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Point of view

Combinatorial searches of inorganic materials using the ink-jet printer: science, philosophy and technology

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Abstract

The juxtaposition of direct ceramic ink-jet printing with high throughput screening, data-mining and interpretation methods using artificial neural networks is bringing to the ceramics community a capability for combinatorial analysis presently enjoyed mainly by the pharmaceutical industry. This paper attempts to set out the potential and scope for high speed, high resolution sample preparation, high throughput screening and informatics-driven local optimisation methods. It describes the distinct philosophical basis for this approach to discovery and identifies it as primarily Baconian. It examines in detail the aspirating-dispensing systems being used for ceramic sample preparation from powder suspensions, explores their likely strengths and limitations and how these may be mitigated through the application of sophisticated computational methods.

Keywords: Compositional optimisation; Screening

1. Introduction

While some outstanding materials scientists suggest that the main purpose of the subject is to delineate structure–property relationships,[1] a broader outlook encompasses the relationships between *composition, processing, structure* and *properties*. The prevailing view is certainly that processing is an essential component of materials science.[2,3] The role of composition, on the other hand, is rather more ambiguous. New compositions are often explored in close association with precedent; the methodologies are often slow and costly. They frequently follow an incremental model to be distinguished from an automated optimisation protocol. The capacity of theory for predictive guidance in compositional decision-making is often very limited. A good example is in the area of high critical temperature superconduction[4] but examples abound in other property domains. The ease with which the periodic table yields its compositional treasures sometimes owes more to accident that predictive theory, however much we may not like to admit it.

The activity that has become known as combinatorial chemistry is often attributed to Joseph Hanak, a chemist who became impatient with the lentitudinous experimental preparation methods in his quest for new low temperature semiconductors.[5] He stated the problem quite succinctly: "*The present approach to the search for new materials suffers from a chronic ailment, that of handling one sample at a time in the processes of synthesis, chemical analysis and testing of properties. It is an expensive and time-consuming approach, which prevents highly trained personnel from taking full advantage of its talents and keeps the tempo of discovery of new materials at a low level*". He evolved a "multiple sample concept" that was well ahead of the available computer hardware and software needed for its implementation. His approach has been extended and developed so that today it provides a standard synthesis and screening strategy for drug discovery in the pharmaceutical industry.[6,7]

The approach embraces five stages; (a) *synthesis*: a method for preparing large arrays of micro-samples; (b) *processing*: a method for conditioning the samples either collectively or individually so that processing variables

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are explored; (c) *screening*: the instrumentation to make automated measurements on the samples; (d) *data archiving*: the ability to store compositional/structural data together with property measurements such as spectra, in large relational data-bases and (e) *interpretation*: the ability to mine the data-base, find optima and make composition-processing-property connections within it.

In placing these issues before the ceramics community, it is beneficial to assuage the natural concerns that this approach is in some way a threat to the conventional scientific method. This paper, therefore, begins by highlighting the significance of combinatorial methods for the philosophy of science. It continues by describing the technical strategies that have been developed so far for meeting the specifications of the five stages. Finally it describes the Search Instrument presently under construction at Queen Mary, University of London. The instrument is based on aspirating-dispensing ink-jet synthesis that will provide high speed searches on samples prepared from ceramic powders and therefore offer scope for multi-component compositional searches in the periodic table limited only by the constraints of toxicity and radioactivity. The mining of the periodic table for the benefit of ceramic science and technology is an undertaking that now begins to look possible.

2. Philosophy

The implications of combinatorial methods in the philosophy of science can be deduced from the pioneering work of Gillies, notably in his assessment of modern artificial intelligence.[8] The popular view of scientific method attributed to Popper [9,10] is that science does not start with observations from which inductive claims are made but rather with conjectures which may subsequently be refuted by appeal to experiment but which are never fully proven. Popper's interpretation superceded the much earlier inductivist theory of scientific method[11] developed by Sir Francis Bacon (1561–1626). In the words that Gillies uses to distinguish these competing views: "Bacon hoped that scientific theories could be generated from observations by some kind of mechanical process which places 'all wits and understandings nearly on a level'. Popper on the other hand, thought that scientific theories (or at least the more interesting ones) are the product of the creative thinking of brilliant scientists".[8] In Gillies' study, modern approaches to artificial intelligence fall more closely in the Baconian arena. The more extreme degree of mechanisation that is possible with combinatorial chemistry brings us much closer to Bacon's ideal. Indeed Bacon's emphasis on assembling experimental data into a 'table' from which inductive truths may be discovered bears a remarkable resemblance to the use of large relational databases within current combinatorial methodology.

The integration of high speed synthesis and screening with, for example, neural network interpretation of the results coupled to steering software allows the search refinement decisions to be implemented by computer rather than by a human 'research manager' (see Section 6). This frees human involvement to concentrate on the architecture of the instrument, the initiation of the search and the wise use of the information gleaned.

It is the idea that human creativity might be displaced that conjures up suspicion. Allied to this concern is the belief that laboratory and time compression (terms that attend combinatorial strategies) will redefine the employability of trained scientists. The likely scenario is, however, quite different. Currently, when new functional ceramic compositions are discovered by serendipity, conventional laboratory work is initiated and new wealth creation opportunities emerge.

It is important to distinguish the incremental and optimisation steps in materials discovery. In high component number systems, for example in the nickel-based super alloys,[12] compositional decision-making has often been based on an incremental model. A combination of informatics with high throughput synthesis and screening then provides a way to find local optima.

Combinatorial methods present the possibility of a vastly increased rate of discovery of novel materials each of which will require a great deal of conventional laboratory work to become established and extensive processing or manufacturing studies to be brought to market. They should, therefore, be seen as comprising a wealth-creating strategy that will expand the conventional laboratory infra-structure. They should also be seen as providing a stimulus to the theoretical development of the subject by offering a wider range of high performance compositions on the basis of which existing theories may be tested and new ones proposed. The latter may possibly be assisted by guiding rules established by inductive approaches to the gathered data; Baconian rule induction.[8] These ideas are as controversial today as they were when Karl Popper advanced his critique of induction. Fiercely polemical articles[13] seek to condemn informatics in research despite its widespread use in some of the most advanced industries. Some of these challenges seek to prove that hypothesis-free machine learning is impossible. The reality is that background knowledge and hypotheses are nearly always tacitly incorporated by the choice of sample space and measurement method. The skill seems to be to integrate combinatorial methods into conventional scientific research programmes and therefore to hypostatise Hanak's[5] original intention.

3. Combinatorial methods

The case for combinatorial methods in drug discovery is made in a number of popular reviews[14] and this is the

principal method now used by medicinal chemists for drug discovery. A hard-working medicinal chemist might synthesise 50 compounds per annum by conventional laboratory means. In a popular combinatorial synthesis procedure, compounds are synthesised on solid supports in the form of beads, typically made from lightly cross-linked polystyrene or polystyrene with grafted polyethylene glycol to confer hydrophobicity. The use of such solid substrates was devised by Merrifield in the 1960's.[15] Analysis of reaction products can be based on indicator tests, FTIR, NMR or mass spectrometry; in drug discovery it is primarily spectrophotometric (UV/visible) methods that identify 'lead' compounds. Such procedures can provide libraries of tens of thousands of compounds per annum.

Ink-jet printers are used for four tasks in contemporary drug discovery: bulk reagent dispensing; redistribution and reformatting of well-plates, for example, into multiple high resolution plates (typically 9600 wells); direct preparation of compound assay plates; and in dilutions over 4–6 orders of magnitude for dose–response curves.[16] Piezoelectric drop-on-demand printers have been deployed for fast automated titration using laser-induced fluorescence detection for indicator end points.[17] Individual unattended titrations are possible at densities approaching $10^6\ m^{-2}$. Droplets in the 100 pl range have been generated from a piezoelectric drop-on-demand flow-through dispenser with an 8 μm diameter nozzle for matrix assisted laser desorption/ionization time of flight mass spectrometry.[18] Well-plate methods are undergoing persistent refinement and 9600-well designs are in place to accept aliquots of 0.2 μl.[19]

The extension of combinatorial methods beyond drug discovery and into other fields, notably materials science, is explored by Whiting.[20] An area of particular interest is heterogeneous catalysis where compositional issues are important but not well guided by theory.

Heterogeneous catalysis remains the backbone of many important industrial processes, and therefore the development of new and more efficient procedures has attracted a great deal of interest.[21] The traditional empirical 'trial and error' approach is currently the only proven industrial methodology in the development of novel catalysts. In the past, it has proved rather labour-intensive, primarily because optimisation is sometimes dependent on the knowledge of a particular catalytic pathway. A more rational approach would be to use detailed information concerning the mechanism and the structure of known intermediates — but this is not always possible. The use of a combinatorial strategy as a solution to this problem does distinguish itself from the empirical approach in that parallel investigation of a large series of catalysts does allow statistically well founded empirical rules to be derived for optimisation.[21] The use of such techniques will clearly speed-up the development process and provide useful insight into the problems associated with the scale-up of functional inorganic solids. The development of 'new' materials with a defined function, such as catalysts for the bulk and fine chemical industries is a very important area and still in its infancy.[22,23] A great deal of research effort annually is devoted to the development of improving the selectivity of numerous catalysts for a variety of chemical processes, such as oxidation and reduction.

Onnes discovered the superconducting state in 1911,[24] reporting that the transition temperature (T_c) for Hg was 4.2 K. It took over 60 years to find metals with T_c up to 20 K.[4] and the paucity of active compositions hindered the development of theory; the BCS model did not emerge until 1957.[25] More importantly superconductivity remained a low temperature property ($T_c < 25$ K) for 75 years until Müller and Bednorz[26] discovered a T_c of 30 K in the Ba–La–Cu–O system after 2 years of persistent but fruitless testing of nickel oxide based systems.[4] This triggered research on Ba–Cu–O compositions and by 1988 ceramic superconductors with a T_c of 125 K had been discovered. However, a room-temperature superconductor still eludes the scientific community.

Sequential sputter coating methods have been used to confirm that combinatorial chemistry can 'discover' known cuprate superconductors.[27] Although this is a very important demonstration, it has been argued that when existing know-how for components and processing (e.g. conditions) is built into a search, the resulting retrospective proofs are circular.[28]

Thin film methods of synthesis also lend themselves to the construction of libraries for the discovery of new phosphors[29–31] and have given rise to the discovery of Gd–Zn–Eu oxide and Y–Eu oxide systems as well as of a blue-white phosphor in the Sr–Ce oxide system.[32] The search for phosphors provides for experimental simplicity at the high speed screening stage: illumination of the library with UV light reveals the active compounds. Electrical conduction and dielectric properties present more of a problem but an evanescent microwave microscopical method has been devised[33] and can identify potential dielectrics in a library with a spatial resolution of 100 nm.[34]

Combinatorial libraries of parallel plate capacitors have been built based on Ba–Sr–Ti oxides to explore the effects of dopants on dielectric constant and loss tangent.[35] The scope and outlook for materials discovery using thin films is amply set out by authors from the Lawrence Berkeley Laboratory[36–39] and has won support from ceramicists.[40]

4. Assessment of sample spaces

It is instructive to explore the magnitude of the compositional space that would need to be explored in a blind search and to survey the library dimensions needed

to accommodate the samples when deposited at reasonable resolutions. It soon becomes apparent that even with the deposition rates and resolutions presently attainable, for example by ink-jet printing, blind compositional searches in the periodic table are not presently viable if the number of components is much greater than four.

Consider single oxides formed from 50 cations (for example those in Fig. 1). These present 1225 binary and 19,600 ternary systems. If the composition axes are divided into n equal parts, then in the former there are $(n+1)$ and in the latter $(n+1)(n+2)/2$ samples to prepare in each system. Thus for compositional resolution at the 10 wt.% level, 13,500 samples are needed to survey the binaries and 1.3×10^6 samples are needed for a blind search in the ternaries.

Current ink-jet printers can deliver droplets with centres spaced at about 18 μm. However a more realistic upper range target for a synthesising ink-jet printer would be 150 μm centres, giving 2.8×10^6 samples to an A4 page. This means that a 10 wt.% resolution search of the ternaries could be accommodated on half a page of A4. Supposing a behind-the-nozzle mixing device supplied by 50 reservoirs were developed that could mix and deliver at 100 Hz (about one tenth the rate of an electromagnetic printer and one hundredth the rate of a piezoelectric drop-on-demand printer), the time needed to deposit the 1.3 million samples needed for the ternary blind search is 13 ks (3.5 h). If the compositional resolution be increased to 5 wt.%, 4.5×10^6 samples are needed and require just over 1.5 A4 pages. Such a device has not yet been built but a somewhat slower aspirating dispenser is presently under construction in the authors' laboratory (*vide infra*).

Since the sample space scales approximately with $(n+1)^{c-1}$ where c is the number of components, higher resolution blind searches in systems higher than quaternary become unviable and search refinements based on optimisation methods are needed (see Section 6).

5. Ink-jet printing

One of the advantages of adapting ink-jet printing methods to combinatorial synthesis of ceramics is that it requires fine, highly dispersed, particulate suspensions.[41–43] Such suspensions can easily be prepared from fine powders and most oxides can be prepared in fine powder form. It follows that a scale of mixing at or close to the ultimate particle diameter is possible, as previously demonstrated in ink-jet printed functionally graded materials.[44] This means that the attainment of compositional equilibrium during sintering involves diffusion distances of the order of a few particle radii rather than diffusion distances of agglomerate dimensions that are required in poorly dispersed powder mixtures.

Direct ink-jet printing, in which ceramic particles are deposited in the form of an ink through a nozzle, has been demonstrated as a solid freeforming procedure. Both the shape of a component and its composition can be delivered in the external world from a computer specification design file.[45–48] Thus combinatorial sample geometry can be modified in three dimensions to suit the measurement procedures — a feature of importance in

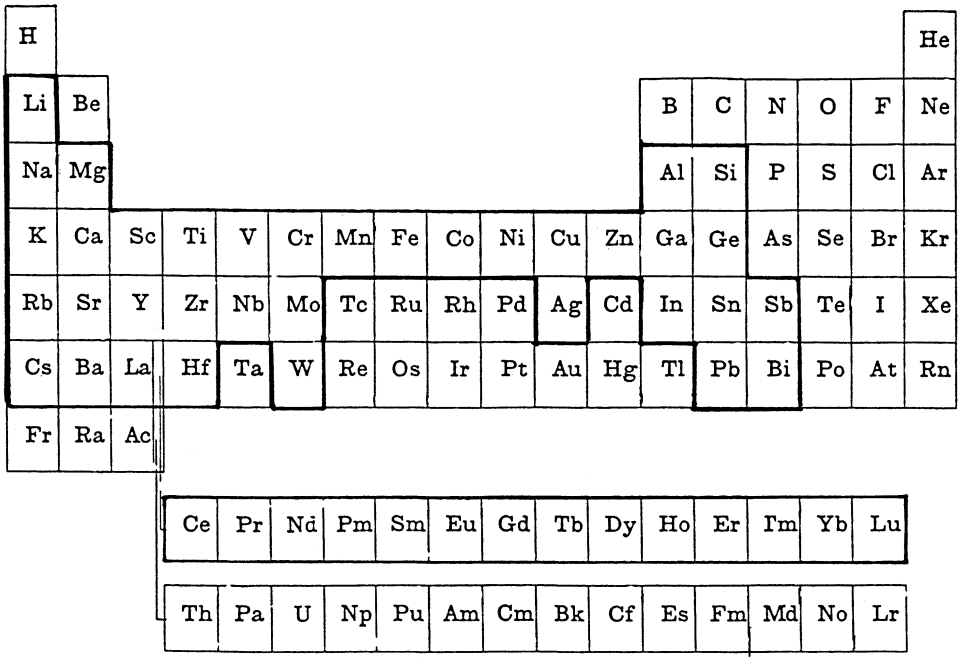


Fig. 1. Periodic table showing a possible selection of 50 cations for investigating oxides.

electrical conductivity measurement and one that is not enjoyed by sputter-coating sample preparation techniques.

A wide range of printers have been used for direct ceramic ink-jet printing. Continuous printers, routinely used for date-labelling of food packaging, in which the droplet destination is controlled by electrostatic deflection,[43,45] are fast (>50 kHz) but the demands placed upon the ink are severe. Piezoelectric drop-on-demand printers have been used to create internal cavities,[47] functional gradients[44] and arrays of pillars such as those shown in Fig. 2.[49] Thermal ink-jet printers have been used successfully to make ceramic components.[50] Electromagnetic printers have also been used and are slower (1 kHz) but have the advantage of a pressurised reservoir and more robust construction.[51] In these printers valve opening time is easily controlled from a PC. Piezoelectric drop-on-demand printers that print molten waxes at about 120°C have also been used to deposit suspensions with up to 40 vol.% ceramic powder.[52] Thus ink-jet printers turn out to be much more forgiving in accepting 'inks' for which they were not designed. Although two fluid parameters, viscosity and surface tension, strongly influence the suitability of a well-dispersed and stabilised ink,[53] it is the former that is the over-riding parameter because the latter often does not vary over a wide range. Thus once the viscosity 'window' is known on the basis of test liquids, printable ceramic formulations can be devised. High energy bead milling provides a very effective means for dispersion of powder. Recent work compares the particle size distribution obtained in this way with twin or triple roll milling methods and ultrasonic dispersion techniques.[54]

6. Informatics and the search for optimal materials

The power of combinatorial approaches becomes manifest once the system under investigation exceeds a certain threshold of complexity beyond which simple, predictive ('deterministic') theories struggle to deliver satisfactory explanations of phenomena. Many aspects of science fall into this category, and indeed, many real world systems, be they taken from physics, chemistry, materials science or biology, can become too complex for an analytical approach to bear much fruit. Some apects of chemistry, materials science and biology are not fully served by predictive theory. Often the theory that exists is of the ex post facto variety. The established systematic experimental approach, wherein one studies the effect on a system of changing one variable at a time with all others held constant, ceases to be useful beyond a notional complexity threshold.

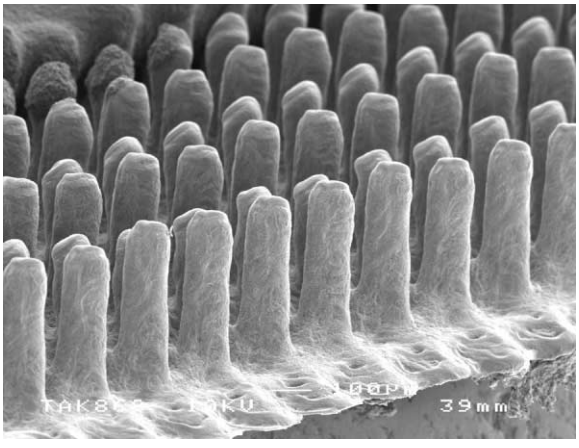


Fig. 2. Array of lead zirconate titanate pillars at a density of 15×10^6 m^{-2} prepared by drop-on-demand ink-jet printing.

Instead, complex systems pose completely new challenges to the modern theoretician and modeller.[55] In computer science, the concept of algorithmic complexity plays an important role in dividing problems into tractable and intractable sets.[56] Intractable problems exhibit a computational time dependence which scales as a power of N, where N is some measure of the size of the problem, while tractable problems scale only as an algebraic function of N. Many real-world problems, most famously the travelling salesman problem (in which a salesman in a cost-cutting era must visit N cities once only, in such a fashion as to minimise the distance travelled) are computationally intractable. Simply put, no systematic deterministic search algorithm exists which can solve such problems on the most powerful computers in existence today once N exceeds even a modest number (say 25 or 30). However, faced with this challenge, computer scientists have come up with smart algorithms, equipped with stochastic features, which are able to solve such problems within acceptable amounts of time. The random aspects of these algorithms are the key elements that enable optimal solutions to be located efficiently. A general, complex problem can usually be thought of in terms of a 'fitness landscape' in a rather high-dimensional multivariate space; the optimal solution will correspond to a global extremum (say a global minimum) on this invariably very rugged landscape.[55] While deterministic search strategies will rapidly become trapped in arbitrary local minima a great distance from the optimum, stochastic routines have the capability to jump out of these states and instead continually strive for improved solutions. These smart algorithms include Monte Carlo schemes, simulated annealing, genetic algorithms, and artificial neural networks (ANNs).

The abstractions of computer scientists have a direct correspondence with many scientific and engineering problems. As we have previously described, many physical and biological systems exhibit enormous complexity, and the search for particular systems with special (optimal) properties, such as room temperature superconduction, is closely analogous to the search for an optimal solution within the class of computationally

intractable problems. When no simple predictive analytical theory exists in a materials problem, the best way forward is to seek correlations between physicochemical (the 'input') parameters characterising the system — usually themselves inferred from specific analytical measurements — and performance properties (the 'output'), with an absolute minimum of prejudicial a priori assumptions. Artificial neural networks stand out in this context as the technique of preference as they make no inherent assumptions about the nature of the correlations. Given a suitably large database of inputs and outputs, such networks will find the functional mappings required. These mappings are, of course, usually complex and non-linear; their inversion (for example, by genetic algorithms) unravels the reverse mapping from performance to physicochemical characterisation. It can thus be used to steer subsequent stages of an automated high throughput search into regions of physicochemical parameter space expected to produce the properties sought. These methods blossomed in the late 1980s and early 1990s; they are now becoming integrated with standard data analysis methods. This philosophy has already been implemented successfully in the context of cement setting: infrared spectra recorded on oilfield cement powders have been shown to correlate very well with the thickening times of their slurries, while the inversion of physicochemistry-to-thickening time ANN mappings has been realised using a genetic algorithm.[57] This application has been deployed in commercial oilfield exploration and production operations.[58]

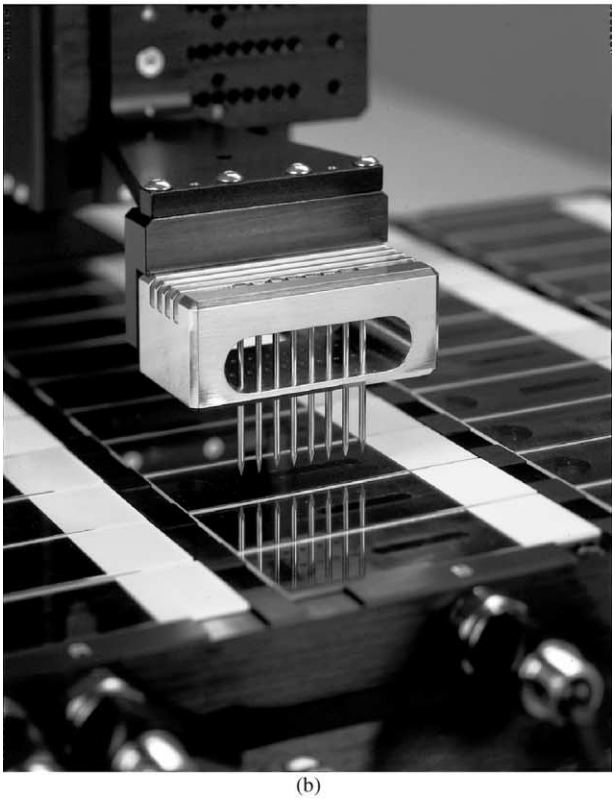
It is beyond the scope of the present paper to discuss the nature of ANNs or the other stochastic methods in any detail; the interested reader is referred to the now copious literature for further information.[55,59–65] For the present purposes, it suffices to point out that a crucial requirement for their successful implementation in practice is the existence of large quantities of experimental data from which correlations may be learned, and this has proved to be a serious limitation in conventional applications. Within an automated high throughput combinatorial context, however, data are rarely lacking so that instead a substantial premium attaches to optimal management and mining of the databases that one can create. Indeed, when the quantities of data under management are large (tens of gigabytes or more), it is necessary to deploy to maximal effect state-of-the-art computational hardware and software, for otherwise the entire combinatorial enterprise will grind to a halt. The combined computational activities of database management and data mining using such algorithms lies at the core of the discipline of informatics.

One of the exciting aspects of informatics-based materials research using the search instrument described in Section 7 is that access to the machine by other scientists can be facilitated through appropriate grid middleware. These scientists should be able to set up, run and steer experiments remotely and make the data available to a distributed set of collaborators.

7. The University of London Search Instrument

The search instrument presently under construction at Queen Mary, University of London, is based on an aspirating-dispensing ink-jet printer workstation (ProSys 6000

(a)



(b)

Fig. 3. A Cartesian SynQuad aspirater/dispenser based on an eight nozzle printer: (a) general view showing the printer mixing from well-plate reservoirs and printing onto sample plates and (b) showing the eight ceramic nozzles dispensing mixed reagents onto plates.

manufactured by Cartesian Ltd., Huntingdon, Cambridge, UK). This is an electromagnetic printer fitted with eight nozzles (example in Fig. 3a) each independently controlled by 192,000-step syringes. The nozzles draw from a well-plate in such a way that the ceramic ink never enters the tubing or valving. The nozzle assembly automatically visits a cleaning station for purging and ultrasonic decontamination thus avoiding the laborious decontamination procedures that attend conventional combinatorial equipment when the search is terminated and a new one initiated.

The printer has 20 nl dispensing capability and the sample building site is an 415×520 mm X–Y table with 20 μm step resolution (Fig. 3b). After drying, the library plates are robotically loaded into a furnace with four independent temperature zones each separately selected by an eight-stage programmable controller. The furnace can also accept a controlled atmosphere so that processing variables (e.g. heating schedule and atmosphere) can be explored.

The samples are then loaded onto a three-axis measurement table that can be addressed by a range of instrument modules. At present these include a luminescence spectrometer (model LS-55 ex Perkin-Elmer, Beaconsfield, UK), equipment to detect superconductivity at liquid nitrogen temperature, a Hewlett-Packard Model 4194A Impedence/Gain Phase Analyser and a high performance liquid chromotography column (Dionex, UK, model DX low pressure gradient HPLC with UV/visible detector).

This equipment is fully integrated robotically and linked to a high band width, low latency, dual 400 MHz, R12000 processor SGI Origin 3200 computer equipped with 1 Gbyte of memory, on which is mounted an Oracle relational database. The local optima discovered by the instrument can be interpreted by steering software that plans search refinements and implements new searches. Project proposals include the search for novel superconductors, for coloured glazes, for dielectrics and for heterogeneous catalysts for a range of chemical reactions. For the grid use of the instrument, visualisation has an important role to play in helping users to invert mappings that generate complex fitness landscapes in order to steer experiments into critical parts of multi-dimensional parameter space.

8. Summary and conclusions

Compositional quests in materials science and in particular in advanced ceramic science are slow and costly when conducted by conventional means. Three important developments have been made in recent years that, if brought together and fully integrated, would provide a potential increase in search rate of between two to four orders of magnitude. These are: (a) ceramic synthesis strategies based on direct ceramic ink-jet printing; (b) high sensitivity instrumentation capable of analysing small samples; and (c) high performance computing methods, in which artificial neural network and other programs can mine, interpret and direct automated searches based on the contents of large relational databases. Such computational methods can be used to 'steer' the search sequence and therefore to act as a 'research manager'. These concepts have their origin in the 16th century vision of Sir Francis Bacon. The instrumentation to achieve this end is now available and a search instrument based upon these principles is under construction at the University of London. With the development of modern computational grid technology, this instrument will become available for use by scientists working in remote locations. This approach to materials discovery aims to increase substantially the rate at which new active compositional domains are identified and hence to provide the resources for wealth creation, enhancements to quality of life through new discoveries and a broader-based platform for the development of theoretical understanding of modern materials.

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