# Predictive Science + Emerging Technologies: Speeding Flavor and Fragrance Innovation

## New tools for formulation challenges and speed-to-market

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Flavors and fragrances are key sensory attributes that consumer goods companies can leverage to enhance and expand their product appeal and drive competitive advantage. Yet they are also notoriously complex—understanding key variables, such as formulation stability, product safety and ensuring that the result is relevant to consumers, has traditionally required multiple experiments, which can ratchet up costs and delay time-to-market. To make matters more complicated, aroma and taste formulations are also subject to increasingly stringent regulatory control and greater public scrutiny.

How can today's consumer and packaged goods organizations respond to these diverse challenges and at the same time differentiate themselves from competitors, expand market share and drive top line growth?

As Rich Boden suggested in an article published in the March 2009 issue of *Perfumer & Flavorist* magazine, "Technology Transfer for Aroma Chemical Research" (available online at *www.perfumerflavorist.com/fragrance/research*), fragrance and flavor researchers would do well to take a page from the playbook of the pharmaceutical and petroleum industries. Both have embraced emerging technologies to streamline and accelerate experimental progress. Similarly, flavor, fragrance, personal care and consumer packaged goods organizations can take advantage of scientific informatics solutions already proven in these other research-driven enterprises to engage in predictive science at all stages of the research and development process, with the goal of reducing the number of experiments needed, slashing costs and speeding product innovation.

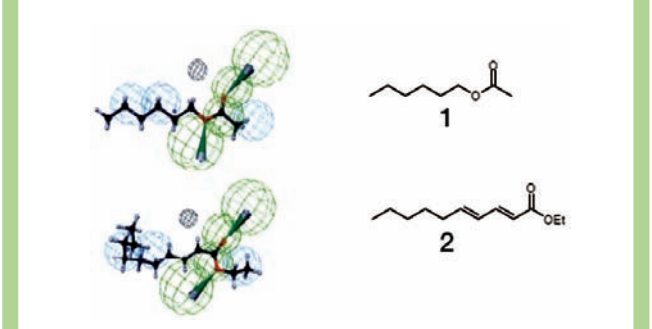
### Accelerate Discovery through Predictive Science

As fragrances have become one of the most important elements of brand differentiation in home and personal care, a clear market for synthetic odorants has emerged—particularly those that can serve as alternatives to expensive, threatened naturals such as sandalwood, or stand in for natural scents such as fruit and citrus. However, using traditional trial-and-error type approaches to discover the right molecular composition often requires a large number of one-off experiments, which can be prohibitively expensive and time-consuming.

This is where technology that facilitates complex molecular simulation can play an important role—not to replace olfactive creativity, but rather to build efficiencies into the creative process. Used widely in pharmaceutical research, software-enabled scientific modeling and analytic techniques make it possible for researchers to design molecular compounds in silico, applying a more streamlined, rational approach. Instead of using trial and error, researchers can take advantage of the scientific principles embodied in the software to more easily explore a host of chemical candidates for a particular flavor or odor, weed out those that won't hit the mark and quickly narrow the search for the most successful leads. Significantly, this process also delivers not just leads but information about those molecular-level features that lead to successful products.

Consider the example of Indian sandalwood. Due to its rich fragrance, excellent performance as a fixative and its scarcity, natural Indian sandalwood is considered one of the most precious essential oils in perfumery. The development of an inexpensive, synthetic alternative to sandalwood is certainly desirable, and a number of sandalwood-evoking molecules are on the market and are well known to perfumers. Yet traditional experimental approaches to produce such materials normally involve the synthesis of thousands of candidate molecules, followed by testing of multiple formulations of those

**Olfactophore model for pear odorants; top: aligned with 1; bottom: aligned with 2; the spherical volumes highlight those features responsible for odor** **F-1**



candidates and a good deal of testing on sandalwood itself for comparison.

With technology that simplifies sophisticated molecular simulation, researchers can take a more rational approach to discovery by leveraging computer-aided tools like olfactophore models. An olfactophore model (**see F-1**) is a 3-D representation of a generalized set of molecular features that are critical for a given odor. In much the same way that pharmacophore models are used to analyze the biological activity of drug candidates, olfactophore models may be developed by comparing the chemical structures of molecules having a similar odor.

This type of model can allow researchers to investigate thousands of potential molecular combinations in silico to determine those that have the highest probability of producing a sandalwoodlike odor—before synthesis of any kind. If an organization can narrow its synthesis candidates from thousands to hundreds, or even fewer, the discovery process will be correspondingly faster and more cost-effective.

Using simulation, organizations can also more easily make use of the "fail early" paradigm: Figure out what doesn't work before investing too heavily in synthesis, screening and testing. This approach can even be extended to patent protection; researchers can incorporate into research workflows automated searches of patent databases to identify those compounds that fit the model, and determine which are protected and which are available for use. Essentially, technologies that enable predictive science can greatly accelerate the identification of new lead odorants and flavorants. Computation can screen many more compounds than experimentation alone. Combined with an ability to search the open literature and patent databases, this provides an efficient means for securing the intellectual property required to challenge competitors, without actually synthesizing an exhaustive list of molecules.

## Benefits of Virtual Screening

Morphology is critical to flavor and fragrance formulation because researchers need to understand the role of each ingredient and/or how the formulation will behave under different conditions. Will the ingredients separate, for example, or break down when the temperature gets too high?

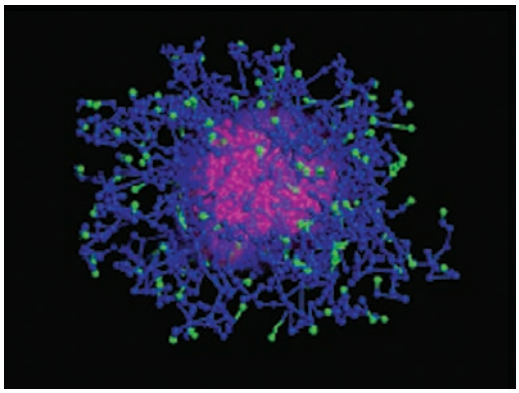
Scientifically aware software can help researchers predict the structure of complex mixtures at a nanometric level. Structure at this level, called morphology, is important for the texture and rheology of soft materials. It can also determine behaviors such as whether an active is locked away within the formulation or made available within a particular solvent environment.

By using software techniques to predict how a formulation's morphology might be impacted by the addition of a particular ingredient (or by the effect of temperature or surfactant architecture), organizations can potentially reduce the need for big investments in costly and

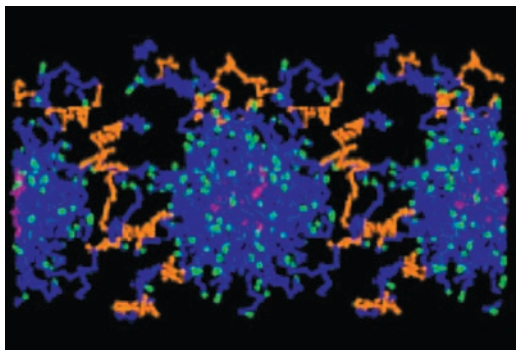
## Illustration: Simulation Technology and Formulation Instability

Simulation software can be applied across a range of industries concerned with formulation stability; here is just one illustrative example: Galderma, a pharmaceutical company specializing in dermatological treatments, was interested in understanding the underlying cause of physical and chemical instability of an active used in a specific topical drug formulation. Simulation enabled researchers to predict the phase morphology of five model systems of increasing complexity. Starting with systems containing only surfactants and water (**F-2**), ingredients were progressively added until obtaining the experimental formulation of active, polymeric surfactant, and preservative (**F-3**). The simulations showed the conditions under which the complete formulation bridging between the micelles occurred, as strands of the polymeric surfactant extended between adjacent micelles (**F-3**). This is a condition that may lead to flocculation and precipitation, consistent with the instability observed experimentally. Importantly, the simulation also indicated the component of the formulation responsible for the bridging. Armed with this knowledge and with a working model, it became possible to examine reformulations that avoided the problem.

**Surfactant micelle in aqueous solution (water not shown)** **F-2**



**Snapshot of the system containing nonionic surfactant, hydrophobic drug and nonionic polymeric surfactant in aqueous solution (water not shown)** **F-3**



time-consuming screening. Equally important, once researchers gain an understanding of the underlying causes of the development of an undesirable morphology at the molecular level, they can solve them, speeding development cycle times.

Applications of this type of in silico technology can benefit domains as diverse as cream formulation and polymer compatibility, as well as optimize the design of the latest forms of delivery systems like liposomes and polymersomes, which are relevant for new flavor delivery technologies such as aromasomes (liposomes to encapsulate flavors). For an illustration of how this approach might be used to address formulation instability, see **Simulation Technology and Formulation Instability.**

As any researcher knows, there are countless variables that can impact a formulation's product safety and trigger undesirable side effects. But testing every possible ingredient is not only extremely costly and time-consuming, but testing methods are also coming under increasing regulatory scrutiny. With the forthcoming ban on animal testing for cosmetic ingredients in the European Union, there is a pressing need for assays that make animal testing obsolete. How can a company comply with increasingly stringent regulations while simultaneously reducing in vivo testing?

Product safety testing is yet another phase of the R&D process in which scientifically aware IT solutions can be of use. For many years, pharmaceutical companies have routinely leveraged quantitative structure-activity relationship (QSAR) prediction models to perform rapid assessments of chemical product safety based solely on a chemical's molecular structure. These models can be used for a wide range of screens, including physical/chemical, environmental fate, ecotoxicity, toxicity, mutagenicity and more. QSAR techniques can easily be applied to cosmetics testing, and even automated so that thousands of compounds can be piped through a model that is updated continuously with the latest experimental results, yielding the best possible predictions. In this way, testing on animals can be reduced to a minimum.

For example, fragrance and flavor companies are investigating ways to integrate data from in vitro and in silico tests to produce models for the prediction of the skin sensitization potential of chemicals. The promising results seen by Natsch et al. anticipate a bright future for this type of approach as a replacement for animal testing.[1] Animal testing is expensive, unpopular with consumers and coming under increasing regulation. Software can offer an alternative that reduces these tests and at the same time provides a framework that can be used to screen thousands of compounds rapidly.

## Productivity and Better Knowledge Management

Looking at R&D beyond the context of a single project, flavor and fragrance researchers often waste time and money repeating experiments that have been done before. This ongoing drain on resources happens mainly because organizations fail to keep track of their information in a way that fully leverages it: relevant results from a previous experiment are hidden away in a lab notebook or chemistry system that nobody but the original author has access to; key correlations between one project and another are not made because of incompatible data formats; valuable knowledge is lost when a key scientist leaves the company.

To make matters more complicated, information related to even a single project—to say nothing of an organization's entire knowledge base—can span a wide array of sources. With experimental findings and relevant information spread across diverse formats, applications and proprietary systems, researchers can spend countless hours tracking down and integrating what they need, or they may simply miss it entirely, burning resources on redundant experiments every three to five years.

It is important for researchers to be able to easily access and apply existing experimental information when needed. New advances in service-oriented architecture and collaborative technologies are finally making this a reality. With an underlying system that enables individual contributors to more easily archive, search and integrate information from past experiments with current projects, huge efficiency gains can be made. For example, a large range of diverse compounds are associated with bitterness; but researchers can only take advantage of existing information on known bitter compounds if they can quickly pinpoint the findings they need and be able to use them to predict bitterness in new formulations. A smarter, more integrated approach to tracking organizational knowledge can enable companies to build on the valuable, yet time-consuming, research they've already invested in, rather than start from scratch with every project. Researchers are able to devote their time to doing research and not to tracking down missing data.

## Conclusion

There are opportunities for research organizations developing flavors and fragrances to decrease the time and cost burdens of trial-and-error experimentation. Emerging technologies used in other scientifically focused industries such as pharmaceuticals—particularly advanced analytics, predictive simulation techniques and better data management—empower researchers by combining several critical elements that help speed the discovery process and improve competitive advantage. These elements include the deep science that fosters innovation, and technology that enables project stakeholders to collaborate better, and do their work more efficiently and cost-effectively.



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