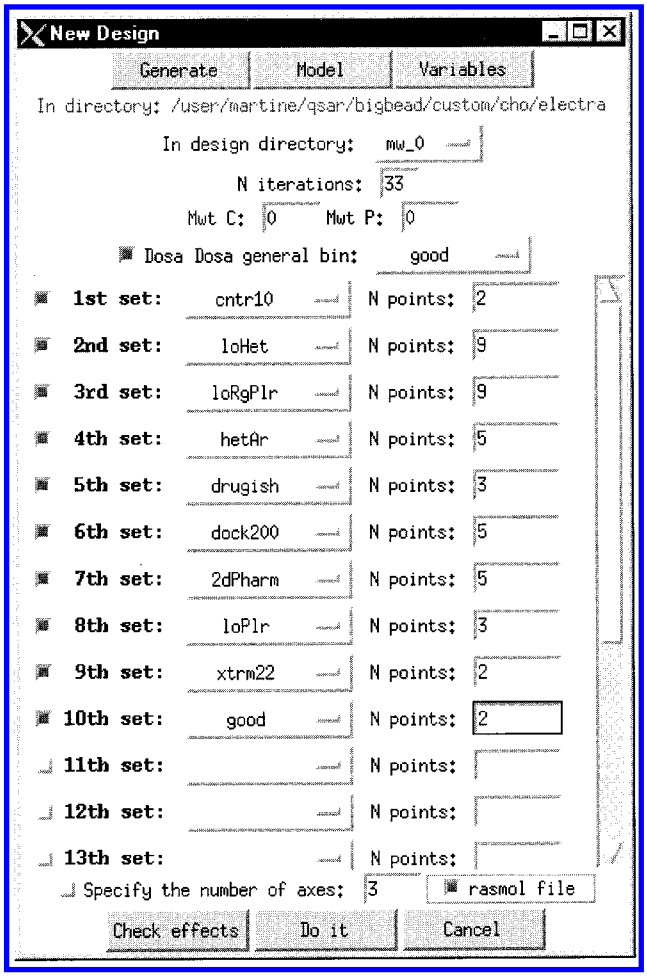

Figure 2. Tcl/Tk graphical user interface from the Tailor program. The user specifies a "profile" of properties consisting of the quota of members that must come from each specified bin.

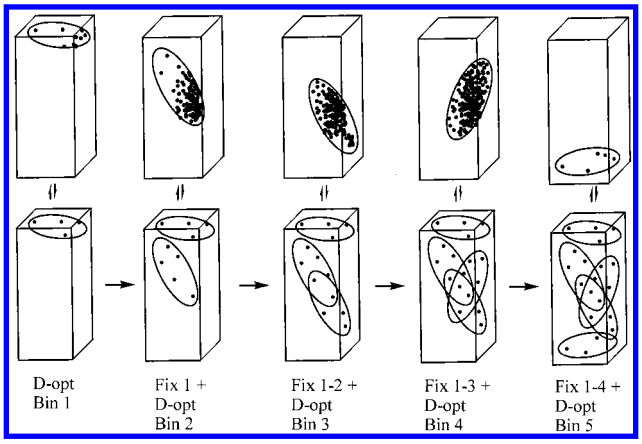

Figure 3. Original serial algorithm, which built up a tailored D-optimal design in sequential stages. A D-optimal design was selected from the first bin. This much of the design was then fixed and was augmented by D-optimal design from the second bin. This process was repeated until the entire design had been built.

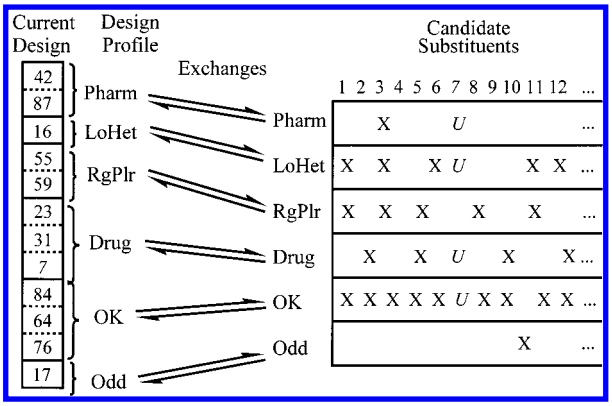

Figure 4. New parallel algorithm showing that for each design point, only unused candidates (marked X) from the bin associated with that position are considered available for exchange. Note that candidate 7 is marked as "U" for "unavailable", because it is already in the current design.

"Parallel Tailored" D-optimal Design Algorithm. The new parallel version of Tailor is a C program that implements a modification of the Fedorov algorithm, much as it occurs in the DOPT.for program. It has been altered to recognize that each position in the design belongs to a particular bin. It also recognizes to which bin catagories each of the candidate points belongs. Pseudocode for the modified algorithm is given in the Appendix. In this algorithm, the entire property space for a saturated design model is used throughout the optimization. An arbitrary but reasonable initial starting design is chosen by picking half of the members from each bin at random, then selecting the remainder, stepwise, by which candidates maximize the rank of the design (i.e., the number of property space dimensions varied by the selected substituents), and then maximizing the subspace determinant for that rank. From that starting guess, it proceeds with the optimization by testing exchanges between the design points and the available candidate points. For each design point, however, only unused candidates from the bin associated with that position are considered available, as depicted in Figure 4. After all possible single exchanges are tested, the current design is updated by performing the exchange that caused the biggest increase in diversity score. The process is repeated until no further improvement can be found. The number of exchanges required by this systematic search may seem inordinate, but it is justified by a well-known fast-update formula that calculates the change in the determinant due to making an exchange, without ever having to actually compute a new determinant.[16] The numerical optimization is still subject to finding local maxima, so a user-specified number of additional arbitrary starting points are tried in an attempt to find the global optimum. Because this procedure is not order-dependent and uses the entire property space throughout, given enough starting points it should be capable of finding the best possible design for a given profile.

Ambiguous MW Penalty. The principal appeals of using bins for tailoring property distributions are generality and simplicity. As long as a medicinal or computational chemist can identify which compounds or fragments are likely to share a property, a bin can be added to influence its contribution to the design. An alternative would be to add the bias directly to the diversity score function. Borth et al. presented a technique to simultaneously optimize additional criteria, such as cost or synthetic difficulty, along with the D-criterion for information content, such as finding the most diverse design possible for a given price.[17] We feel that assigning compounds to bins and selecting a quota from each bin is closer to the way practicing medicinal chemists and biologists think about drug discovery, and thus facilitates interaction within a project team.

However, the number of ambiguous masses in a mixture is one type of bias that is not a property of the individual compounds and therefore cannot be introduced via bins. Like diversity, this is a property of the chosen ensemble of compounds. This bias can only be introduced by adding it to the diversity score function. A small penalty for ambiguous MWs was, therefore, introduced into the score in order to encourage diverse designs in which most compounds can be immediately identified from the parent peak in mass spectroscopy. The adjusted scoring function is

$$\text{exchange-score} = \text{delta}/(1 + W1 \cdot \text{badMW}) - W2 \cdot \text{small} \cdot \text{badMW} - \text{small}$$

where "delta" is the change in $-\log|X'X|$ due to a given exchange, i.e., the usual diversity score in D-optimal design. "small" is a constant that determines the minimum significant score increase, i.e., the convergence criterion. "badMW" is the number of ambiguous MWs that are the same within a specified mass resolution. The weighting constants, W1 and W2, increase or decrease the importance of the MW penalty relative to diversity. The proportional term, W1, usually dominates the mass penalty. W2 simply ensures that there will always be a significant mass penalty, even when delta becomes small. Note that when $W1 = W2 = 0$, this becomes the usual D-optimal design score.

Sensitivity Analysis. Local sensitivity analysis has been incorporated to quantify the trade-off between diversity and each category of bias. An initial bin profile is specified, and one bin must be specified as "general". The general bin is usually the logical OR of all desirable property bins, but does not usually include the bins intended to limit undesirable properties. The sensitivity analysis algorithm then measures the increase or decrease in diversity due to decreasing and increasing the quota for each bin by one and by two, making up the difference in each case from the general bin. Thus,

Table 1. Design Profiles Used for Sample Designs To Compare Tailored Design Algorithms[a]

size	cntr10	loHet	loRgPlr	hetAr	drugish	loRig	loPlr
17	1	5	5	2	1	1	2
32	1	9	9	5	2	2	4
51	1	15	15	8	3	3	6

[a] The candidate substituents were assigned to 7 overlapping bins: cntr10 contains the 10 points nearest the centroid of property space, druggish substituents contain fragments frequently found in the 200 top-selling drugs, heteroaromatics are in hetAr, LoHet holds heteroaromatics with MW below 175, loPlr substituents are both low MW and polar, loRig are low MW and rigid, and loRgPlr are low MW, rigid, and polar. Each of the three designs was onstrained to include the indicated quota of members from each bin.

four tailored diversity designs are run for each bin in the design profile, two with more bias (more members from that bin) than the initial profile and two with less bias. If the "general" bin is a superset of all of the bins that specify desirable properties, then decreasing the bias should lead to an increase in diversity, and vice versa, since at worst the same members that were removed from the specific bin could be reselected again from the general bin. In this case, however, because each bin overlaps with at least the general bin, the quotas specify only a minimum number of members. Often, at least one bin contains substituents that are not members of any other bin, so that an exact number of these candidates can be specified. An example would be a bin of moderately undesirable substituents, from which one or two might be allowed in the design if adding them leads to a large increase in diversity. Increasing the quotas for these bins that do not overlap the general bin typically increases the diversity, by allowing additional unusual substituents to be sampled.

The sensitivity analysis produces a bar chart in which rectangular bars indicate the diversity increase or decrease for a change of ± 1 in each bin quota, and an additional vertical line indicates the additional diversity increase or decrease for a change of ± 2 in that bin's quota. Guided by these sensitivity results, the user may choose a new profile. Since the bins are correlated, and the dependence of diversity on bin quotas is nonlinear, if the new profile is very different from the original guess, then a second (or third) sensitivity analysis should be run.

RESULTS AND DISCUSSION

Comparisons between Serial, Parallel, and Ambiguous Mass-Penalized Designs. To assess the new tailoring algorithm, three realistic tailored design profiles were generated for a candidate set of 908 aldehyde-derived substituents: a small design totaling 17 members, a medium design of 32 members, and a large design of 51 members. The candidates were assigned to 7 bins: cntr10 contains the 10 points nearest the centroid of property space, druggish substituents contain fragments frequently found in the 200 top-selling drugs, heteroaromatics are in hetAr, loHet holds heteroaromatics with MW below 175, loPlr substituents are both low MW and polar, loRig are low MW and rigid, and loRgPlr are low MW, rigid, and polar. The three design profiles are given in Table 1. Table 2 compares the three tailored designs on the basis of the diversity scores and number of ambiguous MWs found from using all three algorithms: the original serial algorithm, the new parallel algorithm without an ambiguous MW penalty, and the new parallel algorithm with the MW penalty. The diversity scoring function is identical for the serial and parallel algorithms, so the results can be directly compared. The MW penalty changes the diversity scale, so the final designs were rescored without the MW penalty for direct comparison to the other designs.

Table 2. Comparing Diversity Scores and Number of Duplicate Masses (within 0.1 Da) for Designs of Three Sizes using the Three Tailoring Algorithms: The Original Serial Algorithm, the New Parallel Algorithm without the Molecular Weight Penalty, and the New Parallel Algorithm with the Penalty for Duplicate Masses

	parallel				serial	
	no MW penalty		with MW penalty		no MW penalty	
design size	diversity	dup. MWs	diversity	dup. MWs	diversity	dup. MWs
17	33.2	2	32.7	0	30.1	2
32	84.2	3	82.7	0	78.8	5
51	137.3	10	136.4	5	126.9	11

Table 3. Diversity Scores for Calibration Designs of 17, 32, or 51 Substituents Drawn from Subsets of the Original 908 Candidates[a]

subset	17	32	51
100%	39.0 ± 0.3	98.9 ± 0.6	160.4 ± 0.9
50%	38.0 ± 0.6	94.3 ± 0.9	153.8 ± 0.8
dock200	36.5 ± 0.3	89.9 ± 0.5	145.0 ± 0.2
rigid	36.1 ± 0.3	89.1 ± 0.6	145.3 ± 1.4
20%	35.2 ± 0.6	89.6 ± 1.2	139.9 ± 4.0
plr	34.9 ± 0.6	87.3 ± 0.5	142.1 ± 1.0
10%	33.0 ± 2.1	80.8 ± 2.0	114.0 ± 3.2
druggish	32.8 ± 0.4	78.0 ± 1.1	127.7 ± 0.7
lo175	31.2 ± 0.6	76.7 ± 0.6	126.7 ± 1.0
hetAr	26.8 ± 0.6	65.8 ± 0.5	101.1 ± 0.4
5%	30.1 ± 1.5	63.3 ± 3.7	
NP	29.3 ± 0.1	62.1 ± 0.3	87.3 ± 0.3
random	13.4 ± 5.1	36.6 ± 5.5	69.6 ± 11.7

[a] No MW penalty was used. Set "100%" used all 908 substituents as candidates. "50%" used only 454 substituents chosen at random. "20%" used 182 random substituents, etc., down to "5%" which used 45 random substituents. "Dock" used the set of 200 substituents that dock best into thrombin when used as a capping group on NAPAP. Rigid used only candidates with two or fewer rotatable bonds. "Plr" candidates had at least one heteroatom and log $P < 2.5$. "NP" used all substituents not in Plr. "Random" refers to a set of exactly 17, 32, or 51 substituents, as appropriate, chosen at random and scored without any design optimization. All calibration designs, including random sampling, were repeated five times, and the listed uncertainties are 1 standard deviation.

Calibrations. To judge the significance of these diversity score differences, a set of standard calibration benchmarks was performed. Table 3 shows the diversity scores of the D-optimal sets of 17, 32, or 51 substituents that can be made from various subsets of the original 908 candidates. Since the optimization is performed on a single candidate bin, there is no difference between serial and parallel design. No MW penalty was used, to obtain the most diverse possible design from each subset. Set "100%" used all 908 substituents as candidates. "50%" used only 454 substituents chosen at random. "20%" used 182 random substituents, etc., down to "5%", which used 45 random substituents. "Dock" used the set of 200 substituents that dock best into thrombin when used as a capping group on NAPAP. Rigid used only candidates with two or fewer rotatable bonds. "Plr" candidates

had at least one heteroatom and log $P < 2.5$. "NP" used all substituents not in Plr. "Random" refers to a set of exactly 17, 32, or 51 substituents, as appropriate, chosen at random and scored without any design optimization. All calibration designs, including random sampling, were repeated five times, and the listed uncertainties are 1 standard deviation. In all cases, even the most strongly biased optimized designs are substantially more diverse than random selection.

Since using all 908 candidates allows the most diverse possible design, the differences between the first line of Table 3 and the second column of Table 2 give the quantitative penalty in diversity for enforcing the tailored property profiles. In all cases, the diversity cost for Tailoring was roughly comparable to randomly eliminating from 80% to 90% of the candidates, or to performing a design on just the rigid, polar, or druggish substituents. This is a substantial, but not unreasonable, amount of diversity to sacrifice in order to obtain a screening set with a druglike profile of physicochemical properties. As expected, the parallel algorithm with no MW penalty produced the most diverse designs, but also produced many duplicate masses. Designs from the parallel algorithm with the small MW penalty eliminated many of the mass duplicates, with only a small loss of diversity. Designs from the original serial algorithm were significantly less diverse than even the MW-penalized parallel-designs, yet had many mass duplications. Still, while designs produced by the new parallel algorithm are significantly better than the previous serial algorithm, the older algorithm, despite its flaws, was able find reasonable designs.

Sensitivity Analysis. A constant practical question in tailored library design is how to choose appropriate bin quotas. Maximizing diversity and incorporating pharmaceutical bias are opposing goals. The calibration benchmarks give a rough measure of which bins contain the most and the least potential diversity. Yet for a given profile, it is also important to know which bins are limiting the diversity, and whether increasing or decreasing the number of members from each bin is worth the corresponding loss or gain in diversity. Local sensitivity analysis has been implemented to address this problem.

A sensitivity analysis was performed on a typical design profile for the 908 aldehyde-derived substituents above. Besides the previously mentioned kinds of bias, this design used some additional bins: "2Dsim" contains the 26 closest analogues to *p*-hydroxyphenethyl as selected by Daylight 2-D similarity searching, "xtrm" includes 22 peculiar substituents that are far from the centroid in property space, and "good" is a general bin that contains all reasonable substituents except those in the "xtrm" bin. The base profile for this design of 45 members was cntr-2, loHet-9, loRgPlr-9, hetAr-5, drug-3, dock-5, 2Dsim-5, loPlr-3, xtrm22−2, good-2. No MW penalty was used. The stacked bar graph in Figure 5 shows the results of increasing and decreasing the quota for each bin by one or two members, making up the difference from the general bin.

The most sensitive bins are seen to be cntr10 and 2dPharm. Unless there was a compelling reason, it would be advisable to decrease the quotas for these bins. Unlike the 2-D similarity bias, the design is very insensitive to including more members of the "dock" bin. This is a typical result. Structure-biased libraries can typically include many targeted substituents with only a modest loss of diversity. Thus, structure-biased libraries can be profitably used for general screening as well.

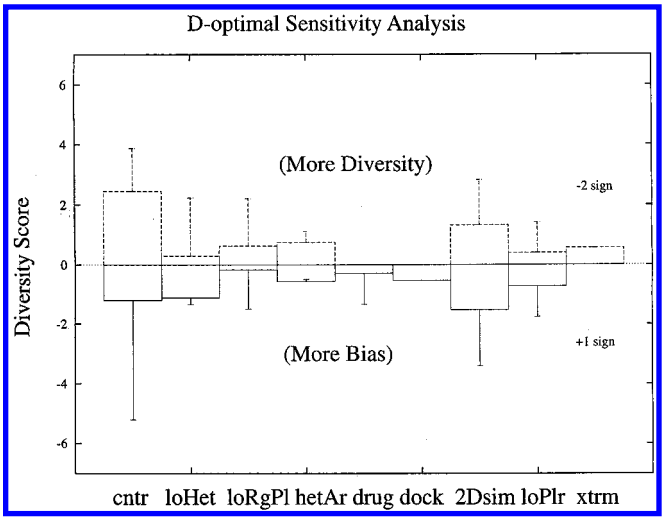

Figure 5. Sensitivity analysis bar chart showing which bin quota adjustments have the biggest effect on the overall design diversity.

CONCLUSION

"Tailoring" combinatorial libraries is a very general and powerful method to design diverse compound collections while controlling the profile of pharmaceutically relevant properties. The original "serial" algorithm was easy to implement from available D-optimal design codes, but was an order-dependent method that in principle was not expected to find the most diverse possible set of compounds for a given property profile. A rigorous "parallel" algorithm has now been implemented that is better able to find the most diverse possible design. Comparisons showed that designs found by the older method, although extremely useful, have been significantly improved by the new algorithm. Adding a small penalty for ambiguous molecular weights eliminated most mass duplications with only a negligible loss of diversity. This simplifies identifying compounds by the parent peak in the mass spectrum. Sensitivity analysis is an important addition to the tailoring software that identifies which kinds of bias are limiting the diversity for a particular library profile. A graphical display shows the user which particular bins could be sampled more heavily without much loss of diversity, or which bins should be sampled less if more diversity is desired. Together, these improvements to the Tailor software allow medicinal chemists to synthesize the most diverse possible libraries that are still consistent with virtually any other requirements of their drug discovery programs.

APPENDIX

Pseudocode for the Parallel Tailor Algorithm.

(I) For each attempt to find the global maximum {

(A) For each bin {

(1) Choose half of the bin members at random.

(2) Choose rest stepwise to maximize the rank and then maximize the subspace determinant for that rank.

(3) This gives the starting guess for the design.}

(B) Repeat {
(1) For each bin, starting from a random bin number, and iterating over all bins {
(a) For each possible exchange within that bin between the current design and available candidates {
(i) Calculate the change in the determinant (delta) using update formula.
(ii) Calculate the number of ambiguous molecular weights (A).
(iii) Calculate the change in score as
(iv) (delta/(1 + W1·badMW)) − W2·small·badMW − small
(v) where W1 and W2 are constants and small represents the minimum significant score increase.}
(2) Perform the single exchange that maximizes the change in the score.}
(C) Until no exchange improves the score.}
(II) Return best attempt; hopefully, it scores near the global optimum.}

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