Electronic Supplementary Information for: Exploring Experimental Fitness Landscapes for Chemical Synthesis and Property Optimization

Katharine Moore Tibbetts, a Xiao-Jiang Feng, b Herschel Rabitz, c

a Department of Chemistry, Virginia Commonwealth University, Richmond, VA 23284, USA
b Kadmon Corporation, 450 East 29th Street, New York, NY 10016, USA
c Department of Chemistry, Princeton University, Princeton, NJ 08544, USA

SI Proof of Fitness Landscape Topology

This section presents a proof of the two conclusions of the OptiChem theorem: (1) the existence of a trap-free topology of fitness landscapes for chemical and material synthesis and property optimization and (2) the allowed existence of connected “level sets” of optimal solutions. The proof below is adapted from Ref. 1. A more detailed discussion of the proof and its consequences can be found in Refs. 1, 2. These conclusions depend on the satisfaction of the assumptions of (i) a well-posed optimization goal and (ii) no significant limitations imposed on the control resources such that free movement on the landscape is accessible. Implicitly, the analysis requires the basic considerations that synthesis is bounded by 100% yield and chemical properties generally have finite values. Although the analysis below also implicitly assumes continuous variables and that the objective function J is continuous and differentiable, trap-free landscape topologies have been observed for a variety of systems with discrete variables as well, considering a reasonable level of resolution (see Refs. 2–4 and Figures S23 and S24 below). These assumptions constitute sufficient conditions for the performance of a landscape analysis. Milder conditions might exist (perhaps with specific different conditions for the system and environment as defined below) that reveal further information about the landscape. Such an analysis is an ongoing...
area of study. The present derivation of the landscape topology draws on convex optimization theory and quantum mechanics; appropriate references are provided for further background.

The OptiChem theorem applies to a target chemical system (e.g., collection of reagents) that interacts with a surrounding environment (e.g., solvent). Both the chemical system and environment are described quantum-mechanically, with the system being open (i.e., to the environment). The state of an open quantum system containing $m$ accessible energy levels may be represented by an $m \times m$ density matrix $\rho$. In practical applications, the value of $m$ could be very large; the analysis below holds for any finite value of $m$. The elements of $\rho$ are generally complex numbers, and $\rho$ must have the following properties:

i. $\rho$ is Hermitian, i.e. $\rho^\dagger = \rho$.

ii. $\rho \geq 0$ is a positive semi-definite matrix.

iii. $\rho$ has unit trace, $\text{Tr} (\rho) = \sum_j^m \rho_{jj} = 1$.

The physical basis of these properties is as follows. Hermiticity is required to ensure that the eigenvalues of $\rho$ are real numbers, i.e., that the associated quantum mechanical observables are real measurable quantities. The $j$th diagonal element $\rho_{jj}$ is the probability of the $j$th state being populated, so the positive semi-definite requirement $\rho \geq 0$ means that the probability of populating each state is greater than or equal to zero and $\text{Tr} (\rho) = 1$ ensures that the probabilities sum to unity. With these properties, it is straightforward to show that the set $\mathcal{D}$ of all density matrices $\rho \in \mathcal{D}$ is a convex set. A convex set $\{x\}$ of elements $x$ (e.g., matrices with specific properties) has the feature that for any two members of the set, $x_0$ and $x_1$, their convex sum, $x_\lambda = (1 - \lambda)x_0 + \lambda x_1$ for $0 \leq \lambda \leq 1$ produces $x_\lambda$ that is in the set $\{x\}$, i.e., has all the required properties of elements in the set. The set $\mathcal{D}$ is convex because (1) $\rho_\lambda$ is the sum of two positive semidefinite matrices and therefore is a positive semidefinite matrix, and (2) $\text{Tr} \rho_\lambda = (1 - \lambda)\text{Tr} \rho_0 + \lambda \text{Tr} \rho_1 = 1$. Therefore $\rho_\lambda$ is also a positive semidefinite matrix with unit trace, meaning that it is in the set $\mathcal{D}$.

The OptiChem theorem rests on the assumed ability to generally describe chemical transformations of open systems specified by some $\rho \in \mathcal{D}$. The general transformation of an initial state $\rho_0$ (i.e., before the chemical transformation has occurred) to the state $\rho$ (i.e., the state of the products after the
chemical transformation) can be represented by a function $\Phi$ such that $\rho = \Phi(\rho_0)$. The transformation described by $\Phi$ has the properties of being trace-preserving (i.e., $\text{Tr} \, \Phi(\rho_0) = \text{Tr} \, (\rho) = \text{Tr} \, (\rho_0) = 1$) and completely positive (CP). The trace-preservation property of $\Phi$ maintains the sum of state population probabilities at unity. In particular, the CP requirement ensures satisfaction of the positive semidefinite property $\rho \geq 0$ under transformation of $\rho_0$ to some other density matrix $\rho$. Such CP, trace preserving functions $\Phi$ are called Kraus maps, which can be uniquely determined by Kraus matrices $K$. For an open $m$-dimensional system, the matrix $K$ describing a Kraus map is an $m^2 \times m^2$ matrix composed of $m^2$ complex $m \times m$ sub-matrices $K_{ij}$. Using Eq. (S.1), the action of the Kraus map $\Phi$ on the initial state $\rho_0$ produces an $m \times m$ matrix $\rho = \Phi(\rho_0)$ with elements

$$\rho_{\nu\mu} = \sum_{\sigma,\tau=1}^{m} K_{(\mu\nu),\sigma\tau}(\rho_0)_{\sigma\tau},$$

where $(\mu\nu) = \mu + m(\nu - 1)$ and $(\mu, \nu = 1, 2, \ldots, m)$ and $K_{(\mu\nu),\sigma\tau}$ is the appropriate matrix element of $K$.

The CP and trace preservation conditions imply certain constraints on the structure of the $K_{ij}$ matrices. The CP condition of the map $\Phi$ is equivalent to the matrix positivity condition $K \geq 0$. The condition of trace preservation becomes $\text{Tr} \, K_{ij} = \delta_{ij}$ for all $i, j = 1, \ldots, m$. These two constraints imply that the collection of all possible Kraus matrices $\{K\}$ for the transformation of $\rho$ forms a convex set.

In order to show the convexity of the set $\{K\}$, choose two arbitrary matrices $K_0$ and $K_1$ and consider their convex sum $K_\lambda = (1 - \lambda)K_0 + \lambda K_1$, $0 \leq \lambda \leq 1$. In order for the set $\{K\}$ to be convex, the matrix $K_\lambda$ must be positive and trace-preserving, as described above. First, the sum of two positive matrices $(1 - \lambda)K_0$ and $\lambda K_1$ must also be positive, so $K_\lambda$ satisfies the matrix positivity requirement. Second, if $(K_\lambda)_{i,j}$ denotes the $(i, j)$ block of the matrix $K_\lambda$, then $\text{Tr} \, (K_\lambda)_{i,j} = (1 - \lambda)\text{Tr} \, (K_0)_{i,j} + \lambda \text{Tr} \, (K_1)_{i,j} = (1 - \lambda)\delta_{i,j} + \lambda \delta_{i,j} = \delta_{i,j}$, so the matrix $K_\lambda$ satisfies the trace-preservation requirement. Thus, $K_\lambda$ is in the set $\{K\}$, thereby implying that the set of Kraus matrices is convex.
Combining the convexity property of \( \{K\} \) with the physical definition of the fitness \( J \) is used to prove the inherent existence of trap-free landscape topology. A chemical fitness objective \( J \) is characterized by a suitable quantum mechanical observable \( O \), expressed as an \( m \times m \) Hermitian matrix
\[
J \equiv \text{Tr}[\rho O],
\] (S.3)
where \( \rho \) is the state of the system after the chemical transformation described by the Kraus map in Eq. (S.2). The initial state \( \rho_0 \) is transformed through the actions of the \( N \) laboratory accessible variables \( x = [x_1, x_2, \ldots, x_n] \) discussed in the main text that specify the associated Kraus map \( K \). The value of the objective \( J \) then becomes
\[
J = J(x) = J(K^x) = \text{Tr}[\Phi_{K^x}(\rho_0)O] = \sum_{\sigma,\tau=1}^{m} K_{(\mu\nu), (\sigma\tau)}^{x} \rho_0^{\sigma\tau} O_{\nu\mu}. \tag{S.4}
\]
In Eq. (S.4), the variables \( x \) determine the fitness \( J \) by acting on the system through the matrix \( K^x \), where the superscript indicates that the Kraus matrix depends on the variables \( x \). The explicit dependence of \( K^x \) upon the variables \( x \) may be complicated and determined by the particular system under study, but detailed knowledge of this relationship is not necessary to establish the landscape topology of \( J(x) \). The formal description of chemical transformations using the analysis below in terms of the set of Kraus matrices \( \{K\} \) is general for all chemical systems and synthesis or property optimization objectives.

We can combine the convexity property of the set \( \{K\} \) with the inherent linear dependence of \( J(K) \) upon \( K \) (i.e., from Eq. (S.4)) to show that the resulting landscape \( J \) contains no local minima or maxima (traps) and that multiple connected regions on the landscape producing an optimal value of \( J \) may exist. These properties hold regardless of the particular nature of the chemical system specifying the initial density matrix \( \rho_0 \) or the chemical optimization objective described by the Hermitian observable operator \( O \); the analysis only relies on \( J \) being linear in \( K \). The trap-free nature of the landscape can only be shown to hold when \( \{K\} \) is a convex set, that is, the convexity of \( \{K\} \) is a sufficient condition to produce a trap-free landscape topology. Constraints placed on the variables \( x \) that limit the possible Kraus matrices that can be generated in the laboratory could make the set \( \{K\} \) non-convex and thereby destroy the trap-free property of the landscape.

First, we show that the function \( J(K) \) contains no local maxima; establishing that \( J \) contains no local minima is equivalent. Suppose that there exists a local maximum \( K_{(0)} \) on the landscape. This means that
(1) There exists a neighborhood of $K(0)$ denoted as $U(K(0))$ within the convex set $\{K\}$ such that for all $K(i) \in U$, $J(K(i)) \leq J(K(0))$ (i.e., $K(0)$ is a maximum).

(2) There exists a maximum $K(1)$ such that $J(K(1)) > J(K(0))$ (i.e., $K(0)$ is not a global maximum).

Since the set $\{K\}$ is convex, then $K(\lambda) = (1 - \lambda)K(0) + \lambda K(1)$ is in $\{K\}$. Consider $J(K)$ to lie on the line connecting the points $K(0)$ and $K(1)$. $J(K)$ is a strictly monotonic function of $\lambda$, that is, $J(K(\lambda_2)) > J(K(\lambda_1))$ for any $\lambda_2 > \lambda_1$. In particular, for any $\lambda > 0$, $J(K(\lambda)) > J(K(0))$. But, if $\lambda$ is small enough, we may consider $K(\lambda)$ to be in the neighborhood $U(K(0))$, which contradicts condition (1) above. Thus, $K(0)$ cannot be a local maximum; only global maxima exist on the landscape. Importantly, this argument only holds when $\{K\}$ is a convex set, meaning that convexity of the set $\{K\}$ is a sufficient condition to guarantee a trap-free fitness landscape topology.

A “solution” to a posed chemical synthesis or property goal is specified abstractly here by the Kraus transformation $K$. The convexity of the set $\{K\}$ also results in the solutions of $J(K)$ with the same $J$ value, i.e., “homologous” solution, being connected. To prove this property, let $K(0)$ and $K(1)$ be two homologous solutions with $J(K(1)) = J(K(0))$. Thus, we have that $J(K(\lambda)) = (1 - \lambda)J(K(1)) + \lambda J(K(0)) = (1 - \lambda + \lambda)J(K(0)) = J(K(0))$, for all $\lambda \in [0, 1]$, so any point on the segment connecting $K(0)$ and $K(1)$ is also a homologous solution, implying that the homologous solutions are connected.

In summary, the following landscape properties were shown to hold in terms of a general chemical transformation described by the Kraus map $K$: (i) for any initial density matrix $\rho_0$ and any physical observable $O$, the function $J(K) = \sum_{m=1}^{m} K(\mu, \sigma)(\rho_0)_{\sigma, \tau} O_{\mu, \tau}$ does not have local minima or maxima and (ii) connected optimal homologous solutions exist. In order for the same landscape topology to hold in terms of the laboratory variables $x$, the two Assumptions of a well-posed objective and sufficiently unconstrained variables discussed in the main text must be satisfied. Furthermore, the connectivity of optimal homologous solutions may not hold if practical constraints on the variables $x$ reduce the set of reachable optimal transformations to possibly multiple isolated sets of Kraus matrices, leading to multiple isolated global maxima, as observed in the landscape in Ref.10 that is discussed in Sections 3.2 and 4 of the main work and shown in Figure 7.
SII Support Vector Regression (SVR) Details

The following discussion of Support Vector Regression (SVR) is adapted from Ref. 11. SVR approximates a multivariate function \( f(x) \) as

\[
\hat{f}(x) = \sum_{k=1}^{n} w_k \phi_k(x) + b = \langle w, \Phi(x) \rangle + b.
\] (S.5)

SVR is a tool to find the best model of the above particular form in Eq. (S.5) (i.e., the optimal values of the unknown coefficients \( w \) and \( b \)) from a given set of \((x, y)\) data, while assuming that the model is as “flat” as possible to ensure satisfactory model prediction quality. *Flatness* here means that \( w \) has the smallest \( L_2 \) norm.

The optimal construction of Eq. (S.5) poses a convex optimization problem

\[
\begin{align*}
\text{minimize} & \quad \frac{1}{2} \| w \|^2 \\
\text{subject to} & \quad y(s) - \langle w, \Phi(x(s)) \rangle - b \leq \epsilon, \\
& \quad \langle w, \Phi(x(s)) \rangle + b - y(s) \leq \epsilon,
\end{align*}
\] (S.6)

where \( \epsilon \) is the required precision. Sometimes, however, solving such a convex optimization problem may not be feasible (i.e., there is no solution for \( w \) and \( b \) that satisfy the required constraints), and relaxation to allow for consideration of some errors is needed by introducing slack variables \( \xi_s, \xi_s^* \) to deal with otherwise infeasible constraints of the optimization problem given in Eq. (S.6), which was proposed by Vapnik 12:

\[
\begin{align*}
\text{minimize} & \quad \frac{1}{2} \| w \|^2 + C \sum_{s=1}^{N} (\xi_s + \xi_s^*) \\
\text{subject to} & \quad y^{(s)} - \langle w, \Phi(x^{(s)}) \rangle - b \leq \epsilon + \xi_s, \\
& \quad \langle w, \Phi(x^{(s)}) \rangle + b - y^{(s)} \leq \epsilon + \xi_s^*, \\
& \quad \xi_s, \xi_s^* \geq 0.
\end{align*}
\] (S.7)

The constant \( C > 0 \) determines the trade-off between the flatness of \( \hat{f} \) and the amount up to which deviations larger than \( \epsilon \) are tolerated. In the simulations for the present work the values of these parameters are fixed at \( C = 20 \) and \( \epsilon = 0.05 \).
Instead of solving Eq. (S.7) directly, it is much easier to pose a dual optimization problem with non-negative unknown parameters $\alpha_s$ and $\alpha^*_s$

maximize $\frac{1}{2} \sum_{r,s=1}^{N} (\alpha_r - \alpha^*_r)(\alpha_s - \alpha^*_s)\langle \Phi(x^{(r)}), \Phi(x^{(s)}) \rangle$

$- \epsilon \sum_{s=1}^{N} (\alpha_s + \alpha^*_s) + \sum_{s=1}^{N} y^{(s)}(\alpha_s - \alpha^*_s)$,

subject to $\sum_{s=1}^{N} (\alpha_s - \alpha^*_s) = 0$, $\alpha_s, \alpha^*_s \in [0, C]$ (S.8)

which can be solved by quadratic programming.\(^\dagger\) The resultant vector $\mathbf{w}$ is then given by

$$\mathbf{w} = \sum_{s=1}^{N} (\alpha_s - \alpha^*_s)\Phi(x^{(s)}).$$ (S.9)

Note that $\mathbf{w}$ has the same dimension of $\Phi(x)$, i.e., it can be infinite. For a given $x$, the output value $f(x)$ can be estimated by

$$\hat{f}(x) = (\mathbf{w}, \Phi(x)) + b = \sum_{s=1}^{N} (\alpha_s - \alpha^*_s)\langle \Phi(x^{(s)}), \Phi(x) \rangle + b$$

$$= \sum_{s=1}^{N} (\alpha_s - \alpha^*_s)K(x^{(s)}, x) + b.$$ (S.10)

Eqs. (S.9) and (S.10) show that $\mathbf{w}$, and consequently $\hat{f}(x)$, are completely described by the data points with non-zero parameters $\alpha$ or $\alpha^*$ (referred to as support vectors), and $\hat{f}(x)$ can be expressed as a linear combination of at most $N$ kernels $K(x^{(s)}, x)$ with combination parameters $\alpha_s$ or $\alpha^*_s$, which can be both zero, but not both nonzero. The point $x^{(s)}$ with non-zero parameter $\alpha_s$ or $\alpha^*_s$ corresponds to one of the two constraints in Eq. (S.7) not being satisfied. This implies that all data points within the required error bound have no contribution to the model $\hat{f}(x)$ and forms the basis for SVR requiring very limited data samples to construct the model. Importantly, the difficulty with high dimensionality for $x$ or $\mathbf{w}$ is no longer a problem. All these properties make SVR a valuable tool for high dimensional model construction.
SIII  Details of the Gradient Search Algorithm

The constrained optimization routine fmincon implemented in MATLAB\textsuperscript{14} was employed. The gradient vector was calculated by finite differences. The other relevant algorithmic parameters were fixed to the following values for all simulations presented in Sections 4 and 5 of the main work:

- Change in variables $x$ for finite-difference gradient $\text{DiffMaxChange}: < 10^{-2}$
- Stop criterion for change in variables $x$ between consecutive iterations $\text{TolX}: < 10^{-6}$
- Stop criterion for change in $f(x)$ between consecutive iterations $\text{TolFun}: < 10^{-8}$
- Initial barrier for constraint satisfaction $\text{InitBarrierParam}: 10^{-2}$
SIV Landscape plots constructed from Design of Experiment/Response Surface Methodology data

The three-dimensional landscape plots for the references reported in Tables I and II of the main work are presented here. All of the landscape plots shown are made using the isosurface function in MATLAB, where the surfaces are generated by cubic spline interpolation between the experimental data points. Error bars shown adjacent to the color bars in the plots report the standard deviation in the value of one or more data points (typically repeated 3-5 times in experiments). The source of the error bar is noted for each experiment. A brief summary of each reference is followed by the associated figure(s).

For the landscape in Figure S1, the objective is to maximize the yield of fatty acid ethyl esters (FAEE) from sunflower oil and ethanol, catalyzed by NaOH. The variables are the temperature, ethanol/oil molar ratio, and percent NaOH loading. FAEE purity (%) is the observable. The reported error bar is the average of standard deviation values, which were provided for two runs at each combination of the variables. Note that the optimum lies at the highest values of all three variables.

![Figure S1: Yield of FAEE as a function of temperature, ethanol:oil molar ratio, and NaOH loading.](image)

The synthesis of ethers from glycerol was optimized using temperature, ethanol:glycerol molar ratio, and arenesulfonic acid-functionalized mesostructured silica catalyst loading (%) as variables. The observables are (a) conversion of glycerol (i.e., consumption of starting material) and (b) yield of ethers (i.e., desired products), as plotted in Figure S2. The error bar in each plot is based on standard deviation of three experiments performed with the values of the variables at the center of the landscape. Both land-
scapes are shown at the same orientation with respect to the variables. Note that the global maximum is at a different location on each landscape, which suggests some competition between the two objectives.

Figure S2: (a) Conversion of glycerol and (b) yield of ether products as a function of temperature, ethanol:glycerol molar ratio, and catalyst loading.

The oxidation efficiency (%) of arsenite to arsenate was optimized using the variables ultrasonic power density, initial concentration of arsenite, and H$_2$O$_2$ concentration. The landscape is in Figure S3, with the error bar based on the standard deviation of three experiments run at the central values of the variables. The error bar appears to have no height because the reported error is small compared to the observable value. The landscape maximum lies near the edge of the search space at the highest ultrasonic power and lowest arsenite concentration, but at the center of the range of H$_2$O$_2$ concentrations. This is consistent with the authors’ choice of H$_2$O$_2$ concentration range based on an earlier experiment.

Figure S3: Oxidation efficiency of arsenite to arsenate as a function of ultrasonic power density, arsenite concentration, and H$_2$O$_2$ concentration.

The production of molecular hydrogen by *Rhodobacter sphaeroides* was optimized in a photobioreactor using the variables are DL malic acid concentration, L lutamic acid concentration (both in g/L), and temperature. The chemical reaction is $\text{C}_4\text{H}_6\text{O}_5 + 3\text{H}_2\text{O} \rightarrow 4\text{CO}_2 + 6\text{H}_2$. The observable in the
landscape of Figure S4 is the rate of H$_2$ production in mL/L/hr. No error was reported. The optimum lies in the interior of the search space, indicating that the ranges of all three variables were well chosen.

The maximization of H$_2$ and minimization of CO$_2$ yield from aqueous-phase reforming of sorghum biomass as a biofuel production goal was optimized using the process temperature, feed flow rate (mL/min) and biomass concentration (mg/L of carbon). Landslapes for the observables H$_2$ volume, CO$_2$ volume (mL), and fractional gas conversion of initial carbon (\%) are shown in Figure S5(a), (b), and (c), respectively. The reported error bar for each plot is the standard deviation of three experiments performed at the central landscape point.

The decomposition of tetracycline in water was optimized using an electrochemical process with the variables applied current (mA), initial pH and initial tetracycline concentration (mg/L). The observable is the percentage (\%) of tetracycline removed after 5 min, 10 min, 20 min, plotted in Figure S6 (a), (b),
and (c), respectively. The error bar is the standard deviation for three measurements performed at the central landscape point at 5 minutes.

Figure S6: Removal of tetracycline from water by an electrochemical process with variables applied current (mA), initial pH, and initial tetracycline concentration (mg/L).

The optimization of ammonia and chemical oxygen demand (COD) removal from raw landfill leachate through an electrochemical process was performed with the variables current density (mA cm$^{-2}$), inter-electrode gap (cm), and reaction time (min). Observables are the percentage % of ammonia and COD removed from the raw matter. The two landscapes are plotted in Figure S7, with the reported error bar in each plot based on the standard deviation of three experiments at the central point. These bars are very small due to the small errors. Note that the landscape maxima are not the same, so the observables are competitive to some degree.

Figure S7: Percentage of NH$_3$ (a) and COD (b) removed from landfill mass. Variables are the electrochemical current (mA/cm$^2$), electrode separation (cm), and reaction time (min).

The removal of methylene blue and methyl orange dyes was optimized using a pulsed discharge in water. The variables are ultrasonic power (W), gas flow rate (m$^3$/hr), and electrode spacing (mm). The observable is dye removal efficiency (%) using UV-VIS detection, shown in Figure S8 for methylene
blue (a) and methyl orange (b). The reported error bar in each plot is from the standard deviation of five measurements taken at the central landscape point.

Figure S8: Percentage of methylene blue (a) and methyl orange (b) dyes removed from water by DC plasma processing. Variables are the ultrasonic power (W), gas flow rate (m$^3$/hr), and electrode separation (mm).  

The composition of phenolic mixtures (catechin, genistein and daidzein) was optimized as a pre-thermal processing technique to reduce the presence of reactive carbonyl species methylglyoxal, glyoxal and 3-deoxyglucosone in ultra-high temperature (UHT) bovine milk. The variables were the concentrations of each of the three phenols. The observables are the levels of the three reactive carbonyl species ($\mu$M) after phenol treatment. Figure S9 shows the landscapes for methylglyoxal (a), glyoxal (b), and 3-deoxyglucosone (c), with the error bar in each plot showing the standard deviation of three measurements taken at the central landscape point.

Figure S9: Removal of reactive carbonyl species methylglyoxal (a), glyoxal (b), and 3-deoxyglucosone (c) from bovine milk with a mixture of phenols. Variables are the concentration of the three phenols catechin, genistein, and daidzein in mM. 

The yield of sage oil extraction from the dried and ground leaves in ethanol was optimized with the variables temperature (°C), time (min), and leaf concentration in ethanol (wt/vol %). The observable
in Figure S10 is the wt% oil extracted/initial sage amount. The reported error bar is based on the standard deviation of five measurements of the central point.

Figure S10: Fraction of sage oil extracted from ground leaves in ethanol. The variables are temperature (°C), time (min), and initial concentration of sage leaves (wt.%/vol.).

Figure S10: Fraction of sage oil extracted from ground leaves in ethanol. The variables are temperature (°C), time (min), and initial concentration of sage leaves (wt.%/vol.).

The microwave assisted grafting of poly(acrylamide) on to Aegle marmelos gum (a natural polymer in the fruit of this species) for novel drug delivery systems was optimized using the variables concentration of Aegle marmelos gum (wt %), Microwave exposure time (s), Microwave power (%). The grafting efficiency (%) is the observable in Figure S11; no error was reported.

Figure S11: Microwave-assisted grafting efficiency of poly(acrylamide) onto natural fruit polymer. The variables are gum concentration (wt%), microwave time (s) and microwave power (%).

The activity of the enzyme laccase following immobilization onto bacterial cellulose was optimized for biocatalytic reactor design. The variables are enzyme concentration (µL/L), contact time (h), and
pH, with the observable of recovered activity plotted in Figure S12. The error bar is based on three measurements of the central point.

![Figure S12: Recovered activity of the enzyme laccase following immobilization. Variables are enzyme concentration (µL/L), contact time (h), and pH.](image)

The properties of copper ferrite (CuFe₂O₄) nanoparticles were optimized with the variables temperature, reaction time, and pH. Landscapes are plotted in Figure S13 for the observables of (a) particle size, (b) saturation magnetization ($M_s$), (c) remanence magnetization ($M_r$), and (d) coercivity ($H_c$), with the latter three being magnetic properties of the material. Error bars for each plot are based on three measurements of the central landscape point. The optimization goals are to minimize particle size and maximize $M_s$, $M_r$, and $H_c$. The landscape (a) contains a saddle point near the middle of the search space and two disconnected global minima at the edges of low and high pH.

The properties of nanostructured lipid carriers for the anti-cancer drug irinotecan were optimized using the variables sonication time (s), organic:aqueous phase ratio, and drug:lipid ratio. Three observables: particle size (nm), zeta potential (mV), and efficiency of transport (%), are plotted in Figure S14 (a), (b), and (c), respectively, with error bars based on standard deviation from three measurements of the central point.

The properties of poly-$\epsilon$-caprolactone (PCL) based polymeric nanoparticles for oral delivery of the drug lopinavir were optimized with the variables concentration of surfactant (%wt/vol), amount of polymer (mg) and time of homogenization (min). The observables particle size (nm) and delivery efficiency
Figure S13: Landscapes for properties of copper ferrite nanoparticles with variables temperature, time, and pH: (a) particle size, (b) saturation magnetization ($M_s$), (c) remanence magnetization ($M_r$), and (d) coercivity ($H_c$).\textsuperscript{27}

Figure S14: Formation of nanostructured lipid carriers for the drug irinotecan. Variables are sonication time (s), organic:aqueous phase ratio, and drug:lipid ratio. The observables are (a) particle size, (b) particle zeta potential, and (c) drug transport efficiency.\textsuperscript{28}
(\%) are shown in Figure S15(a), and (b), respectively, with error bars based on the standard deviation of three measurements taken at the central landscape point.

![Figure S15](image)

Figure S15: Optimization of delivery of the drug lopinavir in lipid nanocapsules. Variables are surfactant concentration (% wt/vol), amount of polymer added (mg), and homogenization time (min). The observables are (a) particle size and (b) delivery efficiency of the drug.  

The extended release of the drug cefpodoxime proxetil (CP) was optimized with the variables fractional loading of the polymers hydroxypropyl methylcellulose (HPMC K4M), sodium alginate (SA) and microcrystalline cellulose (MCC). The observable in Figure S16 is the percent of the resulting drug tablet dissolved after 24 hours, and the error bar reflects the standard deviation of three measurements at the central point.

![Figure S16](image)

Figure S16: Percent of drug tablet dissolved after 24 hours as a function of the percent concentration of polymers hydroxypropyl methylcellulose (HPMC K4M), sodium alginate (SA) and microcrystalline cellulose (MCC).
The encapsulation efficiency of curcumin in the natural polymer \(\gamma\)-Polyglutamic acid (\(\gamma\)-PGA) as drug delivery system was optimized with the variables are PGA concentration (\%), curcumin concentration (\%), and surfactant content \%. The observable is experimental encapsulation efficiency (\%), plotted in Figure S17. The standard deviation from two experiments was reported for every experimental point; the error bar in the plot is the mean of these standard deviations. The optimum is at the central landscape point and is obscured by the lower yield surfaces.

![Figure S17: Encapsulation efficiency of curcumin in \(\gamma\)-polyglutamic acid (PGA). Variables are PGA concentration, curcumin concentration, and surfactant concentration as percentages.](image)

The self-emulsifying drug delivery system by encapsulating the drug fenofibrate in oil-based capsules was optimized with the variables (surfactant + cosurfactant)/oil ratio, surfactant/cosurfactant ratio, and percentage of cosolvant mixture (%). The oil is extra virgin olive oil, cosolvant is PEG300 (solvent is water), surfactant/cosurfactant are Tween 80/Span 85. The two observables particle size and the percentage of drug released in 20 min are plotted in Figure S18(a) and (b), respectively. The goal was to minimize particle size, which appears to correspond to the maximum drug release at the central point on the landscape. The reported error bar in each plot are based on the standard deviation of four measurements of the central point. The small error bar in (a) reflects the small reported error in particle size.

The immobilization conditions of lipase onto Florisil via a polysuccinimide spacer arm were optimized with the variables pH, time (h) and initial lipase concentration (mg/ml). Observables are fraction of protein bound and activity of bound protein to catalyze asymmetric acylation of 2-amino-
Figure S18: Encapsulation of the drug fenofibrate in lipid nanoparticles. Variables are tween80:span85 ratio, (tween80+span85):oil ratio, and % PEG300. The observables (a) particle size and (b) percentage of drug released after 20 minutes are reported. 32

1-phenylethanols, plotted in Figures S19(a) and (b), respectively. One unit (U) of specific activity of lipase activity was defined as production of 1 µmol of p-NP per minute under the assay conditions. The observables are reported in U/mg protein. The error bar in (a) is the standard deviation of three measurements of the central data point and the error bar in (b) is the average of the standard deviations over all 15 landscape points.

Figure S19: Percentage of lipase bound to target polymer surface (a) and specific lipase activity towards acylation of 2-amino-1-phenylethanols (b). Variables are pH, immobilization time (h), and enzyme concentration (mg/mL). 33

The cationic character of cassava starch grafted with poly-diallyldimethylammonium chloride (poly-DADMAC) using ceric ammonium nitrate was optimized with the variables concentration of poly-DADMAC g per 10 g starch, concentration of ceric ammonium nitrate g per 10 mL water, and temperature (°C). 34 The landscape is plotted in Figure S20, with the reported error bar based on the standard
deviation of five measurements of the central landscape point. There are two isolated maxima on opposite edges of the landscape, with one appearing to be a trap. However, the limited ranges of the variables prevent determination of whether this is a true trap possibly caused by constraints on the variables.

Figure S20: Percentage of starch molecules made cationic by grafting of poly-DADMAC through gradical-initiated reaction with ceric ammonium nitrate (CAN). The variables are concentration of DADMAC, CAN, and temperature.34

SV Other landscapes from Tables II and III

The high sensitivity of the optical and electronic properties of noble metal nanoparticles to the particle size makes selective control critical for practical applications.35 The most common optimization goal is to specify a particular particle size and simultaneously minimize the particle size dispersity (PDI, i.e., deviation of particle sizes from the mean). In the Turkevich-Frens synthesis of Au nanoparticles, the effects of the concentration of chloroauric acid (HAuCl₄) and sodium citrate/HAuCl₄ ratio on the Au nanoparticle size and PDI was investigated over wide ranges of both variables, which resulted in the synthesis of Au nanoparticles with mean diameters ranging from 13.5 – 30 nm with relative PDI ranging from 1 – 30% (measurements conducted by dynamic light scattering (DLS)).35 The original work plots one dimensional slices of Au nanoparticle size or PDI as a function of HAuCl₄ concentration or citrate/HAuCl₄ ratio in a total of six separate figures. Plotting the available data as a function of both variables with cubic spline interpolation results in the two-dimensional landscapes of particle size
and PDI shown in Figure S21. The error bars on Figure S21(a) are the standard deviation of replicates of two synthesis conditions producing two distinct Au nanoparticle sizes. The landscape S21(b) shows large regions of low PDI over multiple nanoparticle sizes, suggesting that the separate objectives of controlling the size and PDI are not competitive.

Figure S21: Mean AuNP diameter (a) and percentage size dispersity (b) as a function of Au and citrate concentrations. Circles denote data points, surfaces are made by a cubic spline interpolation of the data.

Another synthesis route to AuNP involves reduction of HAuCl$_4$ by tannic acid. The AuNP size was optimized using the concentration of HAuCl$_4$ and the ratio of tannic acid/HAuCl$_4$ as the variables. The particle size was measured by DLS and plotted in the original work as a series of one-dimensional slices of the landscape of Figure S22. The colored circles are measured data points and the surfaces are made by cubic spline interpolation.

Figure S22: AuNP diameter as a function of HAuCl$_4$ concentration and tannic acid/HAuCl$_4$ ratio.
The composition of binary Pd-M catalysts for the oxygen reduction reaction (ORR) was optimized with the Pd:M ratio varied from 0:1 to 1:0 and eight metals M. The metal M is ordered by the adsorption energy of O\(_2\) for Pd\(_2\)M and PdM\(_2\) clusters (calculated by DFT): Au Ir Co Fe Ru Mo Ni V. Figure S23 shows the resulting landscape with two disconnected optimal catalysts.

![Figure S23: ORR activity as a function of Pd wt. % and alloyed metal, with metals ordered by oxygen adsorption energy, as calculated with DFT.]

The composition of binary Pd-M catalysts for Li-oxygen battery activity was optimized with the percentage Pd content and six elements M as variables. The ordering of the metals M = Ce, Ni, Co, Ru, Ir, Pt was chosen to produce the smoothest landscape in Figure S24. There appear to be two disconnected optimal catalyst regions (the two dark red regions on the plot).

![Figure S24: Li-oxygen battery activity of catalysts containing Pd and a second metal. Ordering of the metals was done by inspection and the surface was made with cubic spline interpolation.]

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SVI  Gradient search results in Section IV of the main work

Figure S25 shows the probabilities of finding each optimal solution on the HDMR model landscapes. Each symbol corresponds to one of the 20 landscapes in the respective HDMR landscape library.

Figure S25: Probability of finding each optimal solution on the HDMR landscapes. The inset shows the low probabilities of finding one of the traps $x_A^*$ or $x_B^*$. 
SVII  Additional figures related to Section V of the main work

The objective $J$ is defined as follows from the grayscale image in Figure S26.

![Grayscale image of phosphor materials](image)

**Figure S26: Grayscale image of phosphor materials from Ref. 39 with indication of the objective $J$.**

The poor performance of the POLY3 kernel with this data set appears to arise from over-fitting of the experimental data during HDMR modeling, as shown in Figure S27. For both the PL objective (Figure S27(a)) and $J$ objective (Figure S27(b)), the prediction MAE of the 150 compounds in the data set used for modeling (red dots) is significantly lower than the prediction MAE of the 75 compounds not in the data set (blue dots).

![Truth plots for HDMR functions](image)

**Figure S27: Representative truth plots for HDMR functions using the POLY3 kernel for a data set with the PL objective (a) and $J$ objective (b).**
The probabilities of finding each local minimum on the HDMR model landscapes are shown below in Figure S28. Each symbol corresponds to one of the 50 landscapes in the respective HDMR landscape library (RBF2 or POLY2 HDMR kernel).

![Figure S28: Probabilities of finding each local minimum on the HDMR model landscapes.]

References


