

Simulation vs. Understanding: A Tension, in Quantum Chemistry and Beyond. Part C. Toward Consilience

Roald Hoffmann* and Jean-Paul Malrieu*

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Abstract: In the last part of our Essay, we outline a future of consilience, with a role both for fact-seekers, and for searchers for understanding. We begin by looking at theory and simulation, surrounded as they are by and interacting with experiment, especially in Chemistry. Experimenters ask questions both conceptual and numerical, and so draw the communities together. Two case studies show what brings the theoretician authors joy in this playground, and two more detailed ones make it clear that computation/simulation is anyway deeply intertwined with theory-building in what we do, or for that matter, anywhere in the profession. From a definition of science we try to foresee how simulation and theory will interact in the AI-dominated future. We posit that Chemistry's streak of creation provides in that conjoined future a link to Art, and a passage to a renewed vision of the sacred in science.

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In the second section of our paper we fleshed out our complaints against thinking and unthinking uses of artificial intelligence in science and in society. No getting around it, it began to read like a jeremiad, even as we tried to voice the optimistic contrary opinion of the artificial intelligence community. We now begin the road back.

The wave of AI represented by machine learning and artificial neural network techniques has broken over us. Let's stop fighting, and start swimming, so to speak. First, by taking a look at what gives the two of us joy in doing theory. We will be reminded that most everything we do anyway comes from an intertwining of the computational, several kinds of simulation, and the building of theories.

We will then take a turn. The mastery and joy recognized along the way as being important to us (and not just us; we turn to the reader to reflect on what pleases them) point us to more than science—to emotions, art, and the sacred. The way to remain human in the age of AI will lead us, we think naturally, to ways of recognizing and enhancing the artistic element in Chemistry. And actually through recognition of that conjunction of Art and Chemistry to a future where theory and simulation do so much more than coexist.

To begin the journey toward consilience,^[1] we turn to the elephant (really many small elephants) in the room, whose interests transform understanding, theory, and simulation, and shape the relationship between the three.

[*] R. Hoffmann


Dept. of Chemistry and Chemical Biology, Cornell University
Ithaca NY 14850 (USA)
E-mail: rh34@cornell.edu

J.-P. Malrieu

Laboratoire de Chimie et Physique Quantiques
Université de Toulouse 3

118 route de Narbonne, 31062 Toulouse (France)

E-mail: malrieu@irsamc.ups-tlse.fr

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C1. We Are Hardly Alone

The triangle redefined. Experimentalists want understanding and they want numbers.

So far it seems we have been talking about simulation, theory and understanding as if... the world was made up of the people who do just these. It isn't. Chemistry remains an experimental science, and even in the more theoretically educated physics community the majority of practitioners are experimenters.

"Experimentalists" turn to "theoreticians" in several ways. One is qualitative: Can you explain (to me) this property of a set of molecules? Or of that specific molecule, a property which is absent or different in that other one? The easy questions are of color (spectra), structure, magnetic moment, or thermodynamic stability. Much more difficult are question of "stability"—mostly a matter of kinetic persistence in the chemical context, but in the presence of which reagents? Still harder and persistent, given that chemistry is the craft and science of molecules and their transformations,



Photo: Santiago Alvarez

Roald Hoffmann was born in a part of Poland that is now Ukraine in 1937. The US was good to him, as to many immigrants, and he became in time a theoretical chemist. He has taught several generations of chemists how one could productively use molecular orbitals in thinking about organic, inorganic and solid state chemistry. With time, he also built his own land between chemistry, poetry and philosophy. Relevant to this paper, one way to see Roald's involvement with computers is that the science he did was entirely dependent on those marvelous tools. And yet he spent all his efforts, over fifty years, in a way fighting computers, transforming the multitude of numbers they produced into chemical explanations.

Jean-Paul Malrieu was born in 1939, son of a couple of philosophers. He went through the Ecole Normale Supérieure in Paris and started his research in the Pullman's laboratory. He moved to Toulouse in 1974, where he gathered an important Quantum Chemistry group. His targets are both methodological, developing original techniques to treat the electron correlation problem (with a particular focus on magnetism), and interpretative, since he considers that the production of rationalizations, models and even metaphors is as important as reaching accurate numbers. Jean-Paul values deduction and loves translations from one language of Quantum Chemistry to another, for instance between Molecular Orbitals and Valence Bond Theory. He draws, and his social concerns have led him to write several non-scientific essays.

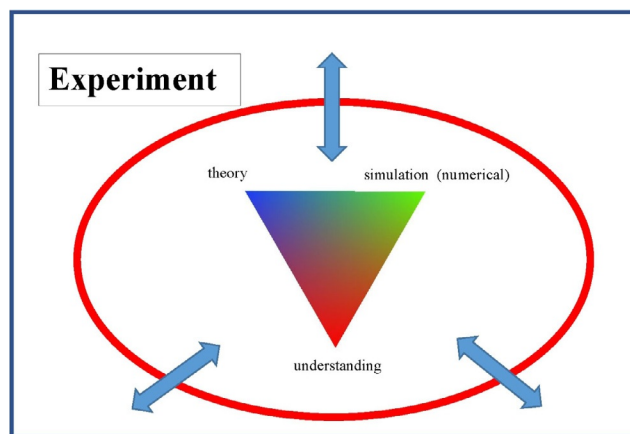


Figure 1. A more realistic triangle, with experiment, especially in chemistry, impelling interaction between theory, numerical simulation and understanding.

is chemists' desire to effect very specific reactions in a controlled way.

The practicing chemist is not unreasonable. "It's OK if you do a calculation, but please explain to me what is going on," the experimentalist says to the theorist, "It's OK to use words and/or equations," the experimentalist continues, "I will try to follow. Please help me." The theorists' response, if they go beyond the numerical evidence ("this is what the basic equations say"), is the story-telling part of their activity. Note how naturally it comes to the fore! And how the intelligibility and portability of a theoretical explanation count.

The demand may also be, frequently is, numeric: tell me the likely value of this property of that molecule. The experimentalist wants a number, and they want it precise and accurate, as they demand of their spectrometers. The experimentalists are not unreasonable—their questions are commensurate with the state of the field of knowledge. This kind of request has increased enormously in the last decades, as quantum chemistry codes became able to provide rather accurate values of observables. The paradigmatic query here, actually a mark of how good theory has gotten, is the astrophysicist's reliance on quantum chemical calculations of vibrational and rotational spectra of metastable molecules in outer space. At least for small molecules. Quantum chemistry then becomes a "theoretical spectrometer", to be added to the panoply of experimental techniques of interrogation of matter.

Except for seeking prestige (some people think this might be conferred by a computational section in a chemistry paper, whether something is gained by the presence of such or not), this demand addressed to a collaborating theoretician is meaningful. But if the criterion of accuracy becomes the central goal, the quantum methodologist will naturally focus on searching for more accurate theoretical treatments, applicable to larger molecules. In this, he or she may either introduce more and more experimental information in a multi-parametric functional^[2] (apologies here for the jargon of the trade), or try to go closer to the exact solution of the Schrödinger equation. The two strategies, deeply different

from an epistemic point of view, both respond to a search for numerical accuracy.

The first strategy says: “I am quite sure that everything happens as if...”, the second one “I have almost reached the way nature behaves in this system, I have numerically almost duplicated nature”. Most experimentalists will not care much about this distinction, provided that both predictions are reliable.

One interesting feature of modern simulations is that there is a special quality to those that show molecular dynamics, illustrating trajectories through sequential snapshots, animations. The spectator may have the feeling that he has really entered the molecule. This type of time-dependent simulation is very attractive in our civilization of moving pictures. We have discussed the power of images above, in the second paper in this series, Section 17. One has to exercise judgment in using these seductive representations of a virtual world. Or reality.

But experimentalists want more than numbers. For the decreasing number of theorists committed to understanding in the incipient age of simulation, we say (nonreligiously) “Thank God for the experimentalists!” “And for teachers, too!” For both demand understanding. If the demand for understanding is sufficiently intense, it will prevail. The simulator will have to provide a meaningful (theoretically grounded) narrative, answering the question: “Why?” Or, more intelligently: “What are the leading contributions to that property in this molecular architecture(s)?” And, interestingly, if one has performed the most exact calculation, with the least number of approximations, one often has to go back to “poorer” descriptions if one wants to provide understanding. One has to identify effects, to do an order of magnitude estimate of them, so as to quantify their relative importance in determining the property, and establish a relevant structure-property relation based on their contributing effects, cooperative or antagonistic.

A reviewer of our paper has aptly commented:

I think what impresses theoretical chemists and all chemists is the ability of our “understanding” to be predictive both in qualitative terms, e.g., getting the energy ordering of SiH_n clusters right, and in quantitative terms, e.g., getting the energies themselves right. This is a very utilitarian point of view, but this is “Chemistry” to most practicing chemists.

Both of us have had the good fortune to taste the special flavor of theory–experiment interaction: We have in mind asking the experimentalist to perform a different experiment in order to control an interpretation, or (paradise) suggesting to him/her the synthesis of a realistic new molecule for which we expect some special behavior. There is nothing more satisfying than the iteration of such interactions.

The iteration we describe is a wonderful part of our life, and what really draws young people into what we do, as they observe the family life of an active research group. They hear, as we do in our ears, the daily dialog of a theoretician (Nathalie Guihéry) with her coordination chemist experimentalist partner (Talal Mallah), in search of architectures for molecular qubits with demanding properties regarding magnetic anisotropy, decoherence lifetime. It’s an animated, persistent discussion, full of tentatives, suggestions of numer-

ical tests, consideration of chemical accessibility or expected stability. The cooperative character of the interaction is hardly a rational step by step process, with questions and answers. It becomes a joint fight. And a clear argument for reality turning the single arrows of Figure 2, Part 1 into bidirectional ones in Figure 1 of this essay.

A final comment, actually an apology. We have failed to give experiment its true place in the process of forming understanding. The epistemological questions—how do we move from signals to measurements, what truth-value shall we assign to the observables observed—they have been thought about for millennia. More recently, philosophers of science have described, with examples from various sciences, how understanding is shaped by the nature of the experiments performed, by the laboratory equipment, by the observations.^[3] We have not done justice to this extensive literature, which returns experiment to its central, ideating, role.

C2. Neither Theorists nor Experimentalists Want This

The perfect simulation ends the fun

One further reflection on the experiment-theory/simulation tension. The chemist desires as accurate as possible an answer to his or her questions. Or do they? Have they thought through the consequences of the omnipotent and infallible program? That simulator to end all simulators, the infallible oracle, would, of course, make the experimentalist simply and utterly unimportant. It is not in the nature of human beings to want to be made redundant. This is why the published computer programs for guiding organic syntheses are often exemplified by showing their power in besting the syntheses of other people, or reproducing an already accomplished earlier synthesis by the author.

Of course, one wants one’s life made easier. One wants a million combinations of functional groups or possible cathode materials for a battery tested, not just the handful your graduate student man- and womanpower allows. The realistic expectation is of 1. help, and 2. reliable numbers for observables that are difficult, if not impossible, to measure. But one wants human ingenuity reserved for human beings.

We return to the thread of our convoluted argument. Simulations proceed through models, as much as they may claim to be ab initio or first principles. These simulations then lead to numerical predictions of observables. Which are desired by experimenters, but may or may not be viewed as providing understanding and meaning. The experimentalists also want understanding, a theoretical, teachable and learnable tool in their hands. Under pressure in their scientific community, (chemistry or physics, say) simulators will provide explanations, whether they actually emerge from their calculations or are just sketched for the purpose.

We mentioned satisfaction in the merger of theory, experiment and numerical simulation, all in the service of understanding. We want to share with you that joy.

C3. The Joy of Understanding

Fundamentally emotional. But also a close tie to teaching.

The joy of understanding is one of the great emotional experiences of our life. In saying this, we do not belittle other pleasures—that of a child holding up a flower to a grandmother's face, that of having walked five days in a corner of Catalunya. And pleasure is so individual; it is in the nature of human beings to find pleasure in whatever they do, no matter if other people might belittle an activity or a job. But the mind opening up—now that is a rare joy!

We can see it in our students' faces. This is one of the great satisfactions of teaching—not that we have given the student a fact, be it the new way of making a C–C bond, or that Bessel functions are the solutions of Laplace's equation in cylindrical coordinates. It is the light that goes on in the student's eye, reinforced by the motions of facial muscles that only Leonardo could catch in his etchings, that signals that the student has been empowered. That he or she have understood, using their own mental facilities, the road to the solution to their problem, be it small or large. The teacher is not fact-giver, the teacher is the enabler.^[4]

Understanding is teaching oneself. Then teaching others, to teach oneself in greater depth. We enter a problem with a tentative explanation, and then play with it, and with other explanations. We settle tentatively on one, write it down or voice it, and then enter the context of justification, marshaling arguments pro and con. Others enter—listeners, doubters, enrichers. If we face a contradiction, we go with it, see if that contradiction can be explained, or if it must lead to serious revision. In the end, for us, just as it is for the fortunate student, there is illumination. The explanation dawns.

Note the light metaphors in our language here. For Strevens, whom we've cited earlier, the metaphor is tactile, grasping.

Here are two short stories from our experience, stories detailing the construction of this joy in theoretical chemistry. But—and this may surprise you—these stories also made an important point to both of us: they would not be possible without a definite place for simulation and numbers. And this will give us a hint of the structure of the theoretical world we would like to inhabit.

C4. What Gave JPM Pleasure?

Real Space Renormalization Group and Effective Interaction Theory made easy

Jean-Paul's joy, told in first-person below, is aesthetic. To have you join in it, we need relate it in the language of our field:^[*]

[*] We highlight in grey those sections throughout this paper which use more than the normal dose of quantum chemistry jargon. We need the technical language, we feel, but we are painfully aware of the barrier to understanding that technical jargon may create.

One sometimes encounters a wonderful idea coming from a bright spirit. In my case it would be the Real Space Renormalization Group (RSRG) of K. Wilson,^[5] here described as simply as possible. Consider an antiferromagnetic spin lattice, for instance a 1D chain of $1/2$ spins. On each site you have either a spin up or a spin down. Instead of considering the single sites, consider a triad of adjacent sites as a new unit. Remembering the preference for spin alternation in antiferromagnetic lattices, the ground state of this triad is a doublet, of either spin up or spin down.

Next, neglect the excited states of the triad (another doublet and a quartet) and reduce the Hilbert space used to describe the chain to products of the doublet ground states of the triads. The problem is then isomorphic to the original problem; it now appears as an anti-ferromagnetically coupled chain of “meta-spins $1/2$ ”. The interaction between these meta-spins is different from the interaction between the elementary spins, and you may calculate it in detail by considering the dimer of these *meta*-spins and the interaction between the products of the triad ground states.

Then as a next step you may consider triads of triads, which have again a doublet ground state. Thus meta-meta spins. You enter into an iterative process, in which each iteration entails a scale change. The problem keeps an invariant structure, but the amplitudes of the interactions decrease and may tend to vanish or go to an asymptotic value. Yet some properties will emerge as asymptotic fixed points. Of course one might change the triads to pentads or heptads (i.e. larger meta-spins) and get better approximations. As anyone, once I grasped the idea, I was fascinated by the beauty of this representation.

In my theoretical background, the effective Hamiltonian theory took an important place, thanks to my interaction with Philippe Durand. This theory was formulated in the early days of Quantum Theory in a perturbative approach, the Quasi-Degenerate Perturbation Theory. It was more generally formalized around 1960 by two French nuclear physicists, Bloch and des Cloizeaux.^[6] Notice here the calling on a concept elaborated in a very distant discipline, high energy physics, to study a typically low-energy problem, spin ordering in materials. I learnt from their papers that one may reduce the degrees of freedom of a complex problem (or the size of the Hilbert space) in a very efficient manner, by transforming the original Hamiltonian, operative in the large Hilbert space, into an effective Hamiltonian, working in the truncated one. This could be done provided that the interactions are changed or “dressed” as effective interactions. Knowing a few exact solutions (exact energies and exact

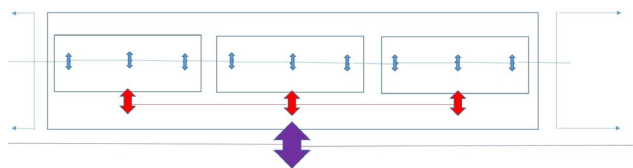


Figure 2. Scale changes in RSRG, starting from 3-site blocks, going to 3-block meta-blocks, and so on.

eigenvectors) of the original Hamiltonian defines in a unique manner the effective interactions.

So my (at that time young) colleague Nathalie Guihéry and I had the idea to use the effective Hamiltonian Theory inside the RSRG scheme. We might have used it in the Hückel framework itself. We might have considered a triad of adjacent sites as a unit and calculated the effective interaction between these meta-sites. But the exact solutions of Hückel Hamiltonians for periodic lattices are available, and so we concentrated on spin systems. Instead of considering simply the bare interaction between the ground state functions of the triads, we could exploit the exact energies of the six-site problem (easily computed) to define an improved value of the interaction between the 3-site meta-spins. And this definition of effective interactions is applicable all along the iterative scale-change process.

We had married the RSRG's beautiful structure with the computationally efficient Effective Hamiltonian Theory, calling this tool RSRG-EI (for effective interaction).^[7] Very accurate values for the periodic lattice could be attained, and we could exploit it to study beautiful phase transitions in spin lattices. For instance, if one introduces interactions between second-neighbors, a phase transition appears at a given ratio between first neighbor and second neighbor interactions. One may then, for instance, follow the (dis)appearance of the spin-gap as local interactions change.

Important for where we are heading—a conciliation in the struggle between simulation and understanding—is that detailed calculations were done. Extrapolated DMRG (Density Matrix Renormalization Group) calculations numerically confirm the predictions. Without those calculations we would have no idea whether the scaling procedure was effective. We needed the simulation. With it in hand, we could not only be assured that the approach was physically meaningful, but we could also go on to extend the theory to what at first seem wildly different problems. These, of ribbons of organic π -delocalized molecules, are amenable to a similar approach, with interesting physical results.

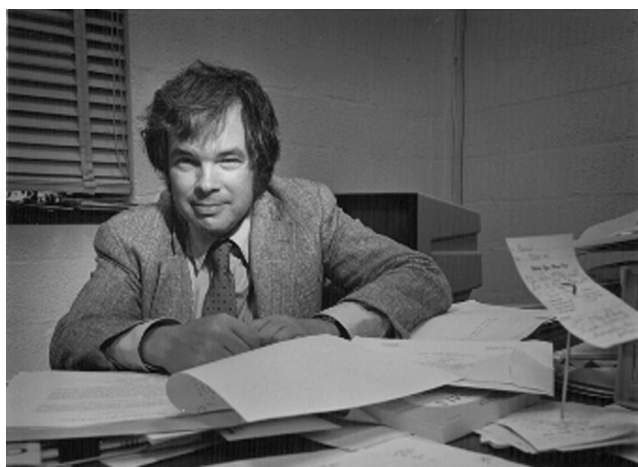


Figure 3. Kenneth G. Wilson. Reproduced by permission from “Kenneth G. Wilson: Renormalized After-Dinner Anecdotes”: P. Ginsparg, *J. Stat. Phys.* **2014**, *157*, 610–624.

Where is the joy there? Not one, but many: The first joy is in understanding something not understood before, an interpretative tool coming from a different field, which you can transfer to your own domain. The second joy is the rational sophistication of this interpretative tool (calling on logical knowledge from a totally different domain), and its possible improvement as an efficient computational method. The third joy is to reach general predictions from this philosophy of mapping a complex graph into a simpler one. Detailed simulations enter, inevitably serving to check, validate, and extend the calculations. We experienced no gap, no disjunction between theory and simulation. The fourth joy, was having contemplated, and used, a theory of intrinsic beauty.

What fun this was!

C5. What Gave RH Pleasure?

Lone pair interactions, through space and through bonds

Early on in my career, in the brief three years when extended Hückel calculations could be called state-of-the-art, I computed the orbitals of pyridine and the three diazines. At that time, the delocalization of the MOs was by itself a publishable result.^[8] For the 1,4-diazabenzene, pyrazine [Figure 4], two molecular orbitals mainly localized on N, were seen. Two striking things about these N-lone pairs, for that is what they roughly looked like, emerged: they were split in energy by several eV, and the antisymmetric combination of the two was lower in energy.

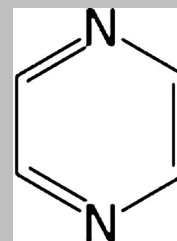


Figure 4. Pyrazine.

Both facts provided some numerical satisfaction in comparison with experimental reality, as they explained some hitherto known but not understood spectroscopy of pyrazine. In time, when those experiments became available, Edgar Heilbronner's measurements of the photoelectron spectra of pyrazine confirmed the “anomalous” order of the orbitals. The result remained on the face of it puzzling—if the lone pairs were localized, they should not overlap much directly, and to the extent they did, the symmetric combination (the bonding one) should be at slightly lower energy.

We came up with an explanation, involving the symmetry-conditioned overlap/interaction of the lone pairs with the uniquely disposed CC σ bond (and its σ^* counterpart) between them, as shown in Figure 5.

The explanation was not only pretty, it could be extended to other molecules (the benzynes, for instance; also to other heterocycles, such as 1,4-diazabicyclo[2.2.2]octane). In time the phenomenon entered general knowledge in the organic community. And provided a way of thinking about orbital interactions in general—through-space and through-bond.^[9]

It was satisfying to have the numbers, to explain the spectra. It was much more satisfying, a joy indeed, to come up with the explanation. And had the initial computational result (the splitting of the energies of the lone-pair combinations)

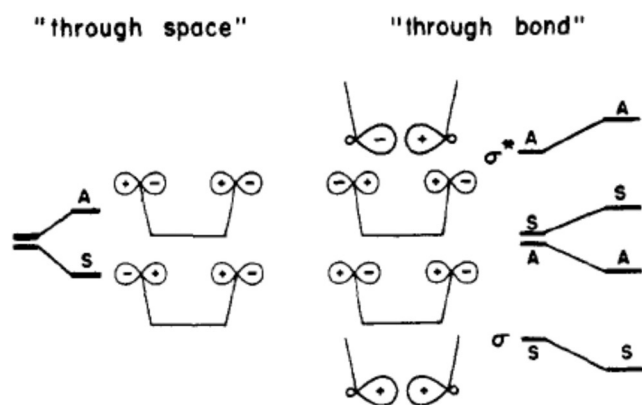


Figure 5. Interaction of two orbitals separated by three σ bonds. At left the two orbitals might be interacting via a direct, “through-space” overlap. S and A stand for symmetric or antisymmetric combination of lone pairs with respect to a mirror plane interchanging the orbitals. At right the S and A p orbital combinations interact in a predictable way (the orbitals involved “repel” each other) with σ and σ^* orbitals of the localized bond of the central bond. The net result is an A below S splitting of the middle orbital set.

been an artifact of the computational method, then this “explanation” would have joined the junkpile of wrong theories. The numbers, and that they were reliable, were essential. But one did not, must not, stop with the numbers.

C6. Subjective

Asking the reader to reflect on what science means to him or her

The wave is not about to break, it has broken over us. Of course, we will survive—not only Roald and Jean-Paul, but all of Chemistry and Physics. The reason for giving personal examples of joy in doing theory and computations is not narcissistic. It was to spur self-examination.

We now turn directly to you. What is your specific, personal experience in doing science? We produce knowledge or technical papers, for sure. And we get paid for doing this (some think too little.) We advance, in the ways each profession defines. All these are aspects of working—the labor of science; they are essential, something to be proud of. And they may constrain our satisfaction. We would ask the reader to reflect less on the professional, and more on the emotional or spiritual experience of what they do.

What importance would you attribute to the

- the utility of what you do, judged by alleviation of pain, improvement of some aspect of people’s standard of living?
- to the advancement of some social need, or empowerment?
- profit to you personally, or your family? Or social recognition, within your profession, locally and globally?
- simple curiosity about the world?
- increase of knowledge that comes from your work?
- search for mastery, the feeling of strength in us that ensues?
- destroying an erroneous explanation?
- joy of understanding?
- pleasure of telling people of what is discovered?
- aesthetic satisfaction, to oneself, and to others?

Of course, more than one feeling, and some we may not have mentioned, may matter to all of us. These incentives are often overlooked, implicit, kept quiet about in the course of normal scientific activity. Most are clearly subjective, but then that’s in part what we are after—what motivates scientists? We are in the realm of psychology, of the principles that guide us, of sociology. There are diverse ways to look at the spurs for human action. With all the problems of the Social Construction of Science (SCS) movement’s analysis,^[10] it has served us in focusing on questions of why we do what we do in science. So did Robert Merton’s wonderful insights, before SCS.^[11]

Consideration of the sources of satisfaction to real scientists doing real science steps outside of the aura of neutrality cultivated by science for more than two centuries. We address the subjective rationales because eventually we want to take you further than the confrontation of simulation and understanding that has preoccupied us. We aim to build up to the desired features of a world in which both intertwine in the search for reliable knowledge. In that world is also an important space for emotions, for Art, and... for the spiritual in the practice of science—yes, in the same breath as we think about dressing an effective Hamiltonian. We respectfully ask the reader to pause and reflect with us, for your reflections will help you to follow that path.

We do not hesitate to tell you how we feel: of course, we are motivated at times, and in part, by rather trivial quests—for recognition of our research, the comfort of a stable position, a sense of rivalry, and the pleasure of mastery. But we also consider ourselves as “seekers of knowledge” (this is not meant to sound pretentious, or fancier than what day-by-day we do). Or, perhaps, “servants of knowledge.” We bring our little tributes to the immaterial, delocalized and moving temple of knowledge. And we do not feel guilty if these tributes do not have a practical consequence, or if they do not realize an increase of mastery or a resolution of some of the many pressing problems of energy or health. It suffices for us if our tributes of incremental or substantial increase of understanding simply shine, excite, stimulate others; if they be stimulating, paradoxical, or elegant.

We know, we know that we are privileged, living in luxury in the temple of knowledge.

In our secular way, we think we may take advantage of the cleric’s function that society assigned to us till yesterday (and whose echoes you see in TV ads of people hawking medications and car insurance in the white robes of the pharmacist and priest.) You probably think that it makes no sense for the atheists that we are to use such language, that we have gone soft in the head to talk of scientists as clerics. We say “cleric,” since at one time the monopoly of knowledge lay with mediators—priests, rabbis, the enlightened. Knowledge was sacred. We know that understanding is in fact available to all. And yet remains sacred. We want to recapture the connection of science to the spiritual, to the sacred. And will in time return to this quest.

The reason we want to shift the discussion to the subjective, and ask you to engage in this introspective exercise, is that we believe that it is essential that we leave the material aspects of what moves us, and also shelve ideological pronouncements of what science should be like.

Thinking about our utility to society, but also about the wonders of understanding we can attain, are both part of being human. They are both part of forming the moral compass of educated men or women in society. Being curious, and rational, and reflective, and feeling awe, are defining human characteristics.

The dominant utilitarianism of our society asks us to reduce the justification of the chemist's task to the first of the above list, the use of what we do. And to exclude in the labor the expression of the emotional satisfaction of an intellectual quest and joy. What do you think?

C7. Looking for Pointers to a Future

In our own work—more than coexistence, a dance between theory and simulation

We are hardly intransigent in our opposition to simulation, maligning its practitioners as joyless purveyors of black boxes. Aware of its dangers and excesses, for society, for our science, we nevertheless recognize the essential role of computation and simulation in our science. We have pointed out earlier how the needs of experimentalists naturally push theorists to provide reliable and precise numbers for experiment. And a careful reading of our two stories of joy in explanation show that in each, numerical simulation, quantum-chemical in nature, played an important role for two theoretical chemists. Yes, with calculations/numbers/simulation critically embedded in stories of explanations/theory/understanding.

We want to point the way to more than coexistence, to a future where good theorists partake of both, simulating and understanding. Once again, we return to our own work, with two examples that show how a theoretician might move, specifically how the two of us were naturally impelled to move from explanation to simulation. And then used the simulations to craft explanations. We were dancing.

These examples are small things, and are not meant as self-praise. And... they are perforce technical, so we beg the reader's indulgence again.

C8. Jean-Paul's Story: Back to Simplicity, But Only Through Complex Computations

Getting right the interaction of two copper radicals

Let us take an a priori simple problem, namely two weakly interacting electrons in remote orbitals. Simple, but central to both organic and inorganic chemistry, where this construct figures in describing organic diradicals^[12,13] and dinuclear transition metal complexes.^[14–16] And, of course, the problem is a prototype of realizations of magnetism in extended systems.

One *modelization* is simple, one can call it a valence bond (VB, really Orthogonal VB) one. There are 6 ways to distribute 2 electrons in 2 boxes (the “magnetic orbitals”): the two electrons generate three singlet states and a triplet

state. The six microstates can be viewed as four if we count the components of the triplet as a single state. We will use here the notation familiar to the inorganic/solid state community, with full awareness of a slightly different parallel nomenclature for the diradical problem for organic diradicals—both of the authors have worked in both fields. In the two “covalent” VB configurations the boxes are singly occupied, their interaction is a direct exchange, favoring energetically the triplet state. In the “ionic” components, two electrons are in the same box, while the other box is empty. For the singlet ionic VB components, interaction (configuration interaction) between them stabilizes the lower singlet state.

These two leading interactions were identified a long time ago,^[17] and enable us to *understand* some structural effects on the magnetic preference of diradicals. At this stage an initial variational *computation* defines the best magnetic orbitals and the optimal mixing between neutral and ionic components in the wave function. Since the two physical effects contend (in the sense of one favoring a triplet, the other a singlet ground state for the system) precise evaluation of their competition is welcome.

If you perform a *computation* (second turn to the computer) in this very limited space, you get (in the inorganic case at least, for two Cu^{II} centers) an extremely discouraging result, usually from 10 to 20% of the *experimental* energy difference. Important effects await discovery; they are beyond this limited space. Almost exact energies, agreeing with experiment, can in principle be obtained from Full Configuration Interaction (CI) computations, which are impossible in most of the systems of chemical interest. And provide no understanding.

Even if this computation would be feasible, it would feel like using a hammer to kill a fly. And teaching us nothing about the art of killing flies.^[18] Quantum mechanical *theory*, in the sense this word is meaningful, must do better. The natural language for stripping away and restoring contributions is perturbation theory, identifying possible effects, important ones, beyond the two-electrons in two-boxes model.

If you implement such an analytic perturbative expansion to understand the role of the other electrons, and of the other orbitals in setting the energy difference, you find that, to the lowest order of perturbation, it is sufficient to play with just two degrees of freedom in the set of the inactive (non-

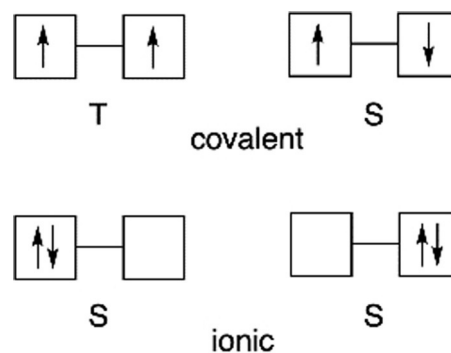


Figure 6. Covalent (a triplet (T) and a singlet (S)) and ionic (two singlets) fundamental electron configurations for a diradical.

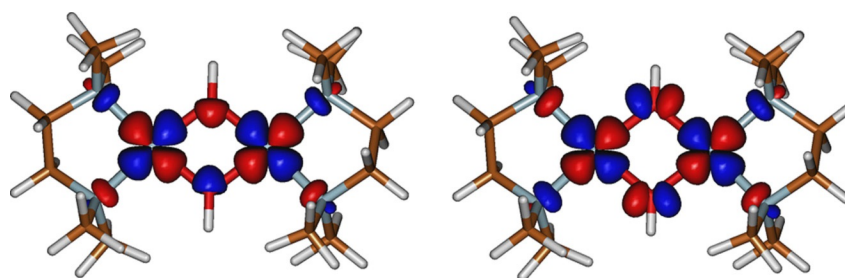


Figure 7. Symmetry-adapted magnetic orbitals for the Cu^{II} dimer, $\text{Cu}_2(\text{OH})_2\text{AFF}$. Reproduced by permission from J. P. Malrieu, R. Caballol, C. J. Calzado, C de Graaf, N. Guihéry, *Chem. Rev.* **2014**, *114*, 429–492.

magnetic) orbitals. Then turn to the *computer* (for the third time) and perform a Configuration Interaction calculation on this set of determinants. You get about $2/3$ of the *experimental* value. With a certain amount of human effort (appreciated by anyone staring at output with numbing lists of CI coefficients) expended to *understand* and analyze our wave function, we identified two major contributions, namely the spin polarization of the inner electrons, which are sensitive to the spin-dependent field of the magnetic electrons, and a “dynamic charge polarization” contribution, which stabilizes the effective energy of the ionic VB components. The physics underlying this effect is that the electric field created by the magnetic electrons is no longer the mean field when they enter a ionic component of the wavefunction; the other electrons react to the fluctuation of the field.

Whew! Was it worth it? Of course it was—we learned some physics, with real chemical consequences. Our resolution was not just a “one-off” result, but a way of thinking that could be applied to (many) other diradical and other electronic structure problems: The basic 2-electron in 2-box model remains valid provided that I change the value of the direct exchange under the effect of the spin polarization and the effective energy of the ionic VB components.

Up to now, no surprise, quantitative changes. But what is the origin of the lacking one third of the experimental value? In coding the dedicated CI for this problem, we added other classes of determinants, involving three inactive orbitals, which, from our naïve theoretical approach, should not contribute to the observable. But their introduction in the *computation* (fourth recourse to elaborate calculation) recovers almost perfectly the lacking third of the experimental value. *Computational experiment*, people may say. Pragmatic as you may be, you are satisfied with this success and sell your “Difference Dedicated CI” as a wonderful tool. And people buy this treatment as standard, implement it in their powerful codes: the numbers are reliable, this suffices.

No, a human being can do better, at what humans are good at (which is not the CI; for that one needed computers). In order to speed up the code I thought I could treat the most numerous (3 degrees of freedom) configurations perturbatively. Fiasco, their *computed* 2nd order effect on the energy was indeed negligible! How did those configurations have an impact? Then we realized that we had identified earlier an unexpected result from our *computations*, huge (relatively) coefficients of some determinants representing ligand-to-metal or metal-to-ligand charge transfers. According to the

original optimization of the orbitals (following Brillouin’s theorem), the low-order coefficient of these determinants should be zero. We identified the higher-order mechanism responsible for this increase, which again could be *understood* as a dynamic polarization effect, a response of the other electrons to the fluctuation of the electric field they feel when one electron jumps from the ligands to the magnetic orbitals or vice versa.

Again and again, along our itinerary, three partners—understanding, theory and computation—had to dialogue to match the experimental response, or to become predictive. This weaving of theory, computation and understanding, in constant confrontation with experiment, is schematized in Table 1, with an attendant chronology.

Over fifty years trying to understand!

One must ask the question that reaches beyond the number: What is the important physics which, when incorporated in this extended computation, gave a reliable number? What have I learned from this calculation that I can teach a younger student in our group? A careful analysis leads you to a revised, new representation of the problem: the boxes in which the two main partners of the game had been put, optimized by a sophisticated variational calculation, are not optimal, they are too localized, we underestimate the fluctuation of their size. Again, the “enlargement” (what we called “tailoring” above) of these main boxes may be interpreted as the necessary physical consequence of a dynamic polarization phenomenon. It’s a lesson to take away.

Table 1: Struggling to **compute** and **understand** magnetic coupling in diradicals.

Initial model : two electrons in two molecular orbitals	1967
Computation → 20% of experimental value	
Theoretical identification of missing effects in 2 nd order PT	1967
Computation → 70% of experiment	1986
Adding variationally another class of excitations	1995
Computation → experiment!	
Numerical surprise : an unexpected phenomenon, supposedly of no impact on observable; its theoretical rationalization	1999
Identification of strong 4th order contribution , providing	2001
Understanding of excessive localization of initial magnetic orbitals.	2003
Generalization : free radicals, bond localization in linear polyenes	2008
Computational and theoretical challenge: direct generation of optimal magnetic orbitals	underway

One of the wonderful things about science is that both mathematical techniques and models map across wildly different areas. They act out the role of metaphors in the arts and literature. Here we worried about diradicals. But suddenly one understands, for an apparently disparate problem, why the usual computations of linear polyenes overestimate their bond length alternation. They over-localize the electron pairs in the double bonds. The wave function incorporates some charge transfer from one double bond to the adjacent ones, but these charge transfer components create a fluctuation of the electric field, and if you do not introduce the dynamical response of the other electrons to this fluctuation, you inhibit it and force bond localization. Again you understand what to do, the necessary and (almost) sufficient conditions for your computation to be relevant to that seemingly totally different problem. There is comfort and joy in this.

Would young theoreticians today be given by their patrons the freedom to undertake the decades-long journey in search of understanding that JPM took?

One final point: This is Jean-Paul Malrieu's story, as synthesized in a recent review paper.^[16] It turns out that Roald once played a part in it, in a paper with Jeff Hay and Jack Thibeault which laid out the simplest ($2e^-/2MO$) model sketched above.^[19] That model, by being predictive regarding the influence of the structure (bond angles especially) on the sign and amplitude of the magnetic couplings, had some experimental impact. The funny thing is that Roald and his able collaborators worked at this time with semi-empirical Hamiltonians, which use appropriate values of the energy differences (U) between the neutral and ionic VB components, just the kind of values JPM and co-workers got after heavy ab-initio computation, and when they express their effect as a dressing of the U parameter. The basic *model*, the one used by RH and co-workers, is safe.

C9. Roald's Story: The Complex Structures of Compressed Alkali Metal Hydrides and Halides

And a suggested way to make sense of them

Roald's pointer toward a future where old-fashioned thinking and theory will coexist with data crunching and simulation is based only in part on his own work, but more directly on research close to his in the high pressure science of alkali metal compounds, drawn mainly from the work of the groups of Artem Oganov and Eva Zurek.

At atmospheric pressure there is nothing simpler than alkali metal ($M = \text{Li, Na, K, Rb, Cs}$) hydrides or halides ($X = \text{F, Cl, Br, I}$). The metal valence is 1, and the compounds expected are MH , MX . One can argue about the net charge on H , with all the ambiguity of what charge means, but that's not the matter of interest to us.

You can see how much fun the playground of high pressure is when I tell you that many other stoichiometries, not just 1:1, have been established theoretically for these elements, and in some cases experimentally, at pressures up to that existing at the center of the earth, $\approx 350 \text{ GPa}$ (≈ 3.5

million atmospheres). The experimental results, of course, do not come from a probe sunk into the earth (we know less directly about that region than we do about the surface of Titan!), they come from studies where matter is compressed between two diamond anvils, and examined spectroscopically.

A short list of the stoichiometries found at one or another pressure includes LiH_2 , LiH_6 , CsH_3 , Na_3Cl_2 , Na_2Cl , Na_3Cl , NaCl_3 , NaCl_7 .^[20–22] The compositions are weird to an introductory chemistry student, or, for that matter, to anyone. Yet Roald trusts them, even if they weren't predicted in his group. How they were found we discussed before—it was by using those structure-searching algorithms which beat our intuition all the time. These simulations in a world difficult to study, of a million atmospheres, are reliable calculations, we estimate. Some of the Na_xCl_y structures predicted are shown in Figure 8.

For a theoretical chemist, you can see also the fun, the enlarged vista of this $P > 1 \text{ atm}$ realm. Unexpected stoichiometries, essentially new compounds, are found not only for sodium chlorides, but appear in virtually all systems at sufficiently high pressures. What more could we also ask of the computer, besides finding the most stable structures (is there a $\text{K}_{17}\text{Cl}_{33}$ phase?), mapping out their transformations, computing if they are metallic?

Well, we could certainly ask for correlations in bonding (say electron densities, ELF—electron localization function, a measure of electron pair localization—maps) between different structures. We could ask for the activation barriers for concerted and nucleated transformations of one phase into another. And so probe metastable structures.

I think what we could ask only a human being is to come up with a framework for understanding the totality of structural types in this microcosm. Not which structures are stable or metastable, but what idea, or principle it is that connects all these structures to each other.

Let us try this, using just what we know of chemistry (only one bit of it esoteric). We begin of course at 1 atm, for our intuition will get us increasingly more into trouble at 100 GPa. And we will be totally out of intuition at the pressure in the interior of a neutron star ($\approx 10^{23} \text{ GPa}$). What the secondary school student knows is that is that the stable phases at 1 atm are ionic 1:1 ones— LiH , HF , LiF .

Suppose we want to have a way to think about NaCl_3 , I suggest we begin the thought construction by writing it as $(\text{Na}^+\text{Cl}^-)\text{Cl}_2$, an intimate mix, on the atomic/molecular scale, of chlorine molecules with ionic NaCl . No structure specified. Now we call in a chapter of inorganic chemistry that is pretty widely known, and this is the existence of the polyhalide ions, X_n^- .^[23] Most familiar among these are, for instance, F_3^- and I_3^- , symmetrical linear triatomic anions bound by electron-rich three-center bonding (Roald's group, among others, has analyzed the bonding in these compounds;^[24,25] the concept is due to Pimentel and Rundle). Thinking anthropomorphically, we imagine a chloride ion would bond to any Cl_2 diatomic molecule in its vicinity. And those are the component pieces of the structure of NaCl_3 , to a good approximation— Na^+ and linear trichloride ions.

There is another way in to think about what happens on the halogen-rich side of these compounds (or of hydrides).

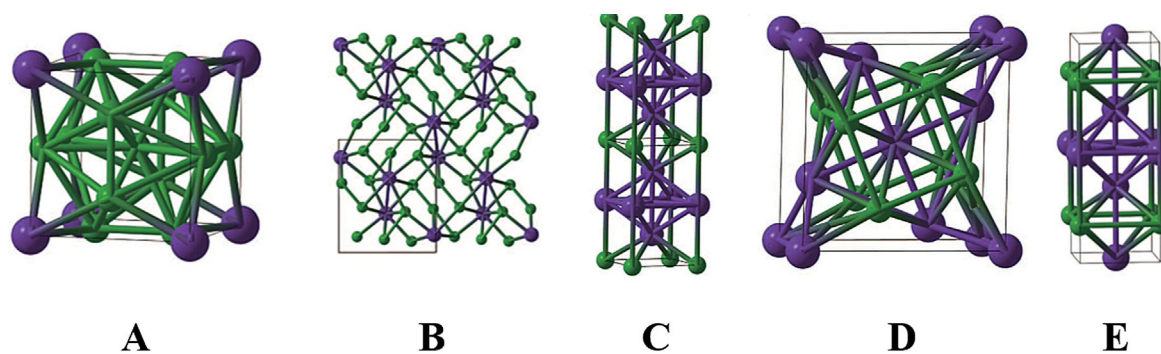


Figure 8. Crystal structures of a selection of sodium chlorides predicted to be stable at some elevated pressure: Purple and green spheres denote Na and Cl atoms, respectively. (A) $Pm\bar{3}$ -NaCl₇. (B) $Pnma$ -NaCl₅. (C) $P4/mmm$ -Na₃Cl. (D) $P4/m$ -Na₃Cl₂. (E) $P4/mmm$ -Na₂Cl.

NaCl₃ can be rewritten as Na₂Cl₆. Imagine the chlorines pair up initially as Cl₂ molecules, as any chlorines would at 1 atm. Na is electropositive, so it can (will) transfer its electron easily to diatomic chlorines, coming to (Na⁺)₂(Cl₂⁻)₂(Cl₂) or (Na⁺)₂(Cl₂)²⁻(Cl₂)₂. Cl₂⁻ is a known molecule, and it definitely has a weaker Cl–Cl bond than Cl₂. The dianion diatomic Cl₂²⁻ is unstable with respect to fragmentation in a nice Coulomb explosion. With either starting point we are into the chemistry of Cl⁻ with Cl₂, the polyhalides, which is where we began from another starting point.

These ways of thinking are not original to me, even as we have published approaches of this type to hydride and halide structures.

What if the compound found in the theoretical search were sodium-rich, say Na₇Cl? We would start again with the ionic bit, and then imagine a piece of metallic sodium wrapped around the ionic NaCl, that is, (Na⁺Cl⁻)Na_{x-1}. There is precedent for these at P = 1 atm, in Arndt Simon's graphically described "Swiss-cheese" metals, exemplified by Rb₉O₂.^[26]

It is important to recognize what we don't know, what we cannot claim. The analytical framework that we've just given (and that is much too fancy a name for simple thinking) does not allow us to predict whether NaCl₄ or Na₅Cl is a thermodynamically stable extended structure. That's a job for good computers, good programs. What we have given the community here is a way of thinking, a framework for understanding. Incidentally, not the only way. Not the way exoplanet intelligences will formulate it. And not a way that explains every structure, at least not yet.

We need both—the numerical simulation/detailed calculation, and the theory—to learn.

C10. Theory as an Adventure

The iterative, fecund entanglement between theory, computation and understanding

The examples just provided illustrate how understanding sometimes requires both formal analytic development starting from a simple entry in the problem (hence theory), adding step by step complex effects in a deductive mode, followed by

confrontation of theory with realistic, necessarily elaborate numerical calculations. Simplicity may be at the beginning of the story and at its end, even as the journey performs passes through complex, accurate numerical calculations.

Good theory never stops with one round of this process. One learns from the numbers, one improves the theory. The confrontation with good simulations, good experiment moves to another level. Eugene Wigner, one of the heroic figures of quantum mechanics and R. A. Hodgkin, in a necrology of Michael Polanyi, have the following apt description of good theory:

"He [Polanyi] knew that a theory, especially a novel one, is more than something to debate, to check and to share with others; it is what we explore with—an extension of ourselves and therefore neither totally impersonal nor infallible. In every exploration there is risk, of error or folly, of misunderstanding or neglect..."^[27]

Theory is a tool, theory is an adventure.

Note that the iterative process of the formation of understanding we have described above finally makes possible a translation of an explanation of an initially numerical finding into images or a verbal formulation of the physics at work. Storytelling and teaching enter. And mathematical formulas are hardly excluded in our narratives.

If a believable resolution emerges—what we call chemical or physical understanding—then we may transfer the diagnosis to completely different systems, and suggest the treatment required to obtain reliable results in the new systems. The joy of understanding is there, proportional to the difficulties we had to solve, and to the simplicity of the diagnosis we reach. Also to the good story we, human beings, construct around the facts.

Notice the stripping away of the numerical as we improve understanding.

C11. Strategies for Remaining Human

Towards the techne of searching for facts and the sophia of making sense of things

No one will mistake our position—we value understanding, and find it much richer, more pleasing to the mind, than

the extreme version of simulation that AI and IT proffer. We also mistrust the uses to which AI is being put, for moral and ethical reasons—as the New York Times article by Cliff Kuang on computers guessing sexual preference, or the use of facial recognition in China or Hong Kong make clear. We are entering an unknown region of space and time where we need to worry less about robots violating Asimov's first law of robotics^[28] than we have to be concerned about neural network programs with social authority, a kind of distributed intelligence that makes small but accumulating incremental decisions about human beings.

Aware of its dangers and excesses, for society, for our science, we nevertheless recognize the essential role of computation and simulation in our science. We have pointed out earlier how the needs of experimentalists naturally push theorists to provide reliable and precise numbers for experiment. We have tried to show in our own work how a turn to numbers was at some stage essential, natural, and enriching.

We think there is a new breed of theoretical chemist, theoretical physicist forming. It is a person who thinks and looks for frameworks of understanding. But here and there, with great ease, moves into the computer to get a number he or she could not get otherwise. That future and present chemist will also be playing computer games all the time. But not the games our companies addict kids to, but games of computer experiments, testing ideas. The division between simulation and understanding will seem irrelevant to such a person. May he or she be one of our students!

A second strategy for remaining human in the world of coexisting human beings and computers: Move up one meta-level, to the relationship of the structures to each other, and the context of chemistry to the bonding concepts involved. As you saw us do for the two structures of compressed SiH_4 or the Na_xCl_y alternatives. A computer can do the statistics of various more stable forms, spotting the common features in them. But it can't discuss the bonding on the level that we can teach it to a graduate student in chemistry or physics.

Actually, this brings us to the third special feature of human beings, closely connected to how understanding forms. This is often through teaching others. The teaching process is not just something professors are saddled with, as we've said before—it is a roadmap for gaining understanding. For both teacher and student, understanding is “activated”; both learn.^[29]

Explanations in chemistry may not have the power of mathematical laws of physics. But even if qualitative—take Hans Bethe's derivation of the crystal field splitting in an octahedral field, or the idea of organic substituents being π -donors or acceptors—their range of application is so much wider than any numerical exemplification. Students and teachers recognize this power of the qualitative, even when they see that it will take elaborate computation to get a definite number.

Ultimately, we seek E. O. Wilson's consilience,^[30] a position that reconciles the inherent value of understanding with the efficiency of simulation, for individual human beings, for society, for the world. In the preceding sections we've sketched two specific and personal examples of our approach

to this middle ground, that of coexistence. Let's go on to a view of the future.

C12. Speculating on the Future of Science

From a definition, to a role for fact-seekers and gnosticians

In the sections above we have joined with others concerned of the effects on society of the proliferation of AI. Ethics and Justice are human inventions as science is, and have served us, even if imperfectly, in regulating our social interactions. But the World-Wide Web runs ahead so much faster, for selfish personal and money-making reasons serving what is not good in us. The controlling mechanisms fall behind, even as they try to adjust.

What does the future hold specifically for science, which is already so much closer to the tools of the AI future?

We begin with a tentative definition of science: An incredibly successful, cross-culturally portable, social invention, mostly Western European in origin,^[31] science is an efficient enterprise for gaining reliable knowledge.^[32] At its heart is careful observation, by human beings and their instruments, skepticism about the accuracy and precision of those observations. We are naturally fallible in exercising that skepticism for our own work. Others will set us straight, which is why an open communication system is necessary for science to function. Intervention, invasive or not, is certainly part of scientific investigation. Reproducibility of theory and experiment figures importantly in the practice of sciences. Also important in any conception of science is thought, mental manipulation of ideas, and the search for causes following logical chains of implications. And the natural language associated with the latter is mathematics.

Science has served scientists, and it has served its masters. Technology provides little hiding room. Intervention shades over to mastery. And its corruptions. A passage in Genesis 1 authorizes that mastery, a passage in Genesis 2 provides an alternative, stewardship. With a helpmeet.^[33]

Notice our exclusion of Truth from the descriptors of science. This comes from a belief that science deals in representation of reality, and that these are conditioned by language and may be ephemeral. We certainly wish to approach truth. Realistically, we'll settle for reliable knowledge and partial understanding.

How to describe the changes wrought by machine learning, neural networks, and more generally by artificial intelligence, in the system of science? They will certainly be major, major. The “reliable knowledge” quality is certainly emphasized in the application of AI; that the value of the observable for a molecule outside the training set is correct becomes the sole criterion of quality, of the “goodness” on which one focuses. Observation, a time-honored fundament of science, almost doesn't seem to matter, though one could imagine programs that attach an estimate of kinetic persistence to the calculation of the stability of a molecule. There could be a place for reproducibility—for instance different climate model simulations resulting in similar temperature excursion predictions.

What disturbs us most is the effect that AI is making on thought and the explanatory process. What heretofore had been considered the jewel of human intelligence, Theory, is labelled as biased. We overreact, we know, but the hype of the AI community in theoretical chemistry, and in science more widely, amplified by journalism, is simply sky-high (Sections 4 and 7, Part B). So we fight.

At the same time, as our own scientific history shows, the two of us repeatedly use detailed calculations, if not machine learning, as part of our way of gaining reliable knowledge. More than just admitting that these AI practices will surely grow, we can even see how we could use them. So how shall we envisage the chemistry of the future?

In chemistry, one prospect is that one day no one will ask what happens if you substitute one atom for another in a molecule. One will just calculate it, by whatever means, with perfect reliability. So the properties (all of them) of all known and not yet synthesized molecules and extended solids will be predictable. If one wishes a specific property, one can search the catalogue of known molecules, and if none are found with the property desired, turn to other programs that focus the training on a property. The gardening of such programs (by this we mean tuning for the property, changing the criteria by which a molecule is indexed) will remain part of the profession of the future “theoretician”, if this term still applies to someone choosing a program in a catalogue...

We believe that there certainly will remain a role for theoreticians (of our, fossil kind) in that world. They will be moving one metalevel up, in search of a degree of understanding which is higher, maybe more abstract. The understanding which explores relationships and/or a deeper level. Roald made that level specific in his view of how to think about the many sodium chlorides at high pressure.

Are then all scientists going to become theoreticians, since robots will take over what graduate students and laboratory technicians do today?^[34] Their replacements will tolerate explosions better, for sure. And will the theoreticians of the future have access to the joy we so graphically described, will they be the philosopher kings of this utopian future? Sorry for the conceit, but no chance. The majority of theoreticians are likely to be like the computational chemists of our time, tending to the AI garden, perfecting it, applying its techniques to chemical problems, one by one. But the search for understanding will never be suppressed. We just cannot believe that there will come a day when “Why” is not asked.

We need some words to describe the metachemist and other theoreticians of the AI future. We believe science will morph; we will have seekers after fact (who might be satisfied with neural networks or purely phenomenologic tools) and seekers after understanding (who would demand the integration in theoretical or deductive representations). Let us for the moment call them fact-seekers and gnosticians (a neologism; apologies).

And whence will the latter come? It is not clear that computational chemistry, because of the mindset it encourages, is likely to beget many general thinkers about chemical bonding. That awful pessimism is countered by a contrary optimism—the belief that in any cohort of people enabled by computers to reliably calculate as widely as it can, there will

be some individuals intrigued by systematics. Or by playing games, to see if there could be some underlying order. Teaching at the highest level, responding to requests to review a subfield—both these actions encourage reflection. The sponsoring agencies of various countries are in a unique position to encourage people, with “carrot-and-stick strategies” to systematize and reflect.

The gnosticians will be synthesizers. The interaction of theory and simulation in their work will be described by words such as constant dialogue, interplay, entanglement. It will be hard work, as thinking is. And at times it will be joyful.

C13. A Second Anxiety

Hands and minds combined

It simply hurts to say that in the future it may no longer be necessary to make a compound, that it will suffice to calculate it. We are talking here about not only the manipulations of the chemical laboratory, but much more generally about craft, the work of human hands. Here is what Roald wrote after a stay at a traditional craft school in North Carolina, Penland:

“There is no question that the crafts are about hands and the senses, especially vision and touch. And sounds too—at Penland I loved the unexpected roar of the iron furnace,

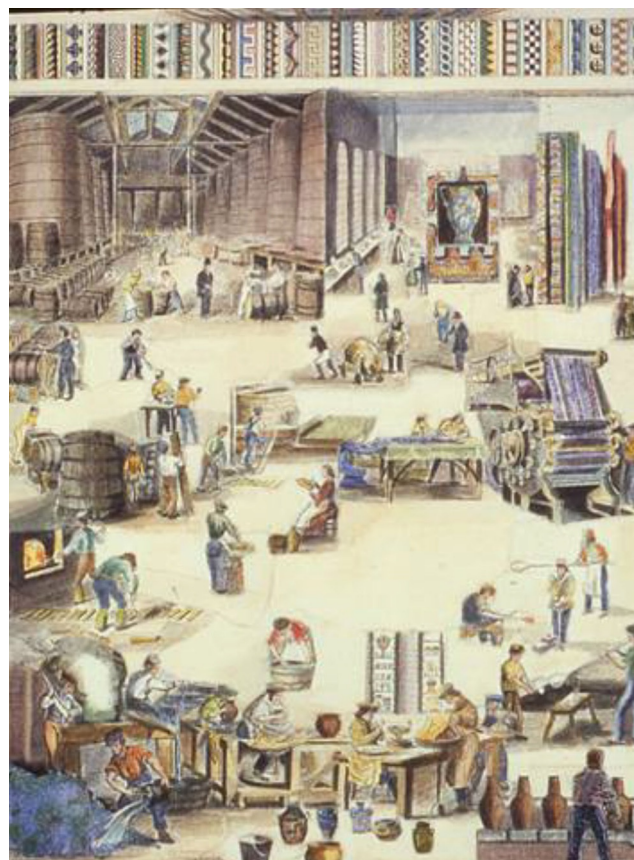


Figure 9. Collage by Vivian Torrence, “Chemical Arts,” from Roald Hoffmann and Vivian Torrence, *Chemistry Imagined*, Smithsonian Institution Press, Washington, 1993.

scissors snipping through paper, even the buzzsaw (at a distance). With a guiding mind, and yes, with tools and chemicals, a photograph is developed, printed, pasted into a book.

And science is about tools, and handwork too. Though the heroic figures of physics are by and large theoreticians (Fermi and Rutherford are the exceptions), the practice even of this quite mathematical science is largely experimental. The tools may be fancier, all those laser spectrometers. But on the “optical bench” are carefully mounted mirrors, machined vacuum chambers, and yes, even now, blown glass containers. All designed and made artifacts.

For the crafts and for science, this—that both thinking and doing are engaged and cooperating—is our finest link. The world is disintegrated—separating mind and body. We cater to the mind through a novel or a Bach Cello Suite on a CD. And to the body through the long sanding of the walls before painting, or those Nautilus machines. Craft and science, both, integrate mind and body.

Could one imagine making a bracelet, linked silver triangles with an inlaid braid, without planning it out, making a mold for the triangles (all different), hammering in the decoration? The synthesis of a molecule shaped like a necklace—yes, there are such—begins with a plan. Which has to be changed a few times as one moves along, for things do go wrong. But the molecule is also a macroscopic substance, a solid, crystalline, each crystal the blue of aquamarines in a real necklace. And being something real and substantive, this necklace-shaped molecule must be made. It happens, in a wondrous ballet of all the glass vessels you can conjure up, the sequences of heating, stirring, of bubblings, filterings, stinky solutions and mother liquors. It's a long day's night to make it, bracelet or molecule.

At the end, there's craftsmanship, the proud, cunning work of human hands and mind, joined in the service of creation.^[35]

But (Jean Paul making Roald more at peace) should we really feel anxious about the possible disappearance of hands and mind creating together? Two points can be made.

First, there is a craft-like aspect to the making of algorithms and programs. In the good old days, when the two of us still programmed, we worried about the memory requirements, and stored one matrix in one half of a diagonal matrix, in the other half another one. The emphasis has shifted, and frankly, we ancient ones may not know where the craftsmanship resides today. The feeling we have is that matters of concern are now closer to the heart of the computing enterprise, with people now worrying about the criteria for dynamically optimizing computing resources and the speed of numerical operations. Making a program versatile, giving it a good interface with infinitely variable users, is a real craft. The code-writers really have their hands in the computer, more than we had.

Second, material (and some mental) enhancement of the so laborious human tasks of gathering food, keeping clean, caring for children and the elderly, should liberate time. It has. That time could be dedicated to art and art/craft. Is it? The ingenuity that goes into designing addictive video games, and creating TV programs for just their entertainment value, that is amazing. But we also think that more people engage in

artistic and craft activities, from painting to poetry. Some might even listen to a chemistry course.

C14. Art and Chemistry

A strong tie, through synthesis and transformation.

The laboratory practice of chemistry will live, even if its scope be diminished as robotic sample processors replace the tedious part of what graduate students do. It is no more possible to think rationally of a world without laboratories than it is of a world free of one-star restaurants vying for the next star from the Michelin guide.

But things will change. We have already outlined one possible future—understanding sitting down at a computer to play a game of chemistry (a game exponentially more difficult than chess) with simulation. With a happier outcome than the game Max von Sydow played in Ingmar Bergman's movie.^[36] Here we wish to take another direction, and this is that in the age of AI, Theory will join hands with Art. We posit that theoretical chemistry, and beyond it all of theoretical science, will respond to its confrontation with AI by developing still further its aesthetic side, in camaraderie with its creative and utilitarian side.

First, let us underline a trivial but strong relation between Chemistry and Art. Chemistry invents the objects it will study.^[37,38] That's exactly what writers, composers, visual artists, working within their areas, working perhaps closer to the soul, do. Lest we get self-congratulatory, Jean-Marc Lévy-Leblond reminds us that “Practically every human activity brings into play creation: cooking, making clothes, gardening.^[39]” We believe that, in fact, this creative capacity is exceptionally strong in chemistry. Mathematicians also study the objects of their own creation, but those objects, not to take anything away from their uniqueness, are mental concepts rather than tangible structures. Some rapidly developing branches of physics and of engineering, the so-called materials sciences, are actually close to chemistry in this matter of synthesis. Perhaps this is a factor in the kinship the chemist-narrator feels for the builder Faussonne, who is the main character of Primo Levi's novel The Monkey's Wrench.^[40]

Chemistry's essential streak of creation moves from the original question addressed to Science: “Why is the world as it is?” to another question: “Shall we not add to the construction of the world?” Of course, in the process Chemistry contributes to the proliferation of objects and tools, characteristic of western modern civilization.

With that proliferation comes potential harm, to ourselves, to nature. Shall we list all the ways we have found to foul our nest? From the back doors of the companies whose ingenious products make our high standard of life possible, which heal and comfort, come also molecules that pollute and endanger. This gives rise to the tension of harm and benefit, the Janus-faced image of chemistry in our society.^[41]

We do not avoid the responsibility, and embrace strongly the ambivalent view of chemistry held by thinking and feeling people. If they think about it, that ambivalence is a kinship of

molecules and people—for that is exactly what human beings can be, good and evil. And every shade in-between.

To return to the design of molecules, Chemistry shares with Art this attention to not-yet-existing figures, forms which are as yet sleeping in the infinite space of the possible. As do the images in the artist's brain. This creativity may be either expressive (as in a Bacon painting) or ludic (as in the dozens of drawings appearing in Picasso's sketch books on the same day).

Quantum chemistry enters this game. For a potpourri of reasons, we love to design molecules not an earth before: Beyond providing answers to good questions raised by experimentalists, or natural extensions of previously established behaviors of matter, we imagine new architectures, perhaps with new properties. Also, as one of us has written:

“The consistent theoretical prediction of viable molecules with unusual structures or properties is the best test of the degree of understanding science has achieved.”^[42]

And thinking up new molecules gives us a stake in creation:

“Knowing is a pleasure in and of itself. So is creation. As is sharing that knowledge, and yes, being thought of well for what one does.”

The predictor leaves the safety of known molecules and properties for the unknown. He or she takes a risk. And, in a way, flirts-in a game of interest and synthesis-with the experimentalist. Predicting new molecules is simply great fun.^[42]

The creative aspect of human beings of course extends to new conceptual tools, flowers of the imagination of the theoretician. To stay within theory in chemistry and physics, think of the shining ingenuity of Feynman diagrams, the Coupled Cluster formalism, or the Real Space or Density Matrix Renormalization Group! In the world of representation, these are new, eminently useful tools for the intellect. This inventive, we would say visionary, side of our activity does not seem (at least now) accessible to AI machines—they can certainly predict a number or the stability of a proposed molecule, but it is the human being who defines the “interesting” characterization to a molecule, or attaches the “ingenious” label to a theory.

Our experience is that artists are especially attracted to a part of chemistry that gives many chemists trouble—alchemy. One should say that our view of alchemy is not that of most scientists, which we think has the following components, predicated on the view of alchemy as pseudoscience:

- 1) accept the chemistry the alchemists pioneered—they did make the strong mineral acids in medieval times;
- 2) Ignore the alchemist's hermetic philosophy;
- 3) Chuckle, a little nervously, at the charlatantry that inevitably accompanied the supposed making of gold.

But alchemy was much more.^[43] It was a philosophy of transformation that partook of the great myths that also powered religions—Persephone returning from the dead, Phoenix rising from the ashes, reincarnation, the Resurrection. And when Alchemy needed an emblem for transformation, what could serve better than chemistry? The philosophy was then coopted by chemistry.



Figure 10. Alchemists at work. The images are from a 1667 edition of the *Mutus Liber* in the ETH Library (C. G. Jung collection). See https://en.wikipedia.org/wiki/Mutus_Liber for the complicated story of the authorship of this book.

What has fascinated artists about alchemy, of course, has been transformation, essential change. As in the defining feature of chemistry—a chemical reaction. The mystical nature of the transformations elicits imagery till this day. And not only artists have been drawn by transformation to our science—one of C. G. Jung's important works is “Psychology and Alchemy,”^[44] which links his theories to the dreams of Wolfgang Pauli, and Jung's theory to alchemical transformations. Jung had a superb collection of alchemical volumes, which illustrate his text.

There is more: the persistent, obsessive search for transformation, in a cluttered laboratory, has a direct counterpart in the artist's studio. James Elkins, a historian of art with an unusually good scientific background, has traced this connection beautifully in his book “What Painting Is.” He argues that

“alchemy is the best language for talking about substances: thickness and weight and heft (they are all different), viscosity and stickiness and tackiness and goo (again all different), color and tint and hue and chroma and the “feel“ of color.”^[45]

C15. Science and Art on a Joint Trajectory

Effervescence, and why aliens will want to visit with us

With some difficulty we tear ourselves away from our enticing chemistry, and return to our eye on the future of simulation and understanding. To begin, let us quote from a startling interview with one of our wisest, E. O. Wilson, as he was asked to contemplate a meeting with an exoplanet civilization:

“What would an alien civilization like to know about this one?” Wilson said. “Not our science—we are juveniles to them. They would like to know very much about our culture. We’ve accumulated this immense mass of imagination and creativity in the creative arts. They would like to know what this is. This is our heritage, what makes us human.”^[46]

Wilson uses technology in his research as we do. He judges correctly that the imaginative power of art—be it in painting, or novels, or Ingmar Bergman’s films—is unique, unparalleled. Try every enhancer you are forbidden to use in the title of a paper, and it is appropriate here. Why? Because of the near-infinite density of signs (meant in a semiotic way; the minimal strokes with which Picasso captured the essence of a bull), blended with an intuitive way of eliciting emotional response. This how art works.^[47]

No, not every work of art, nor every artist all the time. You only have to go to the Barnes Foundation in Philadelphia to see how the greatest painter of young girls’ faces (Renoir) sometimes falls on his brush. And there are labourers in the fields, in science as well as art—routine investigation of the $(n + 1)$ th compound in a well-grazed-over field, or that next still-life, give us that impression. We should be less categorical; the routine is needed as the foundation of the exceptional. There is a reason for classical apprenticeships at the Écoles des Beaux-Arts or in postdoctoral positions. And there is a difference; art has come to be recognized as a legitimate aspiration for all, and an ideal (well, maybe not by the US government, hell-bent on abolishing any grants for artists). There has been a definite democratization of the production of art in society—we have come a long way from the Renaissance Church having a monopoly on talented imagery and architecture.

With emotional intelligence, part of it intuitive, part acquired through training, art always reached more directly the realm of the sacred than science. It has had more time, to be sure—perhaps 30,000 years have elapsed from the Chauvet cave paintings, 2,300 years from Euclid, the latter as convenient a marker for beginning science, pure and applied, as any. The path that science, experimental and theoretical, took necessarily led it along an initial path of desacralization. St. Elmo’s fire, and that 42° angle of the rainbow were explained. And if there were residual mysteries (for instance in the foundations of physics) they were conveniently buried. David Mermin’s shout “Shut up and calculate!” was good advice.^[48] When people once said “By the grace of God, it was given to me...”, that had to be replaced... by “Chance favors the prepared mind.”^[49] Note, parenthetically, how both formulations ultimately are selfish.

The sacred, the repository of higher feelings in humans, was flushed down the toilet in modern science, along with the dark stains of religion. But it’s not so easy to get rid of an essential part of yourself. So good scientists, finding ways to synthesize a molecule in the shape of a cube (Eaton and Cole),^[50] or (Onsager) finding a solution to the problem of the energy of a square lattice with spins on each lattice point,^[51] found themselves with an intuitive feeling of having witnessed something beautiful, something spiritual. The sacred surged up, ascending though the openings of that lattice.

Emile Durkheim had it right, in seeing the source of the sacred (in both religion and science) in what he called effervescence, a surge of emotional energy that an individual feels, often on participating in a ritual activity shared with others.

“A general effervescence results, characteristic of revolutionary and creative times. That excess activity has as its effect a general stimulation of individual energies. People live differently, and more intensely than in normal times.”^[52]

The joy in science we have labored to describe is that effervescence. To Durkheim rituals are re-creations in a commons of the mood and concentration of that sought-after high of effervescence.^[53] And while we think we don’t have rituals in science, what else are the acts of publishing and speaking in meetings in science?^[54]

Art, even if not sufficiently supported by modern equivalents of patronage, survives, of course. For its appeal to higher feelings in us is irresistible, inextinguishable. Art seems a valuable partner of Science; the truths sought by both complement and mesh with each other. But if theory were just predictive practice, if it were just a search for ultimate efficiency through obscure and powerful machineries, it would not stand a chance of “resacralization.” Throughout this essay, we plead for more for science—for, combining the quest for accuracy with understanding and elegance. Because we want to be in the company of the sacred, we want to not only know facts, not only to ameliorate the human condition. But also to touch people, as we have been touched. By understanding.

Science, through the great scientific revolutions, the emergence of new paradigms, already has the feeling of a great edifice of the mind. In one room hangs the Cassini mission image of the lakes of ethane on the surface of Titan. In another, the discovery of archaea. And of how their lipids differ from ours. In a third room we see Onsager’s solution of the two-dimensional Ising model, in a fourth room the synthesis of coenzyme-B₁₂. This is a sacred space, these are artistic and scientific achievements, of pervasive spiritual value.^[55]

And how will the value of these masterpieces in the hall of science be evaluated? Will you need to do an apprenticeship, become a chemist, to appreciate that B₁₂ synthesis? Perhaps. If so, we will help you, talk to you, explain our aesthetic criteria. It can be done, but to do so we must teach.

The theorist who can simulate nature reliably and who from that simulation has gained deeper theoretical understanding—that theorist has regained a piece of sacred ground. We think that the new synthesis of true theory and artificial

intelligence brings back the aesthetic element into science, and returns it to the desired company of Art.

Perhaps then those alien visitors will stop here for a while.

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Conflict of interest

The authors declare no conflict of interest.

- [1] The concept is that evidence of independent origin may converge on a strong conclusion. See <https://en.wikipedia.org/wiki/Consilience> for a history of the idea. The word was coined from “jumping together”; E. O. Wilson extended the idea in his important book, E. O. Wilson, *Consilience: The Unity of Knowledge*, Knopf, New York, **1998**, to a broader notion of the convergent aim of the sciences, humanities and arts.
- [2] For a discussion of where DFT functionals are taking us, see: “Density Functional Theory is Straying from the Path Toward the Exact Functional”: M. G. Medvedev, I. S. Bushmarinov, J. Sun, J. P. Perdew, K. A. Lyssenko, *Science* **2017**, *355*, 49–52; “Is the Accuracy of Density Functional Theory for Atomization Energies and Densities in Bonding Regions Correlated?”: K. R. Brorsen, Y. Yang, M. V. Pak, S. Hammes-Schiffer, *J. Phys. Chem. Lett.* **2017**, *8*, 2076; “Density Functional Theory: Not Quite the Right Answer for the Right Reasons”: M. Korth, *Angew. Chem. Int. Ed.* **2017**, *56*, 5396–5398; *Angew. Chem.* **2017**, *129*, 5482–5484.
- [3] A. Franklin, *The Neglect of Experiment*, Cambridge University Press, Cambridge, **1986**; P. Galison, *How Experiments End*, University of Chicago Press, Chicago, **1987**; “Theory Bound and Unbound: Superstrings and Experiments”: P. Galison, in *Laws of Nature: Essays on the Philosophic, Scientific, and Historical Dimensions*, Vol. 369–408, Walter de Gruyter, Berlin, New York, **1995**; I. Hacking, *Representing and Intervening*, Cambridge University Press, Cambridge, **1983**.
- [4] The theory of learning here goes back to St. Thomas Aquinas: “Thomas Aquinas: Theory of Knowledge and Learning”, S. J. Smith, From the Selected Works of Samuel J. Smith, B. E. Press, <https://works.bepress.com/samuel-smith/95/download/>. Or is it Aristotle? “The State, the Soul, Virtue and Potential: Aristotle on Education,” S. Millett, <https://www.encyclopedia.com/education/applied-and-social-sciences-magazines/state-soul-virtue-and-potential-aristotle-education>.
- [5] “The renormalization group: Critical phenomena and the Kondo problem”: K. G. Wilson, *Rev. Mod. Phys.* **1975**, *47*, 773.
- [6] “Sur la théorie des perturbations des états liés”: C. Bloch, *Nucl. Phys.* **1958**, *6*, 329; “Extension d’une formule de Lagrange a des problemes de valeurs propres”: J. des Cloizeaux, *Nucl. Phys.* **1960**, *20*, 321.
- [7] “Real space renormalization group with effective interactions”: J.-P. Malrieu, N. Guihéry, *Phys. Rev. B* **2001**, *63*, 085110.
- [8] “An Extended Hückel Theory. II. Sigma Orbitals in the Azines”: R. Hoffmann, *J. Chem. Phys.* **1964**, *40*, 2745.
- [9] “Benzynes, Dehydroconjugated Molecules and the Interaction of Orbitals Separated by a Number of Intervening Sigma Bonds”: R. Hoffmann, A. Imamura, W. J. Hehre, *J. Am. Chem. Soc.* **1968**, *90*, 1499.
- [10] <http://sociology.iresearchnet.com/sociology-of-science/social-construction-of-science/>.
- [11] R. K. Merton, *The Sociology of Science: Theoretical and Empirical Investigations*, University of Chicago Press, Chicago, **1979**.
- [12] “Diradicals—A Fifty Year Fascination”: W. T. Borden, in *The Foundations of Physical Organic Chemistry: Fifty Years of the James Flack Norris Award*, Chapter 11, pp. 251–303, **2015**, ACS Symposium Series, Vol. 1209; “Diradicals”: M. Abe, *Chem. Rev.* **2013**, *113*, 7011–7088.
- [13] “Do Diradicals Behave Like Radicals?”: T. Stuyver, B. Chen, T. Zeng, P. Geerlings, F. De Proft, R. Hoffmann, *Chem. Rev.* **2019**, *119*, 11291–11351.
- [14] J.-P. Launey, M. Verdaguer, *Electrons in Molecules*, Oxford University Press, Oxford, **2014**.
- [15] O. Kahn, *Molecular Magnetism*, VCH Publishers, Weinheim, **1993**.
- [16] “Magnetic Interactions in Molecules and Highly Correlated Materials: Physical Content, Analytical Derivation, and Rigorous Extraction of Magnetic Hamiltonians”: J. P. Malrieu, R. Caballol, C. J. Calzado, C. de Graaf, N. Guihéry, *Chem. Rev.* **2014**, *114*, 429–492.
- [17] “The Electronic Properties of Diradicals”: L. Salem, C. Rowland, *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 92–111; *Angew. Chem.* **1972**, *84*, 86–106.
- [18] See “The Brave Little Tailor” one of the original Grimm’s takes. https://en.wikipedia.org/wiki/The_Brave_Little_Tailor. There is no doubt a French and English variant.
- [19] “Orbital Interactions in Metal Dimer Complexes”: P. J. Hay, J. C. Thibeault, R. Hoffmann, *J. Am. Chem. Soc.* **1975**, *97*, 4884.
- [20] “Unexpected Stable Stoichiometries of Sodium Chlorides”: W. Zhang, A. R. Oganov, A. F. Goncharov, Q. Zhu, S. E. Boulfelfel, A. O. Lyakhov, E. Stavrou, M. Somayazulu, V. B. Prakapenka, Z. Konôpková, *Science* **2013**, *342*, 1502–1505.
- [21] “Alkali subhalides: high-pressure stability and interplay between metallic and ionic bonds”: G. Saleh, A. R. Oganov, *Phys. Chem. Chem. Phys.* **2016**, *18*, 2840.
- [22] “A Little bit of lithium does a lot for hydrogen”: E. Zurek, R. Hoffmann, N. W. Ashcroft, A. R. Oganov, A. O. Lyakhov, *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 17640–17643; “Pressure-Stabilized Sodium Polyhydrides: NaH_n (n > 1)”: P. Baettig, E. Zurek, *Phys. Rev. Lett.* **2011**, *106*, 237002; “Hydrides of the Alkali Metals and Alkaline Earth Metals Under Pressure”: E. Zurek, *Comments Inorg. Chem.* **2017**, *37*, 78–98.
- [23] “Recent Discoveries of Polyhalogen Anions—from Bromine to Fluorine”: H. Haller, S. Riedel, *Z. Anorg. Allg. Chem.* **2014**, *640*, 1281–1291.
- [24] “Bonding in the Trihalides (X₃), Mixed Trihalides (X₂Y), and Hydrogen Bihalides (X₂H). The Connection Between Hypervalent, Electron-Rich Three-Center, Donor-Acceptor, and Strong Hydrogen Bonding”: G. A. Landrum, N. Goldberg, R. Hoffmann, *J. Chem. Soc. Dalton Trans.* **1997**, 3605–3613.
- [25] “Electron-Rich Three-Center Bonding: The Role of s,p Interactions Across the p-Block”: M. L. Munzarová, R. Hoffmann, *J. Am. Chem. Soc.* **2002**, *124*, 4787–4795.
- [26] “Group 1 and 2 suboxides and subnitrides—Metals with atomic size holes and tunnels”: A. Simon, *Coord. Chem. Rev.* **1997**, *163*, 253–270.

- [27] “Michael Polanyi, 12 March 1891–22 February 1976”: E. F. Wigner, R. A. Hodgkin, *Biogr. Mem. Fellows R. Soc.* **1977**, 23, 413–448; quote is on p. 435.
- [28] I. Asimov, in his story “Runaround”, in “I, Robot,” New York, Doubleday, **1950**, p. 40.
- [29] From Seneca the Younger’s “*Homines dum docent discunt*” to modern times, this idea has been rediscovered and tested. See references in the Wikipedia pages on “Learning by Teaching,” https://en.wikipedia.org/wiki/Learning_by_teaching, and the Lancasterian system, https://en.wikipedia.org/wiki/Monitorial_System, and references within. See also “Reinforcing Math Knowledge by Immersing Students in a Simulated Learning-By-Teaching Experience”: *J. Artif. Intell. Educ.* **2014**, 24, 216–250.
- [30] E. O. Wilson, *Consilience: The Unity of Knowledge*, **1998**.
- [31] This statement is bound to get us into trouble, as the origins of modern science and the scientific way of thinking remain debated. Here we give two references to the sustainable claim of the necessary contribution of Arab learning: G. Saliba, *Islamic Science and the Making of the European Renaissance*, MIT Press, Cambridge, **2007**. And the remarkable technical and scientific development over millennia in China: J. Needham, *Science and Civilisation in China*, Cambridge University Press, Cambridge, **1954**.
- [32] The phrase is used after J. Ziman, *Reliable Knowledge*, Cambridge Univ. Press, Cambridge, **1978**.
- [33] See Chapter 1 in R. Hoffmann, S. Leibowitz Schmidt, *Old Wine, New Flasks: Reflections on Science and Jewish Tradition*, W. H. Freeman, New York, **1997**, pp. 1–54.
- [34] For a glimpse into what may be in the offing see “A Robotic Platform for Flow Synthesis of Organic Compounds Informed by AI Planning”: C. W. Coley, et al., *Science* **2019**, 365, eaax1566.
- [35] “Science and Crafts”: R. Hoffmann, in *The Nature of Craft and the Penland Experience* (Ed.: J. MacLaughlin), Lark Books, New York, **2004**, pp. 58–64.
- [36] “The Seventh Seal” (“Det Sjunde Inseglat”), film written and directed by Ingmar Bergman in 1957. Paul Kantor reminds us of another view—that even though the knight joins the dance of death, he distracts Death so that the young couple escapes.
- [37] M. Berthelot, *Chimie Organique Fondée sur la Synthèse*. Tome 2. Mallet-Bachelier, Paris, **1860**. See also J.-P. Malrieu, Le design, une pratique où la chimie a cent ans d’avance, *L’Actualité Chimique*. **1987**, No. 3, p. IX; *Alliage*, **1991**, 9, p. 59–64.
- [38] “In Praise of Synthesis”: R. Hoffmann, *Am. Sci.* **1991**, 79, 11–14; (in French) *Alliage*, **1991**, 9, 65–75.
- [39] J.-M. Lévy-Leblond, private communication, April 4, 2020. His original phrase is “Pratiquement toute activité humaine de valeur met en jeu la création: cuisine, couture, jardinage.”
- [40] Primo Levi, *The Monkey’s Wrench*, 1986. Simon & Schuster, published originally as *La Chiave a Stella*, **1978**. Giulio Einaudi editore s.p.a., Torino.
- [41] R. Hoffmann, *The Same and Not the Same*, Columbia University Press, New York, **1995**, Chapters 23–26, 41, 44.
- [42] “Why Think Up New Molecules?”: R. Hoffmann, *Am. Sci.* **2008**, 96, 372.
- [43] For contemporary views of alchemy, see L. M. Principe, *The Secrets of Alchemy*, Univ. of Chicago Press, Chicago, **2013**; W. R. Newman, *Atoms and Alchemy: Chymistry and the Experimental Origins of the Scientific Revolution*, University of Chicago Press, Chicago, **2006**.
- [44] C. G. Jung, *Psychology and Alchemy*, 2nd Edition, *Collected Works of C. G. Jung*, Routledge, London, **1980**.
- [45] J. Elkins, *What Painting Is: How to think about oil painting, using the language of alchemy*, Routledge, New York, **1999**.
- [46] E. O. Wilson, in an interview (WBUR; <http://www.wbur.org/hereandnow/2014/10/14/human-existence-wilson>) on his 2015 book “The Meaning of Human Existence”.
- [47] N. Goodman, *The Language of Art: An Approach to the Theory of Symbols*, Hackett, New York, **1976**.
- [48] The fuller quote is: “If I were forced to sum up in one sentence what the Copenhagen interpretation says to me, it would be ‘Shut up and calculate!’” in “What’s Wrong with this Pillow?”: N. D. Mermin, *Physics Today* **1989**, April 1989, <https://doi.org/10.1063/1.2810963>.
- [49] “... Savez-vous à quelle époque il vit le jour pour la première fois, ce télégraphe électrique, l’une des plus merveilleuses applications des sciences modernes ? C’était dans cette mémorable année 1822: Oersted, physicien suédois, tenait en mains un fil de cuivre, réuni par ses extrémités aux deux pôles d’une pile de Volta. Sur sa table se trouvait une aiguille aimantée placée sur son pivot, et il vit tout à coup (par hasard, direz-vous peut-être, mais souvenez-vous que dans les champs de l’observation le hasard ne favorise que les esprits préparés), il vit tout à coup l’aiguille se mouvoir et prendre une position très différente de celle que lui assigne le magnétisme terrestre. Un fil traversé par un courant électrique fait dévier de sa position une aiguille aimantée voilà, messieurs, la naissance du télégraphe actuel. ...” Extrait du discours prononcé par Louis Pasteur, à Douai, le 7 décembre 1854, à l’occasion de l’installation solennelle de la Faculté des lettres de Douai et de la Faculté des sciences de Lille (source: *œuvres complètes – textes recueillis par Louis Pasteur Vallery-Radot, tome VII*).
- [50] “The Cubane System”: P. Eaton, T. W. Cole, *J. Am. Chem. Soc.* **1964**, 86, 962; “Cubane”: P. Eaton, T. W. Cole, *J. Am. Chem. Soc.* **1964**, 86, 3157.
- [51] “Crystal Statistics. I. A Two-dimensional Model with an Order-Disorder Transition”: L. Onsager, *Phys. Rev.* **1944**, 65, 117–49.
- [52] “Il en résulte une effervescence générale, caractéristique des époques révolutionnaires ou créatrices. Or cette suractivité a pour effet une stimulation générale des forces individuelles. On vit plus et autrement qu’en temps normal.” E. Durkheim, *Les Formes Elementaires de la Vie Religieuse*, Quadrige, PUF, **1960/1998**, p. 301 For the dangerous side of such stimulation, see E. Canetti, *Crowds and Power*, Viking, New York, **1963**. Durkheim was well aware of the potential danger of such effervescence: “Les passions qui l’agitent sont d’une telle intensité qu’elles ne peuvent se satisfaire que par des actes violents, demesures : actes d’heroïsme surhumain ou de barbarie sanguinaire.” (also p. 301).
- [53] K. Allan, *Explorations in Classical Sociological Theory*, 3rd ed., Sage, Los Angeles, **2013**, Chap. 4.
- [54] For a further discussion of the intersection of the sacred and the profane in the context of chemical processes, see M. Eliade, *The Forge and the Crucible* (trans.: S. Corrin), Harper and Row, New York, **1962**; 2nd Ed. Univ of Chicago Press, Chicago, **1978**.
- [55] Adam Frank has written with feeling of science and the sacred: “Can Science Be Sacred”. https://www.huffingtonpost.com/adam-frank/can-science-be-sacred_b_1213082.html. See also his book A. Frank, *The Constant Fire: Beyond the Science vs. Religion Debate*, University of California Press, Berkeley, **2009**. Frank uses Mircea Eliade’s idea of a hierophany, an experience of sudden perception and penetration into a shared, yet singular human understanding which is the sacred.

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