ACS Combinatorial Science

Editorial

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Combinatorial Science: Taking Inspiration from Biology and Youth

The American Chemical Society is, well, a chemistry-focused organization. However, the content of its journals, including this one, confirms that chemistry has planted its flag in a large and exciting portion of biology's territory. Aside from the principle of natural selection, no concept so defines modern biology and medicine as the understanding that organisms and their actions are molecular in nature. From the chemist's point of view, biology provides the most complex and successful molecular systems from which to learn about chemical function, as well as one of the most challenging and significant arenas for the application of new molecules.

As students come to understand biology to be a molecular enterprise, and find so much of biology's material—proteins, nucleic acids, polysaccharides—to be modular in composition, I would hope that some ask a molecular question: how can the vast and diverse functions of biology emerge from so few building blocks? The answer steered me, and should steer some of them, to the subject of this journal: different *combinations* of components give different properties—and what amazing properties they can be! Do you need a smart material that responds to light, heat, or a change in pH? How about a way to inactivate one kinase out of a hundred close relatives, or a system that packages a cargo for delivery across barriers? Combinatorial solutions are presented by biology to a vast array of such problems—one does not have to be a biologist to be inspired by this matchless ability to create, sift, and refine.

Biological molecules illustrate several essential principles of combinatorial science.

- Successful combinatorial efforts require powerful synthetic methods.

- Combinatorial approaches also require powerful methods of analysis. Biology's great advantage in this regard is its use of *selection* rather than *screening* to distinguish winners from losers—indeed, combinatorial selection is the hallmark of life. Combinatorial experimentalists therefore must pay great attention to analytical methods, the design of which is often the most difficult task.

- The information about *how* to achieve a desired function that emerges from a combinatorial study is often more important than the particular widget produced. Implicit in the combinatorial method, and illustrated forcefully in biology, is the idea that many individual molecular solutions exist to most problems. General principles can often be derived from a consideration of multiple functional structures.

- Molecules are not the only things that are good to test in parallel. Biologists are also active parallel testers of *ideas*, although this excellent practice is not restricted to biology. "The Method of Multiple Working Hypotheses" was coined, but certainly not invented, by geologist T.C. Chamberlin (*Science* **1965**, *148*, 754–759). It suggests that scientists invest their intellectual and emotional capital not in a single explanation or proposal, but rather in sets of competing ideas that can be pared down with satisfaction and without prejudice. (See also the classic "Strong Inference" by biophysicist John Platt, *Science* **1964**, *146*, 347–353.) This approach captures the essential advantage of combinatorial methods, which devalue individual candidates in the service of finding desired function.

- The more complex the target, the more valuable a combinatorial approach can be, because interactions among multiple variables are difficult to predict. Biological systems are marvels of information transfer, nonlinear responses, and feedback loops. Laboratory experiments that even approach such complexity are currently very rare. Many tools of biological origin for combinatorial science, such as phage display, SELEX, and the like, have so far been used mostly for problems of binding. While valuable, this is now relatively simple stuff. We are still only starting to learn how to search for more sophisticated functions, such as catalysis, pathway engineering, energy collection, or adaptive mechanical properties.

Inspired by the function and modules of biology's relentless combinatorial engines, the future of our interdisciplinary field is tremendously exciting. To help the readers of this journal appreciate its breadth, we announce the formation of the *ACS Combinatorial Science* Young Investigators Panel. This group of scientists, ranging from senior graduate students to recent Ph.D.'s, is active in the full range of science and technology published in these pages. Their charge is to highlight publications from any source that they regard as especially significant for the combinatorial science community, in consultation with members of the journal's Editorial Advisory Board. You are encouraged to meet them and peruse their insights on the *ACS Comb. Sci.* Web site, at http://pubs.acs.org/journal/acsccc. Students and postdocs who may wish to participate can contact us at yip@combsci.acs.org.

The *ACS Combinatorial Science* editorial team wishes you an exciting and productive 2013.

M.G. Finn, Editor-in-Chief

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Notes

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