

Library design in combinatorial chemistry by Monte Carlo methods

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Strategies for searching the space of variables in combinatorial chemistry experiments are presented, and a random energy model of combinatorial chemistry experiments is introduced. The search strategies, derived by analogy with the computer modeling technique of Monte Carlo, effectively search the variable space even in combinatorial chemistry experiments of only modest size. Efficient implementations of the library design and redesign strategies are feasible with current experimental capabilities.

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I. INTRODUCTION

The goal of combinatorial materials discovery is to find compositions of matter that maximize a specific material property [1–3], such as superconductivity [4], magnetoresistance [5], luminescence [6–8], ligand specificity [9], sensor response [10], or catalytic activity [2,11–16]. This problem can be reformulated as one of searching a multidimensional space, with the material composition, impurity levels, and synthesis conditions as variables. The property to be optimized, the figure of merit, is generally an unknown function of the variables and can be measured only experimentally.

Present approaches to combinatorial library design and screening invariably perform a grid search in composition space, followed by a “steepest-ascent” maximization of the figure of merit. This procedure becomes inefficient in high-dimensional spaces or when the figure of merit is not a smooth function of the variables, and its use has limited most combinatorial chemistry experiments to ternary or quaternary compounds.

In this paper, we suggest experimental protocols for searching the space of variables in combinatorial chemistry, exploiting an analogy between combinatorial materials discovery and Monte Carlo computer modeling methods. In Sec. II we discuss several of these strategies for library design and redesign. In Sec. III we introduce the random phase volume model that we will use to compare the different methods. The effectiveness of different strategies is discussed in Sec. IV. We conclude in Sec. V.

II. SAMPLING THE SPACE OF VARIABLES IN MATERIALS DISCOVERY

Several variables can be manipulated in order to seek the material with the optimal figure of merit. Material composition is certainly a variable. But also, film thickness [17] and deposition method [18] are variables for materials made in thin film form. The processing history, such as temperature, pressure, pH, and atmospheric composition, is a variable. The guest composition or impurity level can greatly affect the figure of merit [16]. In addition, the “crystallinity” of the material can affect the observed figure of merit [17]. Finally, the method of nucleation or synthesis may affect the phase or morphology of the material and so affect the figure of merit [19].

We assume that the composition and noncomposition variables of each sample can be changed independently [1,14]. Then, instead of a grid search on the composition and noncomposition variables, we consider choosing the variables *at random* from the allowed values. We also consider choosing the variables in a fashion that attempts to maximize the amount of information gained from the limited number of samples screened, via a quasirandom, low-discrepancy sequence [20].

We further consider performing multiple rounds of screening, incorporating feedback as the experiment proceeds by treating the combinatorial chemistry experiment as a Monte Carlo in the laboratory. This leads to sampling the experimental figure of merit E proportional to $\exp(\beta E)$. If β is large, then the Monte Carlo procedure will seek out values of the composition and noncomposition variables that maximize the figure of merit. If β is too large, however, the Monte Carlo procedure will get stuck in relatively low-lying local maxima. The first round is initiated by choosing the composition and noncomposition variables at random from the allowed values. The variables are changed in succeeding rounds as dictated by the Monte Carlo procedure.

Two ways of changing the variables are considered: randomly changing the variables of a randomly chosen sample a small amount and swapping a subset of the variables between two randomly chosen samples. These moves are repeated until all the samples in a round have been modified. The values of the figure of merit for the proposed new samples are then measured. Whether to accept the newly proposed samples or to keep the current samples for the next round is decided according to the detailed balance acceptance criterion. For the random change of one sample, we find the Metropolis acceptance probability

$$p_{\text{acc}}(c \rightarrow p) = \min \{1, \exp[\beta(E_{\text{proposed}} - E_{\text{current}})]\}. \quad (1)$$

Proposed samples that increase the figure of merit are always accepted; proposed samples that decrease the figure of merit are accepted with the Metropolis probability. Allowing the figure of merit occasionally to decrease is what allows samples to escape from local maxima. The random displacement of the d mole fraction variables, x_i , is done in the $(d-1)$ -dimensional subspace orthogonal to the d -dimensional vector $(1,1,\dots,1)$. This procedure ensures that the constraint $\sum_{i=1}^d x_i = 1$ is maintained. This subspace is identified

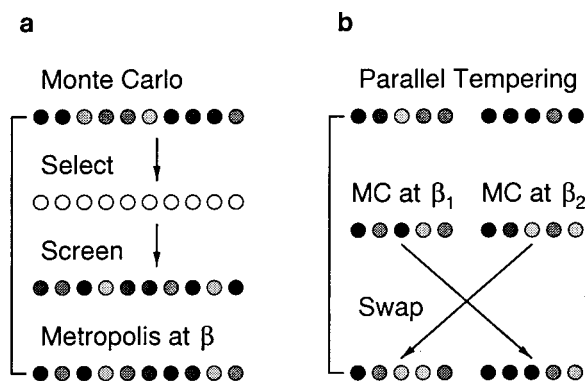


FIG. 1. (a) One Monte Carlo round with 10 samples. (b) One parallel tempering round with 5 samples at β_1 and 5 samples at β_2 .

by the Gram-Schmidt procedure. Moves that violate the constraint $x_i \geq 0$ are rejected. Moves that lead to invalid values of the noncomposition variables are also rejected. For the swapping move applied to samples i and j , we find the modified acceptance probability

$$p_{\text{acc}}(c \rightarrow p) = \min \{1, \exp[\beta(E_{\text{proposed}}^i + E_{\text{proposed}}^j - E_{\text{current}}^i - E_{\text{current}}^j)]\}. \quad (2)$$

Figure 1(a) shows one round of a Monte Carlo procedure. The parameter β is not related to the thermodynamic temperature of the experiment and should be optimized for best efficiency. The characteristic sizes of the random changes in the composition and noncomposition variables are also parameters that should be optimized.

If the number of composition and noncomposition variables is too great, or if the figure of merit changes with the variables in a too-rough fashion, normal Monte Carlo will not achieve effective sampling. Parallel tempering is a natural extension of Monte Carlo that is used to study statistical [21], spin glass [22], and molecular [23] systems with rugged energy landscapes. Our most powerful protocol incorporates the method of parallel tempering for changing the system variables. In parallel tempering, a fraction of the samples are updated by Monte Carlo with parameter β_1 , a fraction by Monte Carlo with parameter β_2 , and so on. At the end of each round, samples are randomly exchanged between the groups with different β 's, as shown in Fig. 1(b). The acceptance probability for exchanging two samples is

$$p_{\text{acc}}(c \rightarrow p) = \min \{1, \exp[\Delta\beta\Delta E]\}, \quad (3)$$

where $\Delta\beta$ is the difference in the values of β between the two groups, and ΔE is the difference in the figures of merit between the two samples. It is important to notice that this exchange step does not involve any extra screening compared to Monte Carlo and is, therefore, “free” in terms of experimental costs. This step is, however, dramatically effective at facilitating the protocol to escape from local maxima. The number of different systems and the temperatures of each system are parameters that must be optimized.

To summarize, the first round of combinatorial chemistry consists of the following steps: constructing the initial library of samples, measuring the initial figures of merit, changing the variables of each sample a small random amount or

swapping subsets of the variables between pairs of samples, constructing the proposed new library of samples, measuring the figures of merit of the proposed new samples, accepting or rejecting each of the proposed new samples, and performing parallel tempering exchanges. Subsequent rounds of combinatorial chemistry repeat these steps, starting with making changes to the current values of the composition and noncomposition variables. These steps are repeated for as many rounds as desired, or until maximal figures of merit are found.

We have chosen to sample the figure of merit by Monte Carlo, rather than to optimize it globally by some other method, for several reasons. First, Monte Carlo is an effective stochastic optimization method. Second, simple global optimization may be misleading since concerns such as patentability, cost of materials, and ease of synthesis are not usually included in the experimental figure of merit. Moreover, the screen that is most easily performed in the laboratory, the “primary screen,” is usually only roughly correlated with the true figure of merit. Indeed, after finding materials that look promising based upon the primary screen, experimental secondary and tertiary screens are usually performed to identify that material which is truly optimal. Third, it might be advantageous to screen for several figures of merit at once. For all of these reasons, sampling by Monte Carlo to produce several candidate materials is preferred over global optimization.

III. THE RANDOM PHASE VOLUME MODEL

The effectiveness of these protocols is demonstrated by combinatorial chemistry experiments as simulated by the random phase volume model. The random phase volume model is not fundamental to the protocols; it is introduced as a simple way to test, parametrize, and validate the various searching methods. The model relates the figure of merit to the composition and noncomposition variables in a statistical way. The model is fast enough to allow for validation of the proposed searching methods on an enormous number of samples, yet possesses the correct statistics for the figure-of-merit landscape. The d -dimensional vector of composition mole fractions is denoted by \mathbf{x} . The composition mole fractions are non-negative and sum to unity, and so the allowed compositions are constrained to lie within a simplex in $d-1$ dimensions. For the familiar ternary system, this simplex is an equilateral triangle. The composition variables are grouped into phases centered around N_x points \mathbf{x}_α randomly placed within the allowed composition range (the phases form a Voronoi diagram [24], see Fig. 2). The model is defined for any number of composition variables, and the number of phase points is defined by requiring the average spacing between phase points to be $\xi=0.25$. To avoid edge effects, additional points are added in a belt of width 2ξ around the simplex of allowed compositions. The figure of merit should change dramatically between composition phases. Moreover, within each phase α , the figure of merit should also vary with $\mathbf{y}=\mathbf{x}-\mathbf{x}_\alpha$ due to crystallinity effects such as crystallite size, intergrowths, defects, and faulting [17]. In addition, the noncomposition variables should also affect the measured figure of merit. The noncomposition variables are denoted by the b -dimensional vector \mathbf{z} , with each component constrained to fall within the range

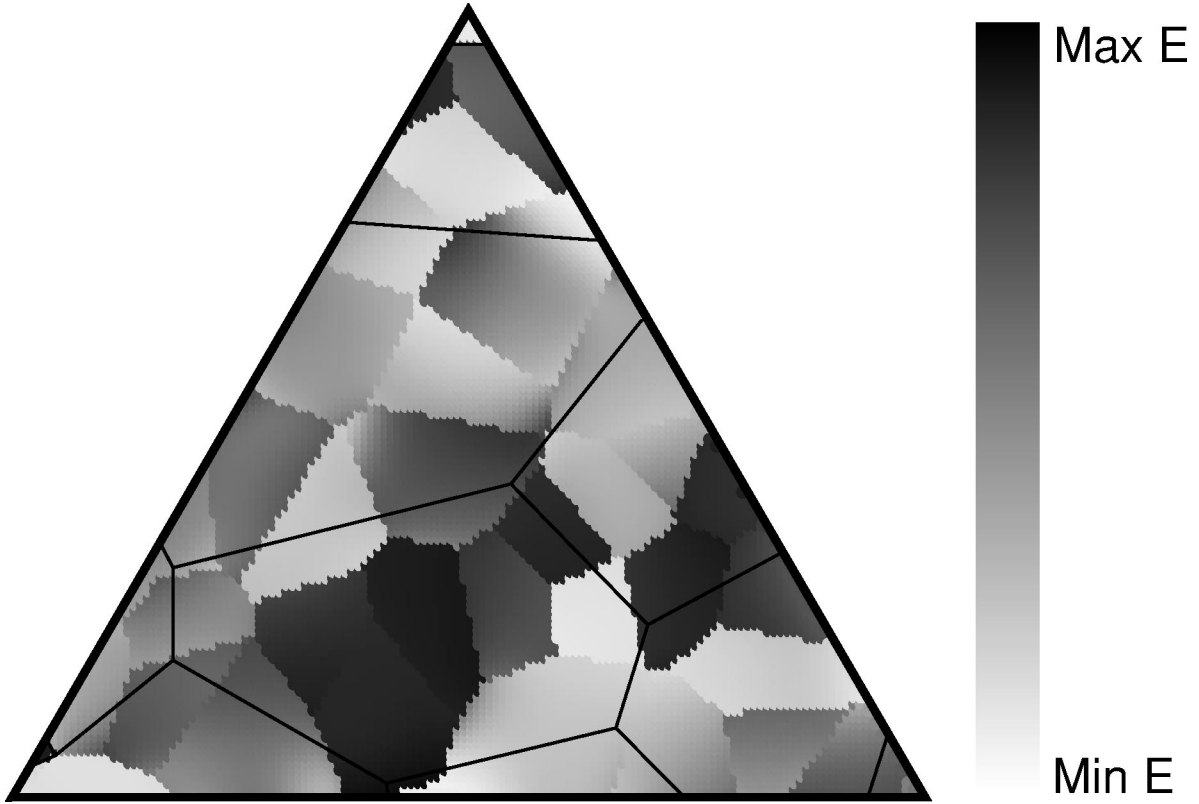


FIG. 2. The random phase volume model. The model is shown for the case of three composition variables and one noncomposition variable. The boundaries of the \mathbf{x} phases are evident by the sharp discontinuities in the figure of merit. To generate this figure, the \mathbf{z} variable was held constant. The boundaries of the \mathbf{z} phases are shown as thin dark lines.

$[-1, 1]$ without loss of generality. There can be any number of noncomposition variables. The figure of merit depends on the composition and noncomposition variables in a correlated fashion, and so the noncomposition variables also fall within N_z “ z phases” defined in the space of composition variables. There are a factor of 10 fewer noncomposition phases than composition phases. The functional form of the model when \mathbf{x} is in composition phase α and noncomposition phase γ is

$$\begin{aligned}
 E(\mathbf{x}, \mathbf{z}) = & U_\alpha + \sigma_x \sum_{k=1}^q \sum_{i_1 \geq \dots \geq i_k = 1}^d f_{i_1 \dots i_k} \\
 & \times \xi_x^{-k} A_{i_1 \dots i_k}^{(\alpha k)} y_{i_1} y_{i_2} \dots y_{i_k} \\
 & + \frac{1}{2} \left(W_\gamma + \sigma_z \sum_{k=1}^q \sum_{i_1 \geq \dots \geq i_k = 1}^b f_{i_1 \dots i_k} \right. \\
 & \left. \times \xi_z^{-k} B_{i_1 \dots i_k}^{(\gamma k)} z_{i_1} z_{i_2} \dots z_{i_k} \right), \quad (4)
 \end{aligned}$$

where $f_{i_1 \dots i_k}$ is a constant symmetry factor, ξ_x and ξ_z are constant scale factors, and U_α , W_γ , $A_{i_1 \dots i_k}^{(\alpha k)}$, and $B_{i_1 \dots i_k}^{(\gamma k)}$ are random Gaussian variables with unit variance. In more detail, the symmetry factor is given by

$$f_{i_1 \dots i_k} = \frac{k!}{\prod_{i=1}^k o_i!}, \quad (5)$$

where l is the number of distinct integer values in the set $\{i_1, \dots, i_k\}$, and o_i is the number of times that distinct value i is repeated in the set. Note that $1 \leq l \leq k$ and $\sum_{i=1}^l o_i = k$. The scale factors are chosen so that each term in the multinomial contributes roughly the same amount: $\xi_x = \xi/2$ and $\xi_z = (\langle z^6 \rangle / \langle z^2 \rangle)^{1/4} = (3/7)^{1/4}$. The σ_x and σ_z are chosen so that the multinomial, crystallinity terms contribute 40% as much as the constant, phase terms on average. For both multinomials $q=6$. As Fig. 2 shows, the random phase volume model describes a rugged figure of merit landscape, with subtle variations, local maxima, and discontinuous boundaries.

IV. RESULTS

Six different search protocols are tested with increasing numbers of composition and noncomposition variables. The total number of samples whose figure of merit will be measured is fixed at $M = 100\,000$, so that all protocols have the same experimental cost. The single pass protocols grid, random, and LDS are considered. For the grid method, we define $M_x = M^{(d-1)/(d-1+b)}$ and $M_z = M^{b/(d-1+b)}$. The grid spacing of the composition variables is $\zeta_x = (V_d/M_x)^{1/(d-1)}$, where

$$V_d = \frac{\sqrt{d}}{(d-1)!} \quad (6)$$

is the volume of the allowed composition simplex. Note that the distance from the centroid of the simplex to the closest point on the boundary of the simplex is

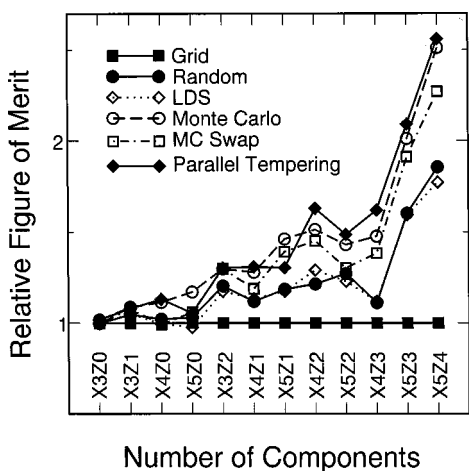


FIG. 3. The maximum figure of merit found with different protocols on systems with different number of composition (\mathbf{x}) and noncomposition (\mathbf{z}) variables. The results are scaled to the maximum found by the grid searching method. Each value is averaged over scaled results on 10 different instances of the random phase volume model with different random phases. The Monte Carlo methods are especially effective on the systems with larger number of variables, where the maximal figures of merit are more difficult to locate.

$$R_d = \frac{1}{[d(d-1)]^{1/2}}. \quad (7)$$

The spacing for each component of the noncomposition variables is $\zeta_z = 2/M_z^{1/b}$. For the LDS method, different quasi-random sequences are used for the composition and noncomposition variables. The feedback protocols Monte Carlo, Monte Carlo with swap, and parallel tempering are considered. The Monte Carlo parameters were optimized on test cases. It was optimal to perform 100 rounds of 1000 samples with $\beta=2$ for $d=3$ and $\beta=1$ for $d=4$ or 5, and $\Delta x = 0.1R_d$ and $\Delta z = 0.12$ for the maximum random displacement in each component. The swapping move consisted of an attempt to swap all of the noncomposition values between the two chosen samples, and it was optimal to use $P_{\text{swap}} \approx 0.1$ for the probability of a swap versus a regular random displacement. For parallel tempering it was optimal to perform 100 rounds with 1000 samples, divided into three subsets: 50 samples at $\beta_1=50$, 500 samples at $\beta_2=10$, and 450 samples at $\beta_3=1$. The 50 samples at large β essentially perform a “steepest-ascent” optimization and have smaller $\Delta x = 0.01R_d$ and $\Delta z = 0.012$.

The figures of merit found by the protocols are shown in Fig. 3. The random and LDS protocols find better solutions than does grid in one round of experiment. More importantly, the Monte Carlo methods have a tremendous advantage over one pass methods, especially as the number of variables increases, with parallel tempering the best method. The Monte Carlo methods, in essence, gather more information about how best to search the variable space with each succeeding round. This feedback mechanism proves to be effective even for the relatively small total sample size of 100 000 considered here. We expect that the advantage of the Monte Carlo methods will become even greater for larger sample sizes. Note that in cases such as catalytic activity, sensor response, or ligand specificity [25], the experimental figure of merit would likely be exponential in the values shown in Fig. 3, so that the success of the Monte Carlo methods would be even more dramatic. A better calibration of the parameters in Eq. (4) may be possible as more data becomes available in the literature.

V. CONCLUSION

To conclude, the experimental challenges in combinatorial chemistry appear to lie mainly in the screening methods and in the technology for the creation of the libraries. The theoretical challenges, on the other hand, appear to lie mainly in the library design and redesign strategies. We have addressed this second question via an analogy with Monte Carlo computer simulation, and we have introduced the random phase volume model to compare various strategies. We find the multiple-round, Monte Carlo protocols to be especially effective on the more difficult systems with larger numbers of composition and noncomposition variables.

An efficient implementation of the search strategy is feasible with existing library creation technology. Moreover “closing the loop” between library design and redesign is achievable with the same database technology currently used to track and record the data from combinatorial chemistry experiments. These multiple-round protocols, when combined with appropriate robotic controls, should allow the practical application of combinatorial chemistry to more complex and interesting systems.

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