CHAPTER 1

Combinatorial Materials Science: Measures of Success[1]

MICHAEL J. FASOLKA and ERIC J. AMIS

Polymers Division
National Institute of Standards and Technology (NIST)
Combinatorial Methods Center (NCMC)
Gaithersburg, Maryland

1.1. INTRODUCTION: THE MOTIVATION FOR COMBINATORIAL MATERIALS SCIENCE

Throughout its history, materials science has been accomplished with the explicit or implicit backdrop that materials can be improved for human use. To a considerable extent, this milieu has governed the systems considered by the discipline, and the kinds of knowledge that materials scientists generate. This technological undercurrent accounts for a thread common to materials science since its earliest days, which the is study of complex systems. For example, our understanding of multicomponent phase thermodynamics would arguably not be as advanced, nor as deep, as it is today without the desire to produce improved metallurgical alloys. Certainly, this technological interplay with complexity could be restated for any number of historical cases and accomplishments across the materials science spectrum—from doped semiconductors to polymer blends.

This trend continues for today's materials scientists, as we strive to understand, and to use, increasingly complex materials systems. In this respect, the discovery, development, and optimization of today's new materials are met by three interrelated challenges (Fig. 1.1):

[1] Official contribution of the National Institute of Standards and Technology; not subject to copyright in the United States.

Combinatorial Materials Science, Edited by Balaji Narasimhan, Surya K. Mallapragada, and Marc D. Porter

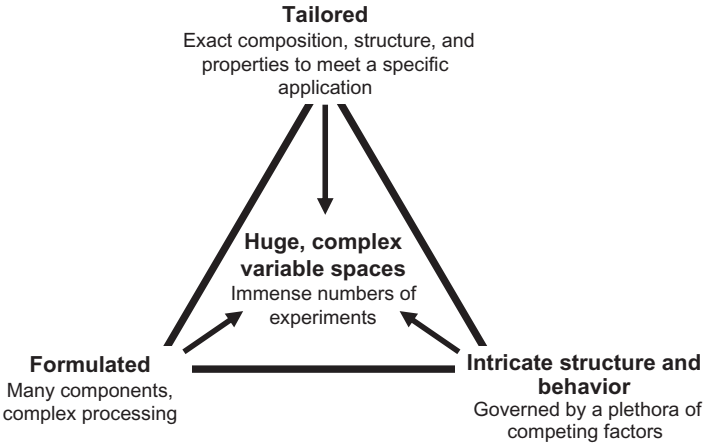

Figure 1.1. Challenges to materials development.

1. Advanced materials are often highly *tailored*, meaning that composition, structure, and properties are optimized to meet a specific application. For example, materials for fuel cell membranes [1] must transport specific ions, and they must also be structurally sound, chemically resistant, and amenable to processing. Given these requirements, it is understandable that there are only a few viable materials for fuel cell applications.
2. Today's materials are usually *formulated* from a number of components, and the structure and properties of these formulated materials can be highly sensitive to constituent levels and processing routes. Although this sensitivity makes them amenable to *tailoring*, the multivariate nature of formulations makes optimization difficult.
3. Today's materials exhibit *intricate structure and behavior*. Tailored, formulated materials often rely on structural hierarchy that includes atomic, molecular, and mesoscopic organization. Structure must often be characterized on multiple scales, and the performance of these materials can hard to measure or predict since it depends on many competing and complementary factors.

These challenges mean materials researchers are faced with large and complex variable spaces, and the reality that a huge number of experiments are needed to understand and develop materials. Materials research is expensive and time-consuming, with estimates for the time to discover and develop a new material ranging from 2 to 10 years, and with R&D costs often in excess of $20 M per new material product [2].

The last 15 years (as of early 2007), or perhaps the past 40 years if we consider the earliest appearance of the concepts in the literature [3], have seen the emergence and application of so called *combinatorial materials science and*

high-throughput methods. Correctly applied, these concepts have the potential to meet the challenges of developing materials [4–6]. Combinatorial materials science and high-throughput methods present means to accelerate materials research through a new experimental paradigm. Salient aspects of this new scheme are illuminated by comparison to traditional experimentation: (1) traditional experiments utilize specimens that express a single point in parameter space, but combinatorial methodology employs sample *libraries* that cover a multitude of points across parameter space (when designed effectively, combinatorial libraries explore a range of parameters in a rational and reliable manner), and (2) where traditional experiments test and analyze samples in a "one at a time" mode, combinatorial libraries are best complemented by *high-throughput measurements* that assess multiple library elements in parallel, or through a rapid serial approach.

Conceptually, it is obvious that the coalescence of these two aspects of "combi" can result in materials research that is rapid and comprehensive in its scope. This promise accounts for the intense interest in recent years surrounding these methods. Yet, it is equally obvious that the realization of these goals for materials discovery and materials science relies on how the methods are implemented. In this respect, strategies often are driven and structured by a priori visions of what *success* in combinatorial materials science entails. On this point the philosophy of combi comes into question.

1.2. THE "CLASSICAL" VISION OF SUCCESS WITH COMBI

Undoubtedly, the initial enthusiasm and inspiration for adapting combi methods to materials was rooted in comparisons with the pharmaceutical industry, which made an unreserved shift to combinatorial chemistry and high-throughput screening approaches in the early 1990s [7–9]. The primary goal of making drug *discovery* faster and more efficient strongly influenced the early vision of success and they have lasting effect on the implementation of combi today. As a noted pioneer states, "this methodology must be constructed a priori such that there are no bottlenecks, the mantra among professionals being 'screen in a day what you synthesize in that day, and analyze in a day what you screen in that day.' " [10] According to this picture, the success of the application of the method is measured largely by the number of experiments it can accomplish, the speed of these experiments, and the design for seamless operation and efficiency.

Following the trend in pharma that places a premium on speed and efficiency, this "classical" vision for combi has driven the implementation of so-called "combinatorial workflows," which are highly developed systems for automated library preparation, measurement equipment, and analysis routines, all assembled to perform according to a well-defined experimental protocol. While many workflow designs have been posited for combi, they have a common set of components and aspects. For illustration purposes, we will

discuss an example scheme (Fig. 1.2), where the workflow is a cycle with steps of *library design*, *library fabrication*, *measurements,* and *analysis.* As visualized in the scheme, the workflow is tied together by an *informatics* system.

The *library design* step is most akin to traditional "design of experiment" (DOE) activities, but modified to accommodate multivariate parameter spaces. Basically, library design determines the materials properties of interest and the portion of variable space that the combinatorial library will include. Exact parameters for library array elements are defined, as well as statistical replicates and reference elements. Library design can include aspects of statistical DOE in an effort to illuminate parameter interrelationships.

Library fabrication is the process of physically producing the combinatorial array. In a well-developed workflow, library fabrication is fully automated, including coordinated operation of devices for materials handling, metering, mixing, and sampling, as well as a means for varying processing conditions over library position and/or time. In addition to accurately reflecting the library design, the fabrication route must couple with measurement and analysis steps. As we discuss below, the latter requirement can be difficult to achieve since a single library design may not be adequate if measurements necessary to characterize a library change or increase.

Measurements in combi workflows are by necessity high-throughput, since libraries can exhibit hundreds or thousands of cases. This can involve development of new instrumentation or the adaptation of existing devices for high-throughput operation. In a workflow scenario, the *measurement* step is met by additional challenges of automating and coordinating the set of instruments needed to sufficiently characterize libraries. System development must accommodate the fact that measurement instruments (whether custom-made or from a vendor) may not be designed for incorporation into a workflow.

Today, most scientific data analysis is computer-aided, if not automated. However, in the vision of the combi workflow, the *analysis* stage goes beyond performing scientific calculations and data handing in a faster manner. The analysis stage can involve data-mining schemes and multivariate statistical

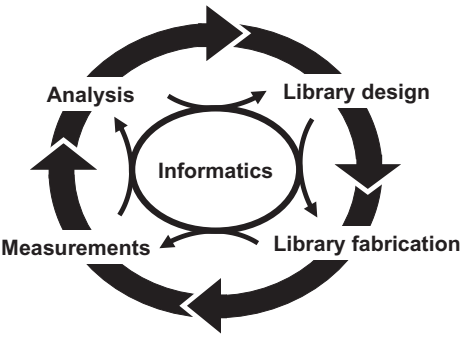

Figure 1.2. Example combinatorial workflow.

treatments for illuminating trends and correlations in the library data space. These difficult routines can be necessary if the library design does not preclude superfluous data points or if the library changes too many parameters at once. An important and challenging aspect of combi analysis is the visualization of combi datasets, which are large, complex, and can consist of a variety of data types including single values, spectra, and images. Finally, a goal of workflow analysis is to provide parameters for the design of libraries, perhaps with a refined or expanded scope, for further rounds of the combi cycle (Fig. 1.2). This "feedback" mechanism is widely termed "closing the combi loop." In the classical view of combi workflows, such feedback is one hallmark of a successful system.

A combi workflow depends on a sophisticated *informatics* infrastructure that coordinates and cements the workflow steps into a functional whole. An informatics infrastructure integrates functions such as DOE, instrument automation, data collection, automated analysis, datamining, and data visualization around a (typically central) database that is structured for research [11,12]. Constructing a combi informatics infrastructure is a formidable challenge, especially if seamless operation is desired. It can take years to develop and requires dedicated, expert personnel to achieve and maintain.

The combi workflow vision is an extremely valuable one, and there is no doubt that significant materials discoveries and knowledge generation have occurred when they are implemented properly. Nevertheless, when considering the concept of success in combinatorial materials science, and of workflows representing the principal realization of this idea, other factors must be considered. Primary among these is the growing body of combi-related materials research that has been pursued and published in recent years; a conservative search of the literature [13] yields nearly 1000 journal articles since 1990, with substantial growth in the number of publications each year (see Fig. 1.3).

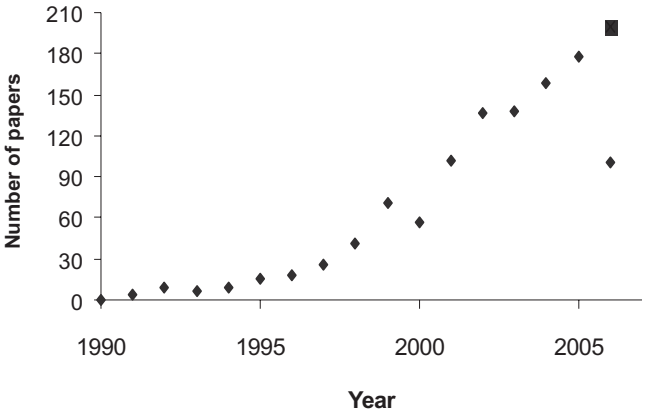

Figure 1.3. Materials combi publications versus year. 2006 value is (■) is projected based on publication count in June 2006.

However, a brief analysis of these papers reveals that only a fraction of this work results from the type of highly developed workflows discussed above. Indeed, these publications are issued from a great number and variety of institutions. These include smaller academic and industrial research groups that arguably do not have the resources to fully accomplish the workflow vision. Moreover, this literature and other reports [14] show that combi concepts are being applied to an increasingly wide set of materials systems, such as emerging technology products (e.g., nanostructured materials and organic electronics) or specialty consumer goods (e.g., personal care and cosmetics). Materials discovery in these areas is extremely fast-paced, and it is questionable whether the construction of a priori, well-developed workflows is commensurate with the rapid product turn-around required from R&D of such systems.

How do we reconcile the classical idea of combi success with these trends? One option would be to say that since they fail to match the workflow vision, most combi studies are "less than successful" or somehow incomplete. We posit that this characterization has implications that are less than positive for the field, since it suggests that (1) successful combi studies can be achieved for only a very small set of materials systems and (2) combi should be pursued only where "full" success is assured. These notions conceptually limit the scope of where combi can be useful, and amplify a sense of risk associated with pursuing combi. So, for institutions already skeptical of combi, this provides an additional excuse for "not to start," and for the initiated, it can be an excuse "not to expand." In either case, a likely result is a fewer number contributions to the state of the art in combi techniques.

Another option is to reconsider the criteria for success. A broader vision, that accommodates different styles of implementation, that focuses on the knowledge produced by combi rather than the number of specimens it can process, and that emphasizes a measured approach to infrastructure development, seems to more accurately reflect the current state of the field. More importantly, a more inclusive idea of success could reduce conceptual barriers (primarily the sense of risk) to implementing combi tools, and this could be key for sustaining the field, and for driving innovation in methods development and their application. These ideas will be discussed further below.

1.3. IMPLEMENTATION OF THE CLASSICAL VISION: WHERE HAS IT BEEN ACHIEVED AND WHY IS IT NOT MORE WIDESPREAD?

Of course, excellent workflows for have been built and some of these have been highly effective in accelerating the discovery and development of a range of materials products [5], including heterogeneous catalysts [15–18], coatings [19–22], and electronic materials [23–27]. A look at these cases (and others) reveals that for the most part well-developed workflows are built where certain

conditions exist. First, we see workflows where significant human and capital resources are available specifically for combi system development or purchase. Accordingly, workflows are often a hallmark of larger companies with large R&D budgets and staffing resources, or specialty companies (e.g., Symyx, HTE, UOP) whose business is development or use of combi technology. In addition, workflows are found where materials researchers are able to leverage existing combi technologies or model processes established for other aims, such as biotechnology or pharmaceuticals. A good example is the case of combi heterogeneous catalysis research, which is widely implemented in ways analogous to pharmaceutical workflows, and which uses fundamentally similar equipment. While the extensive effort needed to modify this equipment for catalysis development should not be diminished, similar parallel chemical reactors and chemical activity sensors were already in place for several years in pharma (the pharmaceutical industry). Finally, combi workflows are found where the goals and processes of materials research are well defined and where experimentation can be accomplished with repeatable protocols. This accounts in part for the highly developed and successful workflows seen in the coatings industries, which were among the first to adapt combi for materials product R&D (for examples, see references [19,21,22,28–32] and citations therein). Indeed, due to customer demands, industrial coatings R&D can include a common set of sample preparation and test protocols, many of which can be automated as part of a combi system.

Certainly, research organizations that have implemented workflows have balanced the economic payoff of combi discovery with the time and expense required for infrastructure development. The key is to realize that in many of these cases, the scales were tipped toward workflows because the barriers to development were lowered because of ample focused resources, or because the system did not need to be "produced from scratch," due to existing technology. However, for many institutions and most materials research situations workflow-enabling conditions do not exist and persistent barriers hamper (and may even prohibit) workflow development. Primary among these challenges is library fabrication. This the major obstacle to starting combi for any specific materials set. Moreover, because of the difficulty of designing flexible library fabrication equipment, it is a problem that can reemerge each time materials research goals change. Even modest alterations in additive sets or processing routes may require extensive reengineering of equipment, plus testing of the new library fabrication process for reliability, repeatability, and so on. For example, a current trend in industrial product formulations (e.g., coatings, cosmetics, personal-care products) is to include nanostructured components (e.g., nanoparticles, nanoscale colloids, and micelles). While at first glance nanostructured components seem to be "just another additive" in a formulation, in fact they present a slew of new library fabrication chal-lenges, which have been identified by industry as key barriers to implementing combi for these systems [14]. In particular, to illuminate structure–property relationships, libraries of nanostructured formulations must be amenable to structural

characterization by nanoanalysis techniques, including light and X-ray scattering, electron microscopy, and scanned probe microscopy. These methods demand highly specific sample conditions (geometry, thickness, planarity, roughness, etc.) that are not accommodated by current automated formulators. Indeed, it is likely that the rigors of nanocharacterization demand the development of entirely new library fabrication strategies.

Our example of nanostructured formulations illustrates a corollary barrier to workflow development, which is the difficulty of integrating so-called "necessary" characterization techniques into a combi system. In the case of nanostructured materials, R&D *necessarily* involves nanoscale measurements like those noted above, yet high-throughput versions of these techniques (or replacements for them) do not always exist. This point is apparent in the case of transmission electron microscopy (TEM). Because it provides essential nanoscale morphological information that cannot be achieved otherwise, TEM is relied on widely by researchers in both academia and industry. Yet, with the exception of a few advances [33,34], TEM remains incongruent with high-throughput experimentation, with no general solution in sight. Mechanical measurements, especially assessments of yield and failure, pose similar problems. In certain cases, specific tests are required because customers, or regulations, demand them. For example, in the coatings industry, "real time" aging and weathering tests are customer-trusted measures of product performance. While there has been progress in accelerated weathering testing methods [29], the current ability to predict real-time weathering properties is still limited. Accordingly, traditional measurements remain a necessity, at least on a subset of promising coatings formulations.

Informatics has been a central challenge to combi since its inception, and this remains the case today. As discussed above, workflow informatics infrastructure is complex, expensive, and time-consuming to achieve. In some respects, informatics development is faced by the same sort of barriers that inhibit library fabrication. Primarily, whether it is built in house or purchased, it is difficult to create a "general" infrastructure that accommodates changing research goals. So, in addition to expense of establishing an informatics system, extensive retooling can be required when new materials are tackled. This issue is exacerbated by several factors. First, it can be difficult to find personnel suited for combi informatics development, since it requires expertise in both computer/information science and materials science. In addition, integrating new instrumentation into an existing workflow can be difficult. Custom-built instruments require the construction of custom automation and system interoperability routines. Moreover, while most commercial instruments are supplied with control software, it is often proprietary and rarely geared for the flexible automation and system interoperability necessary for workflow integration. Accordingly, integration of commercial instruments involves building metaroutines that connect and drive vendor-supplied software. Since a workflow can contain instruments from multiple vendors, formation of a seamless informatics infrastructure is a complicated endeavor. This situation is hampered by a

lack of standard data formats for interoperability, which, if they existed, could streamline infrastructure design and ease device integration. In this respect, there are some promising developments, as XML-based data formats applicable to materials combi have begun to emerge from industry [35], government [36], and academia [37,38].

1.4. AN ALTERNATE VISION OF SUCCESS WITH COMBI

With persistent barriers making the "workflow" vision unattainable in many cases, is there a more useful driving principle for the development and application of combi? What would this revised concept of success look like?

We posit that a measured, and more *immediate*, view of combi infrastructure development is a key philosophical guide. In this concept, the focus is on the effectiveness of a combi system, and its components, for knowledge generation, rather than the number of specimens it may ultimately process. As opposed to an "all or nothing" approach, infrastructure would be built with the goal of attaining benefits of combi implementation, but not necessarily a "complete," seamless workflow. This measured view of success would balance (1) the resources dedicated to *each aspect* of infrastructure development (libraries, high-throughput measurements, informatics, etc.) with the *immediate and apparent* benefits of building that piece—this "matching the hammer to the *current* nail" means that some aspects of the classical workflow model might be developed only modestly, or not at all; against (2) the time to develop infrastructure, such that it meets the R&D timescales required to effectively address the problem of interest. For example, modest infrastructure development, accomplished quickly, can result in timely combi benefits for faster-moving R&D of emerging systems. We will elaborate on these ideas next, and to make our point we will focus on the benefits that can be derived from developing individual aspects of the combi cycle.

Libraries are a solution in themselves. Combinatorial libraries can provide a convenient, compact, and powerful platform for scientific research, even if the rest of the experimental procedure is executed traditionally. When designed well, a library can be a "solution in itself" that amplifies the scientific effectiveness of sample preparation beyond the simple fact that it provides more specimens to analyze and/or measure. From a practical standpoint, since they are fabricated and processed under identical conditions, libraries can minimize errors, and solve consistency problems associated with fabricating equivalent numbers of individual specimens. Moreover, because of the smaller size of typical array elements, combinatorial libraries can minimize waste, and maximize the effective use of expensive additives, or custom synthesized components that may be in limited supply.

Most importantly, combinatorial libraries can provide scientific insight that might not be possible otherwise. By their nature, libraries allow researchers to consider "spaces" rather than individual "points," by realizing whole

parameter spaces in a physical form. As an illustrative example, consider "gradient" combinatorial libraries, which systematically and continuously change in one or more properties as a function of position [23–27,31,39–58]. Gradient specimens are unique in their ability to express comprehensively an entire variable space within a single specimen, and no values are "skipped over" as with individual specimens or discrete arrays. Accordingly, gradients are unparalleled in their ability to map phase behavior, property correlations, optimum conditions and critical phenomenon—which are central goals in materials science—and do so in a single experiment. In this respect, they also can be "self-reporting," meaning that they express key results without extensive analysis. A prime example of this is seen in the gradient polymer phase diagrams developed at the National Institute of Standards and Technology (NIST), which can illuminate phase boundaries [39,40], structural changes in self-assembly [41,42], and dewetting transitions [43–45] on relatively simple visual inspection. Of course, more extensive analyses of gradient libraries yield data that are unmatched in their detail.

To be sure, a fertile library design can transform the way scientists think about specimen preparation, and conduct research. Consider, for example, the "diffusion couple" approach used in metallurgy research [59]. While "combi" was not in the nomenclature when it was conceived more than four decades ago [60], this is essentially a gradient technique, and its ease and efficacy have made it a widespread practice for generating metal phase diagrams in academia and industry. In recent years, Zhao [61,62] has pioneered the extension of the diffusion couple concept to produce ternary libraries. This approach retains the elegance of the original technique and promises similar impact.

"Cosputtering," and other codeposition approaches, are another example of an elegant, flexible, and high-impact library design route. Implementation of these "composition spread" methods requires specialized equipment. However, device designs are straightforward, and once constructed, instrumentation can produce binary and ternary (and higher-order) gradient libraries of metals, ceramics, and organics. As evidenced by a huge record in the literature, nearly any material that can be sputtered, evaporated, or coated via chemical vapor deposition is amenable to this route. For examples, see Refs. 23–27 and 63–68 and papers cited in Refs. 6 and 69. Because of this flexibility, codeposition approaches form a widespread foundation for combi in functional inorganic materials, especially in academic laboratories, where materials research targets can change rapidly. Because this library design is so fruitful, adopters are able to concentrate on other aspects of combi. As a result, academic groups who have applied these technique have produced some highly innovative combi systems [5,34,37,69–75].

A growing number of commercial measurement instruments operate in automated or high-throughput modes. These include plate readers for parallel UV-visible spectroscopy, fiberoptic probe Raman and near-IR spectroscopy, IR microscopy, atomic force microscopy, optical microscopy, nanoindentation, differential thermal analysis, and some scattering equipment. Most of

these measurements are useful for materials research, but appropriate libraries are required to leverage this high-throughput instrumentation. Accordingly, a focus on library design, with the goal producing specimens that can be used with this these devices, can result in "mini workflows" that can be very productive without further system development. For example, gradient approaches often produce planar and smooth libraries that neatly complement automated scanned probe, optical and IR microscopies, and nanoindentation, as demonstrated in a number of studies [14,49,56,76–81]. A similar philosophy is seen in the clever "sector spin coating" technique, developed recently at the Dutch Polymer Institute [82], which is capable of producing polymer specimen arrays for automated atomic force microscopy (AFM) and other high-throughput film characterization techniques.

A little high throughput can go a long way. Even if they are not part of a full workflow, the development and application of automated, high-throughput measurements can have substantial benefits. Undeniably, in any research situation where measurement or analysis resources are in demand, a focus on high-throughput methods can have immediate payoff. For example, automated operation can maximize the impact of expensive, central, or "one of a kind" measurement resources since it can enable characterization of a larger number of specimens by a larger number of users. Automated measurements also offer a consistency that can reduce error, and minimize the human subjectivity associated with certain measurements, for example, the selection of areas for microscopy analysis.

Beyond these practical benefits, high-throughput measurements can have an immediate impact on scientific innovation. In many research scenarios, sample preparation is easy and fast, even without automation, and the potential rate of sample production greatly outweighs the rate of traditional analysis. In these cases, high-throughput methods can liberate researchers, as it removes the *conceptual* barrier of "which sample can I measure today?" When measurement economy is lifted, creative scientists naturally expand their idea of what is possible. Since they can test a larger set of specimens, they consider riskier, perhaps more innovative, materials cases. In this sense, even modest acceleration in measurement or analysis can be effective. From the perspective of a single researcher, the difference between 1 sample/day and 3 samples/day can be great, especially if two of those samples are being measured while he or she is thinking creatively about the next steps.

The development of high-throughput capabilities can also drive innovation in measurement science. The process of building instruments that meet the rigors of high-throughput operation (e.g., fast, automated, and flexible) can result in both fundamental improvement of existing methods, and entirely new approaches to characterize specimens. Take, for instance, the "buckling" metrology developed to rapidly measure the mechanical modulus of polymer film libraries [83]. In addition to being a quantitative high-throughput technique applicable to a wide range of polymer types, it can also serve materials that are otherwise difficult to measure. For example, in nanotechnology

applications, the buckling route is highly effective for measuring nanoporous low-*K* dielectric films [84], and the modulus of ultrathin polymer films down to 6 nm thick [85]. More recently the technique was "reversed" to give measurements of ultrasoft systems ubiquitous in biomaterials, such as elastomers and hydrated gels [86].

A similar trend can be seen in techniques such as AFM and nanoindentation. There is no doubt that AFM instrumentation has become more robust, user-friendly, and versatile in recent years; and a case can be made that these advances were driven in large part by applications for the semiconductor industry, which demanded flexible, automated operation for higher-throughput device characterization. Similar goals may produce measurement innovations in nanoindentation. Take, for example, the ability of some commercial instruments to image the shape of the indentation site and the amount of plastically deformed material around it [87]. Ultimately, this information promises to help make nanoindentation data quantitative, and it may be the key for extending nanoindentation to viscoelastic materials like polymers. However, in the short term, this capability is being developed because it enables high-throughput *screening* that is independent of other instruments, and that is amenable to a wider range of hard materials libraries for which nanoindentation is currently suited [88,89].

Informatics—when is it necessary? As with the other aspects of combinatorial materials science, a measured amount of informatics can have immediate benefits. As discussed above with rapid measurements, the development high-throughput data analyses can provide practical advantages (e.g., error management), reduce computational barriers to creative endeavors, and provide information not otherwise possible. In these respects, the development of *image analysis* routines seems to be a particularly fruitful, perhaps necessary, aspect of materials informatics. Increasingly, the characterization of complex materials involves the analysis of complex, multifaceted images, such as multilayered micrographs (e.g., AFM), chemical micrographs (e.g., IR microscopy), scattering patterns, and multidimensional spectra. The extraction of key structural and chemical information from these rich datasets requires image analysis that is both sophisticated and scientifically sound. In addition to making it more rapid, the process of automating image analysis can fundamentally improve it along these lines. Arguably, the extra rigors of "hands-free," high-throughput operation requires a statistical robustness that might not otherwise be incorporated into a routine. This can make analysis more consistent, better able to handle weak or complex signals, and less subjective. In fact, many of the robust image analysis strategies materials researchers take for granted today were first developed because of the need for high-throughput image processing in astronomy [90,91]. For decades, astronomers have faced huge numbers of multifaceted images acquired with automated telescopes. Accordingly, they have been the historical vanguard of high-throughput image analysis. In comparison, efforts in the materials sciences are rather young and fraught with fresh challenges. For the advancement of

combinatorial materials science, this provides fertile ground for motivated researchers.

The development of a wider informatics infrastructure, especially of aspects related to system integration and "feedback" mechanisms, is more problematic in terms of immediate gains, and the driving question is: "How much informatics is enough?" Of course, some informatics is necessary to realize the benefits of high-throughput measurements and library design/fabrication routes discussed above. However, as one moves beyond what is needed to support these individual elements, the development of informatics infrastructure certainly suffers from diminishing returns. As outlined in an earlier section, the integrating instruments, analysis tools, and database functions into a single system entails significant challenges that can require a great deal of effort to surmount. Moreover, the time and energy required for incremental improvements in infrastructure actually tend to increase as the system is built. This is because seamless workflow function requires close attention to the *details* of interoperability, and the number and complexity of these naturally grow as the system develops. Indeed, the benefits of informatics development for workflow systems are rarely seen until the infrastructure is complete and free of defects, and this can be a long time. Furthermore, as informatics is developed toward a seamless workflow, it naturally becomes less flexible [20]. As discussed above, workflow informatics is typically built for specific, well-defined problems and processes. When the focus of research changes, much of the hard-won infrastructure will have to be modified. Finally, while much is made of the potential of "data mining," "feedback," and "artificial intelligence" in materials informatics, these sophisticated functions are costly to develop, and at this point there are few published works demonstrating that the expense is worth it. As opposed to library fabrication and high-throughput measurements, where careful design can have immediate benefits, development of detailed informatics infrastructure is probably secondary.

1.5. CONCLUSIONS

There is no doubt that the classical "workflow" vision for combinatorial materials science is inspiring to the materials research community. As a driving goal and developmental philosophy, the workflow vision has lead to impressive methods and systems, as well as discoveries and knowledge. However, there are penalties if we consider workflows to be the exclusive measure of success in combi. The process of creating complete workflows is a daunting one, especially for researchers who are new to the field. So, the idea that combi is only truly successful if a workflow can be achieved provides many with an excuse to not begin developing or applying these exciting strategies. This decreases the flow of new ideas into the field, and ultimately, this will hamper innovation.

In contrast, we have proposed and discussed a measured view of success that balances the effort of development with more immediate benefits. This more inclusive idea encourages the development of individual aspects of combi, and flexible, more quickly assembled systems that can be realistically implemented by a wider range of materials researchers. While this balanced infrastructure may not be *the* most efficient and seamless for routine and repetitive applications, all of its elements are built because they add value in themselves, and some elements are not developed at all. Shifting away from the "all or nothing" workflow model lowers the perceptual barriers to entering into combi, and makes it an option for faster-moving research situations, such as smaller materials R&D efforts that have changing targets, and emerging materials systems where rapid knowledge is imperative. Indeed, these entrepreneurial situations could provide the influx of new ideas that will be central to sustaining the innovative spirit that has driven combinatorial materials science thus far. Most generally, however, this vision fittingly paints combi as a creative research philosophy; a way of thinking, rather than simply a capital-intensive shift in the processes. As such, it provides a fresh a priori notion, useful to combi professionals and neophytes alike; substantial benefits can be reaped when you accelerate or deepen any step in materials research. The key to attaining the benefits of combinatorial and high-throughput approaches begins by thinking beyond the single-sample paradigm, to be aware of opportunities to develop these tools, and to apply them with the wisdom that has always characterized successful science.

REFERENCES

1. Prochaska, M., Jin, J., Rochefort, D., Zhuang, L., DiSalvo, F. J., Abruna, H. D., and van Dover, R. B., High throughput screening of electrocatalysts for fuel cell applications, *Rev. Sci. Instrum.* **77**(5) (2006).
2. De Lue, N., Combinatorial chemistry moves beyond pharmaceuticals, *Chem. Innov.* **31**(11):33–39 (2001).
3. Hanak, J. J., Multiple-sample-concept in materials research—synthesis, compositional analysis and testing of entire multicomponent systems, *J. Mater. Sci.* **5**:964 (1970).
4. Amis, E. J., Xiang, X. D., and Zhao, J. C., Combinatorial materials science: What's new since Edison? *MRS Bull.* **27**(4):295–297 (2002).
5. Takeuchi, I., Lauterbach, J., and Fasolka, M. J., Combinatorial materials synthesis, *Mater. Today* **8**(10):18–26 (2005).
6. Zhao, J. C., Combinatorial approaches as effective tools in the study of phase diagrams and composition-structure-property relationships, *Progress Mater. Sci.* **51**(5):557–631 (2006).
7. Adang, A. E. P. and Hermkens, P. H. H., The contribution of combinatorial chemistry to lead generation: An interim analysis, *Curr. Med. Chem.* **8**(9):985–998 (2001).

8. Posner, B. A., High-throughput screening-driven lead discovery: Meeting the challenges of finding new therapeutics, *Curr. Opin. Drug Discov. Devel.* **8**(4):487–494 (2005).
9. Tickle, I., Sharff, A., Vinkovic, M., Yon, J., and Jhoti, H., High-throughput protein crystallography and drug discovery, *Chem. Soc. Rev.* **33**(8):558–565 (2004).
10. Weinberg, H., Foreword, in *High-Throughput Analysis: A Tool for Combinatorial Materials Science*, R. A. Potyrailo E. J. Amis (eds.), Kluwer Adamemic/Plenum, New York, 2003; pp. vii–viii.
11. Harvey, M. J., Scott, D., and Coveney, P. V., An integrated instrument control and informatics system for combinatorial materials research, *J. Chem. Inform. Model.* **46**(3):1026–1033 (2006).
12. Zhang, W. H., Fasolka, M. J., Karim, A., and Amis, E. J., An informatics infrastructure for combinatorial and high-throughput materials research built on open source code, *Meas. Sci. Technol.* **16**(1):261–269 (2005).
13. Based on a search of the ISI Web of Science database, www.isiwebofknowledge.com, keywords=[(combinatorial OR high throughput) AND materials], June 15, 2006.
14. Fasolka, M. J. and Laumeier, C. E., *NISTIR 7332: NCMC-9 Combinatorial Methods for Nanostructured Materials*, 2006 National Institute of Standards and Technology, U.S. Dept. Commerce (www.nist.gov/combi).
15. Smotkin, E. S. and Diaz-Morales, R. R., New electrocatalysts by combinatorial methods, *Annu. Rev. Mater. Res.* **33**:557–579 (2003).
16. Hagemeyer, A., Jandeleit, B., Liu, Y. M., Poojary, D. M., Turner, H. W., Volpe, A. F., and Weinberg, W. H., Applications of combinatorial methods in catalysis, *Appl. Catal. A—General* **221**(1–2):23–43 (2001).
17. Senkan, S., Combinatorial heterogeneous catalysis—a new path in an old field, *Angew. Chem. Int. Ed.* **40**(2):312–329 (2001).
18. Weinberg, W. H., Jandeleit, B., Self, K., and Turner, H., Combinatorial methods in homogeneous and heterogeneous catalysis, *Curr. Opin. Solid State Mater. Sci.* **3**(1):104–110 (1998).
19. Chisholm, B. J., Potyrailo, R. A., Cawse, J. N., Shaffer, R. E., Brennan, M., and Molaison, C. A., Combinatorial chemistry methods for coating development v. The importance of understanding process capability, *Progress Org. Coat.* **47**(2):120–127 (2003).
20. Iden, R., Schrof, W., Hadeler, J., and Lehmann, S., Combinatorial materials research in the polymer industry: Speed versus flexibility, *Macromol. Rapid Commun.* **24**(1):63–72 (2003).
21. Potyrailo, R. A., Chisholm, B. J., Morris, W. G., Cawse, J. N., Flanagan, W. P., Hassib, L., Molaison, C. A., Ezbiansky, K., Medford, G., and Reitz, H., Development of combinatorial chemistry methods for coatings: High-throughput adhesion evaluation and scale-up of combinatorial leads, *J. Combin. Chem.* **5**(4):472–478 (2003).
22. Webster, D. C., Radical change in research and development: The shift from conventional methods to high throughput methods, *JCT Coat. Tech.* **2**(15):24–29 (2005).

23. Takeuchi, I., Chang, H., Gao, C., Schultz, P. G., Xiang, X. D., Sharma, R. P., Downes, M. J., and Venkatesan, T., Combinatorial synthesis and evaluation of epitaxial ferroelectric device libraries, *Appl. Phys. Lett.* **73**(7):894–896 (1998).

24. Schultz, P. G. and Xiang, X. D., Combinatorial approaches to materials science, *Curr. Opin. Solid State Mater. Sci.* **3**(2):153–158 (1998).

25. Wang, J. S., Yoo, Y., Gao, C., Takeuchi, I., Sun, X. D., Chang, H. Y., Xiang, X. D., and Schultz, P. G., Identification of a blue photoluminescent composite material from a combinatorial library, *Science* **279**(5357):1712–1714 (1998).

26. Danielson, E., Golden, J. H., McFarland, E. W., Reaves, C. M., Weinberg, W. H., and Wu, X. D., A combinatorial approach to the discovery and optimization of luminescent materials, *Nature* **389**(6654):944–948 (1997).

27. Xiang, X. D., Sun, X. D., Briceno, G., Lou, Y. L., Wang, K. A., Chang, H. Y., Wallacefreedman, W. G., Chen, S. W., and Schultz, P. G., A combinatorial approach to materials discovery, *Science* **268**(5218):1738–1740 (1995).

28. Cawse, J. N., Olson, D., Chisholm, B. J., Brennan, M., Sun, T., Flanagan, W., Akhave, J., Mehrabi, A., and Saunders, D., Combinatorial chemistry methods for coating development v: Generating a combinatorial array of uniform coatings samples, *Progress Org. Coat.* **47**(2):128–135 (2003).

29. Chin, J. W., Nguyen, T., Gu, X. H., Byrd, E., and Martin, J., Accelerated uv weathering of polymeric systems: Recent innovations and new perspectives, *JCT Coat. Tech.* **3**(2):20–26 (2006).

30. Chisholm, B., Potyrailo, R., Shaffer, R., Cawse, J., Brennan, M., and Molaison, C., Combinatorial chemistry methods for coating development iii. Development of a high throughput screening method for abrasion resistance: Correlation with conventional methods and the effects of abrasion mechanism, *Progress Org. Coat.* **47**(2):112–119 (2003).

31. Potyrailo, R. A., Olson, D. R., Medford, G., and Brennan, M. J., Development of combinatorial chemistry methods for coatings: High-throughput optimization of curing parameters of coatings libraries, *Anal. Chem.* **74**(21):5676–5680 (2002).

32. Stafslien, S. J., Bahr, J. A., Feser, J. M., Weisz, J. C., Chisholm, B. J., Ready, T. E., and Boudjouk, P., Combinatorial materials research applied to the development of new surface coatings i: A multiwell plate screening method for the high-throughput assessment of bacterial biofilm retention on surfaces, *J. Combin. Chem.* **8**(2):156–162 (2006).

33. Lefman, J., Morrison, R., Subramaniam, S., Towards high-throughput transmission electron microscopy imaging using a multi-specimen, cartridge loading device and automated data acquisition, *Biophys. J.* **88**(1):148A (2005).

34. Bendersky, L. A. and Takeuchi, I., Use of transmission electron microscopy in combinatorial studies of functional oxides, *Macromol. Rapid Comm.* **25**(6):695–703 (2004).

35. Zech, T., Sundermann, A., Fodisch, R., and Saupe, M., Using open-source software technologies and standardized data structures to build advanced applications for high-throughput experimentation environments, *Rev. Sci. Instrum.* **76**(6) (2005).

36. Kaufman, J. G. and Begley, E. F., Matml: A data interchange markup language, *Adv. Mater. Process.* **161**(11):35–36 (2003).

37. Meguro, S., Lippmaa, M., Ohnishi, T., Chikyow, T., and Koinuma, H., Xml-based data management system for combinatorial solid-state materials science, *Appl. Surf. Sci.* **252**(7):2634–2639 (2006).

38. Adams, N. and Schubert, U. S., From science to innovation and from data to knowledge: Escience in the dutch polymer institute's high-throughput experimentation cluster, *QSAR Combin. Sci.* **24**(1):58–65 (2005).

39. Meredith, J. C. and Amis, E. J., Lcst phase separation in biodegradable polymer blends: Poly(d,l-lactide) and poly(epsilon-caprolactone), *Macromol. Chem. Phys.* **201**(6):733–739 (2000).

40. Meredith, J. C., Karim, A., and Amis, E. J., High-throughput measurement of polymer blend phase behavior, *Macromolecules* **33**(16):5760–5762 (2000).

41. Smith, A. P., Douglas, J. F., Meredith, J. C., Amis, E. J., and Karim, A., Combinatorial study of surface pattern formation in thin block copolymer films, *Phys. Rev. Lett.* **8701**(1) (2001).

42. Smith, A. P., Sehgal, A., Douglas, J. F., Karim, A., and Amis, E. J., Combinatorial mapping of surface energy effects on diblock copolymer thin film ordering, *Macromol. Rapid Commun.* **24**(1):131–135 (2003).

43. Ashley, K. M., Meredith, J. C., Amis, E., Raghavan, D., and Karim, A., Combinatorial investigation of dewetting: Polystyrene thin films on gradient hydrophilic surfaces, *Polymer* **44**(3):769–772 (2003).

44. Ashley, K. M., Raghavan, D., Douglas, J. F., and Karim, A., Wetting-dewetting transition line in thin polymer films, *Langmuir* **21**(21):9518–9523 (2005).

45. Julthongpiput, D., Fasolka, M. J., Zhang, W. H., Nguyen, T., and Amis, E. J., Gradient chemical micropatterns: A reference substrate for surface nanometrology, *Nano Lett.* **5**(8):1535–1540 (2005).

46. Xu, C., Wu, T., Drain, C. M., Batteas, J. D., Fasolka, M. J., and Beers, K. L., Effect of block length on solvent response of block copolymer brushes: Combinatorial study with block copolymer brush gradients, *Macromolecules* **39**(9):3359–3364 (2006).

47. Xu, C., Wu, T., Batteas, J. D., Drain, C. M., Beers, K. L., and Fasolka, M. J., Surface-grafted block copolymer gradients: Effect of block length on solvent response, *Appl. Surf. Sci.* **252**(7):2529–2534 (2006).

48. Ludwigs, S., Schmidt, K., Stafford, C. M., Amis, E. J., Fasolka, M. J., Karim, A., Magerle, R., and Krausch, G., Combinatorial mapping of the phase behavior of abc triblock terpolymers in thin films: Experiments, *Macromolecules* **38**(5):1850–1858 (2005).

49. Eidelman, N., Raghavan, D., Forster, A. M., Amis, E. J., and Karim, A., Combinatorial approach to characterizing epoxy curing, *Macromol. Rapid Commun.* **25**(1):259–263 (2004).

50. Wang, H., Shimizu, K., Hobbie, E. K., Wang, Z. G., Meredith, J. C., Karim, A., Amis, E. J., Hsiao, B. S., Hsieh, E. T., and Han, C. C., Phase diagram of a nearly isorefractive polyolefin blend, *Macromolecules* **35**(3):1072–1078 (2002).

51. Bhat, R. R. and Genzer, J., Combinatorial study of nanoparticle dispersion in surface-grafted macromolecular gradients, *Appl. Surf. Sci.* **252**(7):2549–2554 (2006).

52. Bhat, R. R., Chaney, B. N., Rowley, J., Liebmann-Vinson, A., and Genzer, J., Tailoring cell adhesion using surface-grafted polymer gradient assemblies, *Adv. Mater.* **17**(23):2802–+ (2005).

53. Bhat, R. R., Tomlinson, M. R., and Genzer, J., Orthogonal surface-grafted polymer gradients: A versatile combinatorial platform, *J. Polym. Sci. (Pt. B—Polym. Phys.)* **43**(23):3384–3394 (2005).

54. Genzer, J., Templating surfaces with gradient assemblies, *J. Adhes.* **81**(3–4):417–435 (2005).

55. Wu, T., Efimenko, K., Vlcek, P., Subr, V., and Genzer, J., Formation and properties of anchored polymers with a gradual variation of grafting densities on flat substrates, *Macromolecules* **36**(7):2448–2453 (2003).

56. Stafford, C. M., Roskov, K. E., Epps, T. H., and Fasolka, M. J., Generating thickness gradients of thin polymer films via flow coating, *Rev. Sci. Instrum.* **77**(2) (2006).

57. Potyrailo, R. A. and Hassib, L., Analytical instrumentation infrastructure for combinatorial and high-throughput development of formulated discrete and gradient polymeric sensor materials arrays, *Rev. Sci. Instrum.* **76**(6) (2005).

58. Potyrailo, R. A., Wroczynski, R. J., Pickett, J. E., and Rubinsztajn, M., High-throughput fabrication, performance testing, and characterization of one-dimensional libraries of polymeric compositions, *Macromol. Rapid Commun.* **24**(1):124–130 (2003).

59. Kodentsov, A. A., Bastin, G. F., and van Loo, F. J. J., The diffusion couple technique in phase diagram determination, *J. Alloys Compounds* **320**(2):207–217 (2001).

60. Kirkaldy, J. S., Diffusion in multicomponent metallic systems: 3. The motion of planar phase interfaces, *Can. J. Phys.* **36**:917 (1958).

61. Zhao, J. C., The diffusion-multiple approach to designing alloys, *Annu. Rev. Mater. Res.* **35**:51–73 (2005).

62. Zhao, J. C., Reliability of the diffusion-multiple approach for phase diagram mapping, *J. Mater. Sci.* **39**(12):3913–3925 (2004).

63. Klein, J., Lehmann, C. W., Schmidt, H. W., and Maier, W. F., Combinatorial material libraries on the microgram scale with an example of hydrothermal synthesis, *Angew. Chem. Int. Ed.* **37**(24):3369–3372 (1998).

64. Orschel, M., Klein, J., Schmidt, H. W., and Maier, W. F., Detection of reaction selectivity on catalyst libraries by spatially resolved mass spectrometry, *Angew. Chem. Int. Ed.* **38**(18):2791–2794 (1999).

65. Schmitz, C., Posch, P., Thelakkat, M., and Schmidt, H. W., Efficient screening of electron transport material in multi-layer organic light emitting diodes by combinatorial methods, *Phys. Chem. Chem. Phys.* **1**(8):1777–1781 (1999).

66. Schmitz, C., Posch, P., Thelakkat, M., Schmidt, H. W., Montali, A., Feldman, K., Smith, P., and Weder, C., Polymeric light-emitting diodes based on poly(p-phenylene ethynylene), poly(triphenyldiamine), and spiroquinoxaline, *Adv. Funct. Mater.* **11**(1):41–46 (2001).

67. Schmitz, C., Schmidt, H. W., and Thelakkat, M., Lithium-quinolate complexes as emitter and interface materials in organic light-emitting diodes, *Chem. Mater.* **12**(10):3012–3019 (2000).

68. Schmitz, C., Thelakkat, M., and Schmidt, H. W., A combinatorial study of the dependence of organic led characteristics on layer thickness, *Adv. Mater.* **11**(10):821–+ (1999).

69. Takeuchi, I., van Dover, R. B., and Koinuma, H., Combinatorial synthesis and evaluation of functional inorganic materials using thin-film techniques, *MRS Bull.* **27**(4):301–308 (2002).

70. Cui, J., Chu, Y. S., Famodu, O. O., Furuya, Y., Hattrick-Simpers, J., James, R. D., Ludwig, A., Thienhaus, S., Wuttig, M., Zhang, Z. Y., and Takeuchi, I., Combinatorial search of thermoelastic shape-memory alloys with extremely small hysteresis width, *Nature Mater.* **5**(4):286–290 (2006).

71. Takeuchi, I., Famodu, O. O., Read, J. C., Aronova, M. A., Chang, K. S., Craciunescu, C., Lofland, S. E., Wuttig, M., Wellstood, F. C., Knauss, L., and Orozco, A., Identification of novel compositions of ferromagnetic shape-memory alloys using composition spreads, *Nature Mater.* **2**(3):180–184 (2003).

72. Takeuchi, I., Long, C. J., Famodu, O. O., Murakami, M., Hattrick-Simpers, J., Rubloff, G. W., Stukowski, M., and Rajan, K., Data management and visualization of x-ray diffraction spectra from thin film ternary composition spreads, *Rev. Sci. Instrum.* **76**(6) (2005).

73. Hasegawa, K., Ahmet, P., Okazaki, N., Hasegawa, T., Fujimoto, K., Watanabe, M., Chikyow, T., and Koinuma, H., Amorphous stability of hfo2 based ternary and binary composition spread oxide films as alternative gate dielectrics, *Appl. Surf. Sci.* **223**(1–3):229–232 (2004).

74. Matsumoto, Y., Murakami, A., Hasegawa, T., Fukumura, T., Kawasaki, M., Ahmet, P., Nakajima, K., Chikyow, T., and Koinuma, H., Structural control and combinatorial doping of titanium dioxide thin films by laser molecular beam epitaxy, *Appl. Surf. Sci.* **189**(3–4):344–348 (2002).

75. Ohkubo, I., Matsumoto, Y., Ohtomo, A., Ohnishi, T., Tsukazaki, A., Lippmaa, M., Koinuma, H., and Kawasaki, M., Investigation of zno/sapphire interface and formation of zno nanocrystalline by laser mbe, *Appl. Surf. Sci.* **159**, 514–519 (2000).

76. Lin-Gibson, S., Landis, F. A., and Drzal, P. L., Combinatorial investigation of the structure-properties characterization of photopolymerized dimethacrylate networks, *Biomaterials* **27**(9):1711–1717 (2006).

77. Crosby, A. J., Fasolka, M. J., and Beers, K. L., High-throughput craze studies in gradient thin films using ductile copper grids, *Macromolecules* **37**(26):9968–9974 (2004).

78. Schenck, P. K., Kaiser, D. L., and Davydov, A. V., High throughput characterization of the optical properties of compositionally graded combinatorial films, *Appl. Surf. Sci.* **223**(1–3):200–205 (2004).

79. Beers, K. L., Douglas, J. F., Amis, E. J., and Karim, A., Combinatorial measurements of crystallization growth rate and morphology in thin films of isotactic polystyrene, *Langmuir* **19**(9):3935–3940 (2003).

80. Meredith, J. C., Smith, A. P., Karim, A., and Amis, E. J., Combinatorial materials science for polymer thin-film dewetting, *Macromolecules* **33**(26):9747–9756 (2000).

81. Smith, A. P., Douglas, J. F., Meredith, J. C., Amis, E. J., and Karim, A., High-throughput characterization of pattern formation in symmetric diblock copolymer films, *J. Polym. Sci. (Pt. B—Polym. Phys.)* **39**(18):2141–2158 (2001).

82. de Gans, B. J., Wijnans, S., Woutes, D., and Schubert, U. S., Sector spin coating for fast preparation of polymer libraries, *J. Combin. Chem.* **7**(6):952–957 (2005).
83. Stafford, C. M., Guo, S., Harrison, C., and Chiang, M. Y. M., Combinatorial and high-throughput measurements of the modulus of thin polymer films, *Rev. Sci. Instrum.* **76**(6) (2005).
84. Stafford, C. M., Harrison, C., Beers, K. L., Karim, A., Amis, E. J., Vanlandingham, M. R., Kim, H. C., Volksen, W., Miller, R. D., and Simonyi, E. E., A buckling-based metrology for measuring the elastic moduli of polymeric thin films, *Nature Mater.* **3**(8):545–550 (2004).
85. Stafford, C. M., Vogt, B. D., Harrison, C., Julthongpiput, D., and Huang, R., Elastic moduli of ultrathin amorphous polymer films, *Macromolecules* **39**(15):5095–5099 (2006).
86. Wilder, E. A., Guo, S., Lin-Gibson, S., Fasolka, M. J., and Stafford, C. M., Measuring the modulus of soft polymer networks via a buckling-based metrology, *Macromolecules* **39**(12):4138–4143 (2006).
87. Warren, O. L., Downs, S. A., and Wyrobek, T. J., Challenges and interesting observations associated with feedback-controlled nanoindentation, *Z. Metallkunde* **95**(5):287–296 (2004).
88. Warren, O. L., Dwivedi, A., Wyrobek, T. J., Famodu, O. O., and Takeuchi, I., Investigation of machine compliance uniformity for nanoindentation screening of wafer-supported libraries, *Rev. Sci. Instrum.* **76**(6) (2005).
89. Warren, O. L. and Wyrobek, T. J., Nanomechanical property screening of combinatorial thin-film libraries by nanoindentation, *Meas. Sci. Technol.* **16**(1):100–110 (2005).
90. Bijaoui, A., Image-analysis—transfer of techniques used in astronomy to diffraction, *J. Phys.* **47**(C-5):63–67 (1986).
91. Ahern, F. J., Digital image-analysis for astronomy, *J. Roy. Astron. Soc. Can.* **78**(5):200–200 (1984).