As a physical chemist or chemical physicist, I've often had to react to uncomprehending or unkind remarks about chemistry delivered by physicists. Typical of such remarks are "A diatomic molecule has one atom too many" and "A topic is dead when it has been turned over to the chemists."

Both those dicta are attributed to Arthur Schawlow. Coming from him, though, such comments seem incongruous. Not only is he otherwise exceptionally genial, but his fine book written with Charles Townes deals largely with polyatomic molecules and with microwave spectroscopy, a field in which chemists had a major role early on. Furthermore, like much else in modern physics, the laser work of Townes and Schawlow is a linear descendant of molecular beam experiments launched decades earlier by Otto Stern, a physical chemist.

Squabbles between siblings are unseemly yet can foster mutual appreciation. Any physicist interested in molecules cannot avoid chemistry, and at the least may find it offers curious historical or cultural perspectives. A genuine symbiosis may also emerge from complementary approaches. The typical chemist wants above all to understand why one substance behaves differently from another; the physicist usually wants to find principles that transcend any specific substances. Here, I present three brief items to exemplify these themes.

Newton's alchemy

In Isaac Newton's papers, there are over a million words, recorded in his distinctive hand, that deal with alchemy (and several million more on theology). These writings, consisting of notes on his reading as well as his experiments and speculations, extend over more than 25 years; about half precede the *Principia*, the rest precede his *Opticks*. Newton owned 138 books on alchemy, amounting to 8% of his collection and more than he had on any other even remotely scientific subject. Compared to physics and mathematics, Newton regarded alchemy as "a more subtle, secret and noble way of working."

His assistant wrote that Newton pursued alchemical experiments for weeks at a time, "... the Fire scarcely going out either Night or Day, he sitting up one Night, as I did another, till he had finished his Chymical experiments, in the Performance of which he was the most accurate, strict, exact..." Authorities still debate whether Newton was searching for a means to make gold. Perhaps he realized there was an easier way; he gave up alchemy when he became Master of the Mint.

Chemical epistemology

I like to contrast the cultural perspectives of physicists and chemists by using two whimsical metaphors. A physicist typically strives to develop predictive or interpretative capacity in a Taylor expansion about some prototypical case, such as the hydrogen atom, by acquiring higher and higher order information about the prototype and its close relatives. Of necessity, a chemist tries instead to develop predictive models in a Fourier expansion, by acquiring low order information over a wider and wider domain. Both approaches have distinct virtues and limitations. However, recognizing the Fourier character of chemical reasoning may help make less dubious or devious the chemist's proclivity for predicting behavior in regions well removed from any safely characterized prototype.

My second metaphor emphasizes a kindred aspect of chemical concepts. Chemistry is like an impressionistic painting. If viewed from too close, all that can be seen is puzzling detail in myriad dabs of paint. If viewed from too far away, the painting becomes just a shimmering blur. Physicists, in
search of basic principles, tend to stand too close (and some biologists too far away). At the right distance, wondrous and lovely things appear. That is the nature of chemical concepts, which, at the appropriate level of approximation or abstraction, often prove remarkably reliable and widely applicable.

**Chemical accuracy**

To many physicists, it is exasperating that chemists blithely invoke a hodgepodge of crude models and rationalizations. However, judicious use of such models can yield marvelously exact results. The synthesis of a neurotoxin molecule, completed at Harvard University in 1993 by Yoshito Kishi and his coworkers, offers a splendid example. The toxin, extraordinarily poisonous, is a natural product found in marine soft corals. Its molecular structure, displayed schematically in the figure on page 11, contains 409 atoms: 223 of hydrogen, 129 of carbon, 3 of nitrogen and 34 of oxygen. Not evident in a planar drawing are the myriad variant structures, termed stereoisomers, that have the atoms linked in the same way but differ in the spatial configuration of bonds. There are twofold configurational choices at 72 sites, hence \( 2^{72} = 5 \times 10^{21} \) such stereoisomeric structures. (See the photo at the right.) Among this vast array, only one particular stereoisomer is the actual biologically active neurotoxin molecule.

The task of synthesizing such a molecule thus calls for tremendous resourcefulness. If one copy of each of the 5 \( \times 10^{21} \) stereoisomers were made, the collection would weigh 22 grams, about a handful. To pluck one particular structure from such an immense molecular haystack would be quite impossible. Yet, Kishi and his team were able to synthesize with virtually 100% selectivity the unique structure that has the desired spatial conformation at all 72 sites. Chemical techniques thereby attained an accuracy better than one part in \( 10^{21} \), far beyond most physical measurements.

The experimental work required by such a project is painstaking. It involves inventing means to assemble various portions of the molecule, often with the aid of reagents and reaction pathways newly devised for the purpose. Intricate schemes must be developed to protect sensitive regions during rather violent construction operations on neighboring regions, or to provide suitable scaffolding.

In contrast to the experimental artistry and tenacity required, however, the synthetic designs that achieve such remarkable stereochemical control invoke just a few typical chemical notions. One of the key notions is illustrated in the figure below. It shows a tetrahedral carbon atom (labeled \( C_1 \)); it is bonded to four tetrahedrally arrayed neighbors (linked by a single bond to a trigonal carbon atom (labeled \( C_2 \); it is bonded to three coplanar neighbors). The C-H bond sprouting from the tetrahedral carbon is in the same plane as the adjacent double bond, so that the other two groups attached to that carbon (labeled \( R_1 \) and \( R_2 \) lie above and below the plane containing the double bond and other attached atoms. By temporarily attaching a bulky group at position \( R_1 \), say, Kishi can force a reagent, say \( R_0 \), to attack the double bond by approaching from the opposite side of the plane, the \( R_2 \) side. In effect the bulky group at \( R_1 \) serves as a Maxwell Demon. This procedure enables Kishi to convert \( C_1 \) to a tetrahedral carbon atom with its attached groups \( R_1 R_2 R_0 \) disposed in the desired fashion with respect to \( C_1 H R_1 R_2 \). Repeated use of such stratagems, in many variants and combinations, has provided powerful tools for stereospecific synthesis.

These tools are derived from empirical structural studies of small molecules, with no direct recourse to quantum mechanics or anything more than rudimentary physics. However, the means to obtain the requisite structural information did come from chemical physics. For instance, the conformational situation shown in the figure below was established from microwave spectra of propylene, a nine-atom molecule. It is gratifying that this structural detail provided key input for constructing the exact biologically active form of the neurotoxin, with 409 atoms. Although the cultural gulf between chemical physics and synthetic chemistry is vast, the atoms and molecules are the same.

This neurotoxin story connects quite directly to Schawlow's dicta. The principles involved in obtaining and analyzing the microwave spectra of molecules like propylene are found in the book by Townes and Schawlow, published over 40 years ago. From the viewpoint of frontiers physics research, the field thus might be regarded as dead, and suitably entombed in the book. Yet, results derived therewith, in the hands of chemists, literally came to life in the synthesis of the biologically active neurotoxin molecule. Perhaps as a chemical physicist I'm entitled to suggest Schawlow's dicta be recast, to wit: "No molecule has too many atoms" and "A topic is not dead when it has been turned over to the chemists; they often will resurrect it in the real world!"

**References**


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**Yoshito Kishi contemplates the kinship of chemical physics and organic synthesis. His right hand holds a model of the propylene molecule, his left hand a quantity of sugar comparable in volume to that of the 272 distinct stereoisomers of the palytoxin molecule.**

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**Equilibrium Conformation for a Tetrahedral Carbon Atom (C1) adjacent to a Trigonal Carbon (C2); the C-H Bond eclipses the double bond. R1 . . . R3 denote attached groups (all H for propylene); R1 lies above and R2 below the plane containing the three carbon atoms and the initial atoms of the other groups.**