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Quantum Chemistry

Simulation vs. Understanding: A Tension, in Quantum Chemistry and Beyond. Part B. The March of Simulation, for Better or Worse

Roald Hoffmann and Jean-Paul Malrieu**

Keywords: artificial intelligence · neural network · philosophy of science · quantum chemistry · simulation

Abstract: *In the second part of this Essay, we leave philosophy, and begin by describing Roald's being trashed by simulation. This leads us to a general sketch of artificial intelligence (AI), Searle's Chinese room, and Strevens' account of what a go-playing program knows. Back to our terrain—we ask "Quantum Chemistry, † ca. 2020?" Then we move to examples of Big Data, machine learning and neural networks in action, first in chemistry and then affecting social matters, trivial to scary. We argue that moral decisions are hardly to be left to a computer. And that posited causes, even if recognized as provisional, represent a much deeper level of understanding than correlations. At this point, we try to pull the reader up, giving voice to the opposing view of an optimistic, limitless future. But we don't do justice to that view—how could we, older mammals on the way to extinction that we are? We try. But then we return to fuss, questioning the ascetic dimension of scientists, their romance with black boxes. And argue for a science of many tongues.*

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In the first part of this paper we have set out in broad strokes the confrontation between understanding and simulation. An attempt was made to define the concepts we value—understanding, explanation, theory. The philosophical literature on these is old and vast; people have naturally thought about how they know what they know.

Theoretical chemistry's romance with numbers developed, in part because the solutions of Schrödinger's equation were perforce approximate. So computational chemistry grew, organically, so to speak. Because chemistry was and is primarily an experimental science, theoreticians in chemistry naturally had to interact with chemical experiment. We sketched how an abiding interest in reliable numbers in chemistry, call it numerism, prepared the way for the new wave of simulation.

That machine learning, neural networks would try to supplant the traditional role of theoretical chemistry and computational chemistry was not unexpected. The incursion of artificial intelligence (or at least simulation) into chemical theory was facilitated by the tremendous computer power developing in our rich society.

In one section in the first part of this Essay we tried to describe the techniques of simulation; in this we are likely to have been less successful than in writing about theory in chemistry. For here we are, for the most part, observers. In this part we will exemplify how the applications of artificial intelligence have spread to every aspect of human society, hardly only theoretical chemistry. And that this permeation carries not only opportunities, but real dangers, not well thought through, to the human condition.

AI's arrival on the stage of life was unavoidable, We will have to live with it—there is no going back. But reaching for more than survival, in the third part of this paper we will sketch the construction of a creative conjoined future.

Encounters with a new world are always personal. So we begin with a story of Roald's, one where he and his able coworkers matched wits with an early structure-searching program.

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 Pullmans' 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.

B1. Where Simulations Beat Chemical Intuition

Roald on SiH_4 structure searching

About fourteen years ago Roald entered the field of high pressure chemistry, drawn in by a then postdoctoral associate, Wojciech Grochala, who was brave enough to go over and talk to an outstanding physicist, Neil Ashcroft. We had been colleagues for 40 years prior, but had never collaborated. Well, we have made up for that, in a series of studies that bring chemistry and physics together in the solid state at pressures that approach those in the center of the earth.

Neil Ashcroft gave us good reasons for examining specifically SiH_4 at high pressure, so we began with that. Silane is a rotational solid at $P = 1$ atm, with only rudimentary knowledge of its crystal structure at ambient or high P available to us. We examined some 13 potential structures, four of which are shown in Figure 1.[1]

The first structure, T2 is just the unit cell of a crystal of silane with one molecule per unit cell. That's as primitive as one can get in the realm of chemical intuition—the discrete molecule exists, and there is a reason Si is under C in the Periodic Table. We also studied variants with more molecules in the unit cell. Structures O1, O2, O3 all contain six-coordinate silicon. Trying these represents a deeper kind of chemical intuition—six-coordination is, of course, tough for carbon. But we know six-coordinate silicon compounds exist (as in the rather common SiF_6^{2-} anion). Structure O2 is the actual structure not of SiH_4 but of SnF_4—more of what chemists call the iso-valence-electronic analogy at work.

It should be clear by now what Roald meant by "chemical intuition" in choosing structures. He had in mind Mendeleyev and Meyer's Periodic Table of course. But not as a prescription for identity (silicon is like carbon), but for its true heuristic value, one that has allowed it, the Table of Tables, to serve us for >150 years. The Periodic Table is a graphic

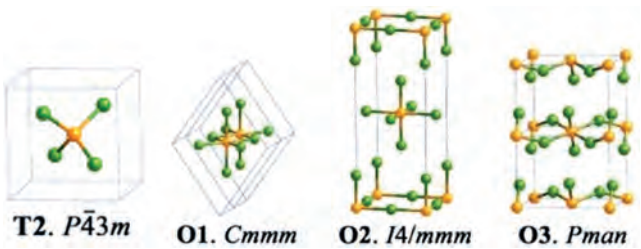

Figure 1. Four chemically-inspired potential structures for SiH_4.

depiction of both similarity and difference; silicon is in many ways not like carbon, even if in other ways it is. Pauling's great concept of electronegativity also enters into our makeup of a chemical intuition. As do the multitudinous measures of atom and ion sizes, and the strength of bonds.[*]

We optimized the structures of these silane forms, and others, using a workhorse of electronic structure theory for extended systems, the extremely useful and reliable VASP program, which does quantum mechanical, so-called DFT calculations, with a plane-wave basis.[2] In the optimizations we allowed departure from the initial symmetry.

As the pressure increases, the only imperative for atoms is to get closer together. After the space between molecules (we call it loosely "van der Waals space") is squeezed out, the atoms approach each other, or to put it in other words, the coordination of atoms increases. For instance many NaCl-type structures of AB compounds (six-coordinate at both atoms), turn into CsCl ones (eight-coordinate) under compression.[3] The program was allowed to change coordination, and smart enough to do it if the enthalpy so dictated. The structure at left in Figure 2 was one we found for SiH_4 at elevated pressure. It has each Si (golden atoms) connected to 8 other Si through 8 symmetrical hydrogen bridges. One has the same number of valence electrons (8 per SiH_4) making for more bonds, now 8 two-electron three-center Si–H–Si bonds. Intriguing, but understandable.

Other people got into the game, with brute force or clever structure searching programs.[4,5] At one end there were algorithms that put one or more formula units into a cell, place the atoms with a random number generator, eliminate clearly untenable geometries, and finally optimize a goodly sample of those that passed simple constraints.[6] Other programs use "simulated annealing";[7] still others use "minimum-hopping" methods,[8] or "genetic algorithm" approaches.[9] In these one begins with a sample of randomly generated geometries, selects the lowest enthalpy ones, then forms a new generation by doing a variety of well-thought-through transformations on previous low-enthalpy structures, such as shearing or straining a structure, moving slabs past each other, exchanging atoms. The intent is obvious—to preserve local order, or what is good about a structure found by chance, but to introduce enough variability to find still better structures.

Soon after we published our best structure, that at left in Figure 2, Pickard and Needs, using a random search algorithm, came up with a lower enthalpy variant, at right in Figure 2.[10] The structure is similar, electronically—you can see the diborane-like hydrogen bridges in it. Each Si in this structure shares four pairs of H atoms with 4 other Si.

Here's the sad report: we have chemical intuition, but in every case, absolutely every one, that Roald's group has tried, the various structure-searching programs—from minimum-hopping, through random searches to genetic algorithms—have never done worse than he and his able co-workers did. To put it another way, when we disagree, these structure-searching methods have consistently beaten us. Meaning that they have found lower enthalpy structures than we did. We have had no option but to join them in using these programs, as we do today.

Yet we have found a way to "add value." so to say, to the initially dismaying recognition of the computer program besting us in finding low enthalpy structures. A hint for how this was done is in the previous paragraph, when we (and Pickard and Needs) apply a simile, "diborane-like bridges". The best structure is what a computer finds. Why it is such, a human being teaches.

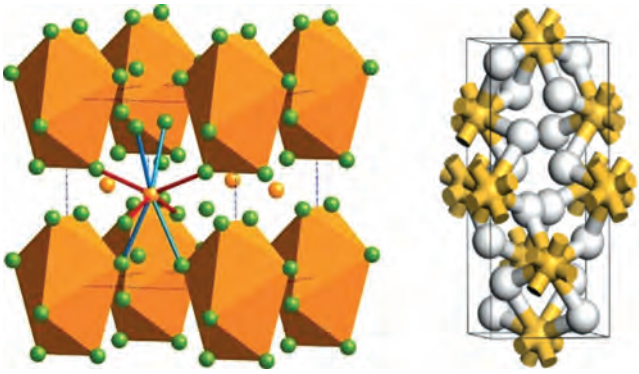

Figure 2. Two structures found for SiH_4 at a pressure of 144 GPa. The one at left, found by Feng et al., by optimizing a lower pressure structure, the one at right by Pickard and Needs through application of a random searching program. In the left image Si atoms are gold, H atoms green. In the one at right Si atoms are yellow, H atoms white. Note the similar 8-coordination of the Si atoms, and 2-coordination of the H atoms. Reproduced by permission from refs. [1,10].

[*] 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.

B2. Who Understands?

Artificial Intelligence, Searle's room, Strevens on Watson

So the computer beats us all the time. Perhaps more so when we escape the comfortable conditions (of pressure or temperature) in which our intuition, based on preliminary knowledge, forms. Not just at something trivial, as tic-tac-toe, but at a game that we once thought marked intelligence, such as chess. Even as we knew all along that chess masters were far, far from Isaac Newtons or R. B. Woodwards. But now we are closer to home—the intelligent game is predicting the structure, say, of SiH_4 at a pressure of 144 GPa. And a variety of software packages does it better than we do, with all the chemical intuition (over a hundred years of chemical knowledge between us) that the authors of that paper could muster.

Our short answer is that the computer that has calculated faster and reached an intellectual, publishable result that is "better" (here a structure of lower enthalpy), i.e., a structure not found by us, that computer… understands nothing of chemistry or physics.

And as we give that answer, we enter several worlds, of philosophy and emotion. In particular, people could say:

1. "What do you mean by "understanding," our friends?"

2. "Who cares, if it is the number you want?"
3. "Bah, you're just finding a way to get out of the situation that the computer beats you at finding the best structure of compressed silane. Human beings are so good at that, inventing self-justifications."

We've touched on understanding, and why human beings want more than numbers in a section above.[11] The question, ultimately that of artificial intelligence, has a long history in philosophy. Let us mention here two professional views, and one pragmatic one.

The philosopher John Searle published in 1980 a scenario called "The Chinese Room Argument."[12] He imagines himself in a room with an all-powerful Chinese language translation program. People introduce into the room slips of paper with Chinese characters. He and his reference books and superb program return translations. You and we have seen in our time how Google Translate has made a significant jump in the last couple of years in approaching just that performance, through an implementation (as we understand it) of neural network approaches. The impression to outsiders emerges that whoever/whatever is in the room knows Chinese. (Figure 3.)

Searle's proposition has occasioned extensive and readable discussion, sufficient to warrant a substantial entry in the Stanford Encyclopedia of Philosophy.[13] You will not be surprised to learn that there is wide disagreement. And the connection to the Turing test[14] is evident. Turing's seminal paper begins as follows: *"I propose to consider the question, 'Can machines think?'"*

They beat us at finding structures, they beat us at chess. Michael Strevens has written an excellent paper on Watson, the IBM computer better at chess, *go* (the game), and *Jeopardy* than we are. In one passage he discusses the computer dealing with the phrase "the moon has set", Strevens writes

"Watson and you both answer questions by seeing connections between things. But they are different kinds of connections. Watson picks up from things it reads that there is a correlation between a sphere's rotating and a fixed point on its surface having a constantly changing view of the rest of the world. You grasp why this correlation exists, seeing the connection between the opacity of the Earth, light's traveling in straight lines, and geometry of the sphere itself. For you the statistics are a byproduct of what really matters, the physical and causal relations between things and people and what they do and say. Grasping those relations is what understanding consists in. Watson lives in a world where there are no such relations: all it sees are statistics. It can predict a lot and so it can know a lot, but what it never grasps is why its predictions come true."[15]

Strevens says that Watson knows many facts, and can build certain relationships between them. But he/it lacks understanding. We imagine that people (not we) would argue with him on the meanings of "grasp" and "why." (Figure 4).

Will the programs in time do better than we can not only in games, but in everything? Some things will be easier for a robotic computer than others.[16] Luciano Floridi makes an important distinction between "historical" and "synthetic" data. The former comes from cases studied earlier—whether medical diagnoses, or games played by masters, the latter generated entirely by the rules of the game. Chess programs started using historical data, but have evolved to synthetic ones. Where the rules of the game are well-defined (say chess or go), the case-crunching speed of the computer will always devise a winning strategy, and expeditiously so. "*Put more epistemologically, with synthetic data, AI enjoys the privileged position of a maker's knowledge, who knows the intrinsic nature and working of something because it made that something.*"[17]

We are not professional philosophers, but we do know how our piece of the world, chemistry and physics, work. Ours are open-ended games, the rules in a way made up as we go along. There is no way to anticipate which molecules and reactions will be at the frontier ten years hence. Who would have predicted the ascent of MOFs (Molecular Organic Frameworks) or topological materials? Yet a significant part of what we do, day by day, is rule-bound, Looking ahead (part C) to a the future of understanding and AI moving

Figure 3. An artists's imagination of Searle's Chinese room. From https://theness.com/neurologicablog/index.php/ai-and-the-chinese-room-argument/.

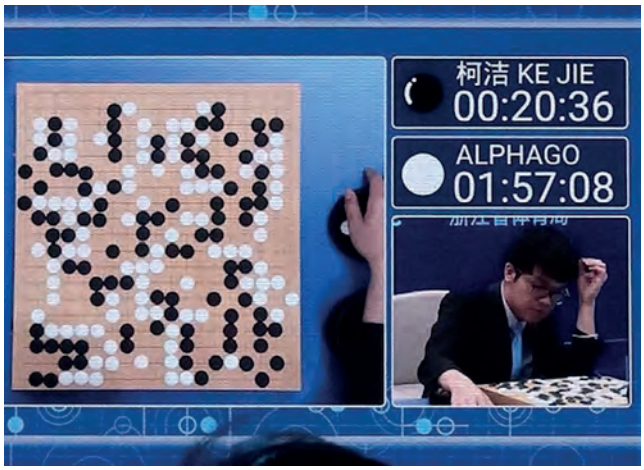

Figure 4. The second game betweenn AlphaGo and Ke Jie. From https://www.intergofed.org/igf-news-feed/google-ai-defeats-human-go-champion-ke-jie.html.

ahead hand in hand, it will be important to find the pieces of our activity which can be handed over to computers and robots.[18]

A matter of interest to an experimentalist might be some observable—be it a dipole moment of a molecule, or the thousands of lines of a rotational spectrum that allow an astrophysicist to identify a molecule in the interstellar medium. *Pace* Dirac, finally one can get that dipole moment, the frequency of those lines, to a level where we (and our ever-skeptical astrophysicist colleagues) can trust them. So suppose a researcher does his or her stuff well, calculates the dipole moment of a molecule to a sufficient accuracy that the experiment measuring it has to revised. And now comes along a fellow chemist, who wants to know whether that dipole moment would go up or down if one substituted a nitro (NO_2) group for a hydrogen. Remember, substitution, variation in chemical structure, is what chemists are exceptionally good at—they've made more that 100 million new molecules in 200 years of frenetic activity.[19]

If the straw-man researcher says "Give me a while; I need to go back to the computer to tell you what happens," then we posit that he doesn't understand the molecule. But who does? Is it the computer? Is it the person who wrote the software? We would argue that none of these understand what a dipole moment is, nor how one might estimate it.

And now we are back to the chorus of our friends who would disagree with Searle, with Strevens, with us.

Meanwhile simulation marches on. How can we remain human in this world? You bet we will. And we will try, just try, to lay out a roadmap for coexistence of simulation and understanding in our profession.

But first let us return to simulation in the context of quantum chemistry, and in the relationship of experiment with theory.

B3. Quantum Chemistry, ca. 2020?

In predicting molecular properties, one could move methodically down the time-honored path of improved theory and associated computation (see section A11 in first part of paper). Or take another way, via the numerical resolution of the fundamental equations, assuming some theoretically grounded approximations, on to more phenomenological models, the parameters of which might in fact be obtained by machine learning from big data sets. The path sketched is not a straight line; we describe a cut-and-paste road, with occasional overlaps of methodology.

But things are moving fast, and a new situation confronts the next generation of chemists. We are seeing the beginning of a flood of papers in which AI methods are specifically applied to molecular energetics.[20–22] The only Schrödinger's equations that will be solved will be those for the training sets. In view of the progress of these tools, it is likely that Machine Learning and Artificial Neural Networks will in the near future compete efficiently—in quality, in cost—with the best quantum chemistry tools.

Then the community of number-oriented quantum chemists, those who now help the experimentalists by providing lacking quantitative information, perhaps beyond them the whole quantum chemistry community, will face a dramatic problem. Will their function be relegated to thinking of the data sets most suitable for the efficiency of machine learning? Or (better) of tuning the architecture of the deep neural networks, so as to allow a program to find the optimum correlation most expeditiously? Will the community of the quantum chemistry code users, follow the destiny of supermarket cashiers these days and that of taxi drivers tomorrow? Not only menial, but highly qualified jobs are indeed threatened by these extremely well-performing artificial intelligence (AI) tools.

There is much attention in the community, and big company competition shading to hype, on the subject of quantum computing. It will come, and it is likely to be implemented in quantum chemistry. But one thing is clear—when we have those quantum computers, they will get the numbers really right. But they will not provide the least bit of interpretative wisdom.

It would seem as if getting the energies of molecules (or their electronic densities) is then within reach, near. But the distance from getting the correct number to Theory, as it was defined for several hundred years, as it was and is taught to chemists and physicists (taught in a way whose value we have affirmed), that distance actually increases. Theory provided and provides understanding. The gray future we have pessimistically sketched provides a reliable number.

And… in some sense the distance to story-telling also increases. This is evident from the extreme case of neural network recognition: we are unable to tell from which sum and combination of details we (and not the App we have purchased for the purpose) immediately recognize Burt Lancaster in this picture of a man peering out between curtains in Palermo.

It may be that the future is rosier than we imagine, and that AI programs that translate what neural networks do to humans will come on line. We hope so; some pointers in this direction have been mentioned at the end of Section 18, Part A.

Ultimately, we believe that Quantum Chemistry as a science may survive if it accepts and develops its story-telling dimension, if it fulfills its duty to identify "why" things are the way they are. The challenge that new predictive tools will present to us is how to keep our discipline a science, rather than a fancy spectrometer.

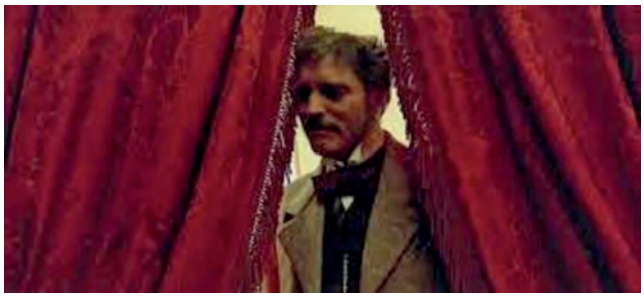

Figure 5. Burt Lancaster in Luchino Visconti's 1963 film "Il Gattopardo." From https://www.imdb.com/title/tt0057091/mediaviewer/rm1042818304.

Optimism is also expressed in a Perspective by Frank Neese and co-workers, with the title "Chemistry and Quantum Mechanics in 2019: Give Us Insight and Numbers."[23]

But before we outline the pathway to that ideal, let us descend further into simulation. Big and bigger, it is with us, testifying to the cleverness of humans guiding those incredibly swift tools of information technology. And the seductions that await them.

B4. Simulation!

Large scale applications in theoretical chemistry

We wish to show some examples of the more ambitious efforts in simulation, in the context of chemistry. The first example does not involve machine learning as such, but a study with a very large number of human and machine-guided computations.

The project was described as follows:

The Harvard Clean Energy Project (CEP) is a theory-driven search for the next generation of organic solar cell materials. CEP has established an automated, high-throughput, in silico framework to study potential candidate structures for organic photovoltaics.

The current project phase is concerned with the characterization of millions of molecular motifs using first-principles quantum chemistry… The results are compiled and analyzed in an extensive reference database and will be made available for public use. In addition to finding specific candidates with certain properties, it is the goal of CEP to illuminate and understand the structure property relations in the domain of organic electronics. Such insights can open the door to a rational and systematic design of future high-performance materials. The computational work in CEP is tightly embedded in a collaboration with experimentalists, who provide valuable input and feedback to the project.[24]

As of 2013, the Project had catalogued and released to the public some 350 million individual DFT calculations on >3 million molecules.[25–27] There was a Phase 2, working with the World Community Grid and IBM.[28,29]

Various physical characteristics of importance to photovoltaic function were calculated. Figure 6 at left shows a calculated (calibrated in a certain way) LUMO (lowest unoccupied molecular orbital) energy for a given HOMO (Highest occupied MO). Figure 6 at right correlates open circuit voltage V_{oc} and short-circuit current density J_{sc} for a large data set (apparently tens of thousands of molecules), which pass a preliminary screening. Desirable molecules for photovoltaics should have high products of these quantities. In a compromise, the authors say "*The best molecules, according to the present study, are located in the upper left region of the figure.*"

The best candidate solar energy harvesting materials from this study are given in the Supporting Information of some of the papers published. A dataset of ≈300 molecules for calibration has been published.[30] It turned out that synthesizability of the compounds was a major factor that wasn't initially considered. The Harvard chemists did in the end come up with a set of acceptors deemed synthesizable.[31] It would be interesting to know the extent of support of this well-publicized project.

The chemists involved learned from their experience. In another study, they came up with DA2T, a very promising (and synthesized in a collaboration with Zhenan Bao) organic semi-conductor.[32] Álan Aspuru-Guzik notes that from this work he learned that "Close collaboration with experimentalists since the conception to the realization is key."[25]

Turning to machine learning and neural networks, we show one recent example.[22] This study looks at 7211 molecules, of which 5000 are in the training set. The program uses neural networks, supervised machine learning, and atoms and coordinates as input. Once written, it takes 24 hours of computation to train the program; the next molecule is computed in 100 ms. 14 molecular properties are examined, computed in several ways. Table 1 shows the average errors of the fitted relationship for 14 computed characteristics of the molecules, calculated by a variety of methods. That's pretty good.

Some of the properties are obviously correlated with each other (for instance the ionization potential computed by a certain method with the energy of the highest occupied MO (HOMO) computed by the same method). Some properties clearly are not correlated, nor would one expect them to be so—for instance the atomization energy of the molecules and its HOMO energy. The lack of correlation is clearly seen in the left diagram in Figure 7. After training, the "Quantum Machine" of the program is applied to 2000 molecules not

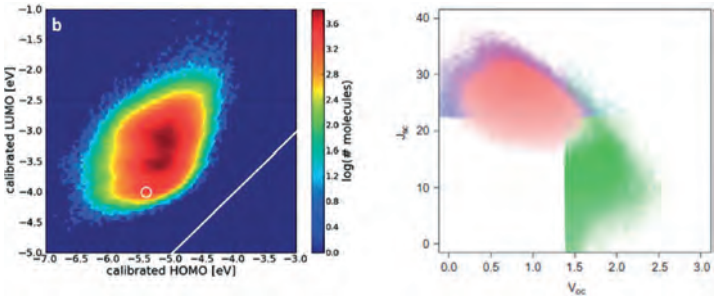

Figure 6. Left: Gap range (HOMO and LUMO energies for 2.3 million molecules in the Harvard Clean Energy Project. Reproduced by permission from Ref. [26], "Lead candidates…."). Sought high performance molecules should have characteristics in the small white circle. Right: Top 10% of molecules with high open circuit voltage V_{oc} (green) and highshort-circuit curent density J_{sc} (blue) and high product of the two measures (red). from "Accelerated...).

Table 1: The quality of the estimate of a number of computed molecular characteristics, from Montavon et al. (Ref. [22]).[a] The acronyms in parentheses refer to various approximate computer methods applied.

Property	Mean	MAE	RMSE	Reference MAE
E (PBE0)	−67.79	0.16	0.36	0.15[a], 0.23[b], 0.09 – 0.22[c]
α (PBE0)	11.11	0.11	0.18	0.05 – 0.27[d], 0.04 – 0.14[e]
α (SCS)	11.87	0.08	0.12	0.05 – 0.27[d], 0.04 – 0.14[e]
HOMO (GW)	−9.09	0.16	0.22	–
HOMO (PBE0)	−7.01	0.15	0.21	2.08[f]
HOMO (ZINDO)	−9.81	0.15	0.22	0.79[g]
LUMO (GW)	0.78	0.13	0.21	–
LUMO (PBE0)	−0.52	0.12	0.20	1.30[g]
LUMO (ZINDO)	1.05	0.11	0.18	0.93[g]
IP (ZINDO)	9.27	0.17	0.26	0.20, 0.15[d]
EA (ZINDO)	0.55	0.11	0.18	0.16[h], 0.11[d]
$E^*_{1,\infty}$ (ZINDO)	5.58	0.13	0.31	0.18[h], 0.21[i]
E^*_{max} (ZINDO)	8.82	1.06	1.76	–
I_{max} (ZINDO)	0.33	0.07	0.12	–

[a] MAE is the mean average error, RMSE the root mean square errors. The mean value of the property is given for all 7211 molecules studies, the RMSE and MAE for the 2211 molecules not in training set. Units are eV for properties except polarizability α.

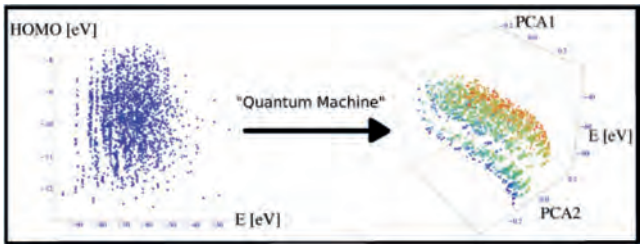

Figure 7. Schematic progress as the Quantum Machine of Montavon et al.[22] works.

part of the training set. In the last layer of the neural network application, the molecules are classified by their values of two principal components (in the statistical sense, PCA1 and PCA2). The color coding corresponds to the HOMO. A clear correlation is evident.

The use of machine learning for deriving "force fields", i.e., the parameters that describe the energy components in a subsequent deterministic or stochastic calculation of observables, is both an obvious application of machine learning,[33] and philosophically a complex process. No matter how those potentials were derived (from empirical ideas, from fitting quantum chemical calculations) they are subsequently used in a numerical simulation. So why not fit them by a program that uses no chemical intuition in the form of the functions fitted? Why waste the time of a graduate student, why demonstrate to him or her the origin and distance-dependence of dispersion energies, for something that a program can do? We would argue that some understanding can both make the fitting process more efficient, and, if fewer terms are involved in the fitting, may even hint at the underlying physics. And there is some recent work along these lines.[34]

To us, however, some line is crossed when in the fitting process, in order to get the best fit for the major factors, one accepts values for some "minor" molecular observables that are nonphysical.

The number of machine learning studies in chemistry and materials science has grown tremendously.[35] Naturally newsworthy are ambitious combinations of proposal of synthetic routes with automated, robotic synthesis.[36] The secondary literature (comments on primary papers) delights in the opportunity these studies offer; journalists can't resist the lure. So in two sequential issues of *C & E News* one sees articles on "Machine learning predicts electron energies,[37]" "Machine learning offers fast, accurate calculation,[38]" and in *Chemistry World*, "Machine learning makes light work of hard materials.[39]" Some of the discussions are sober,[40–42] many are not. As we said at the outset, the feeling one gets is somewhere between a jumping on a bandwagon and being hit by a tsunami.

B5. Learning Theory From Simulation

A few (too few) good examples

None of the fans of simulation and big data will be inclined to think that we can say anything fair about simulation. But let us detail a search we undertook in the literature with the following aim: to find in applications of machine learning any sign that from the good learning exhibited (or the correct 3D structures predicted in a search) that one could draw a novel conclusion with chemical or physical consequences. Something beyond numerical agreement. Something analogous to seeing a diborane-like bond in a silicon hydride at high pressure. We found two examples free of hype; we sincerely hope for more, as they would help to construct the pasarelle between simulation and understanding that we seek.

Mueller, Johlin and Grossman looked at an industrially important material, amorphous silicon, for the physical factors that favor hole trap depths.[43] The reference here is to semiconductors, which have a moderate band gap between filled states (valence band) and ones empty of electrons (conduction band). Defects and impurities, in the form of vacancies, extra atoms, may introduce new levels (holes) as traps for electrons. {Figure 8} It's best to have the authors speak for themselves, in the abstract of their paper:

"*Genetic programming is used to identify the structural features most strongly associated with hole traps in hydrogenated nanocrystalline silicon with very low crystalline*

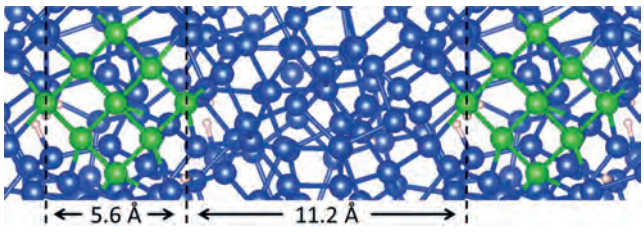

Figure 8. A sample of nanocrystalline Si:H structure. Blue spheres represent amorphous Si, green represent crystalline Si, and white represent H. Reproduced with permission from *Phys. Rev. B.*

volume fraction. The genetic programming algorithm reveals that hole traps are most strongly associated with local structures within the amorphous region in which a single hydrogen atom is bound to two silicon atoms (bridge bonds), near fivefold coordinated silicon (floating bonds), or where there is a particularly dense cluster of many silicon atoms."[44]

The authors' claims are commendably modest. In the body of their paper they say *"…we had not considered bridge bonds to be a likely feature of hole traps prior to the machine learning results."* You can see why we like this study. It adds to our understanding. A chemical theoretician could go on to explain why bridge bonds lead to hole traps.

In a second example, Brandt et al. approached the problem of studying complex conformational rearrangements in biomolecular systems.[44] Let us use their own words to describe what they did:

"Starting with a data set of molecular coordinates (obtained from experiment or simulation) and an associated set of metastable conformational states (obtained from clustering the data), a supervised machine learning model is trained to assign unknown molecular structures to the set of metastable states. In this way, the model learns to determine the features of the molecular coordinates that are most important to discriminate the states."

The very positive feature of this work is that it focuses on structural aspects that any chemist would choose (would some call this "biased"?)—essential coordinates such as specific distances or dihedral angles—in describing the system. Two particular, well-established model problems—the folding of a piece (HP-35) of a protein, villin, and a special "hinge-bending" motion of 4T lysozyme were studied.

The Brandt et al. machine learning approach teaches them (us) that certain slow motions are related to the function of villin, and reveals a mechanism for the lysozyme "which has only recently been detected independently with considerable effort."

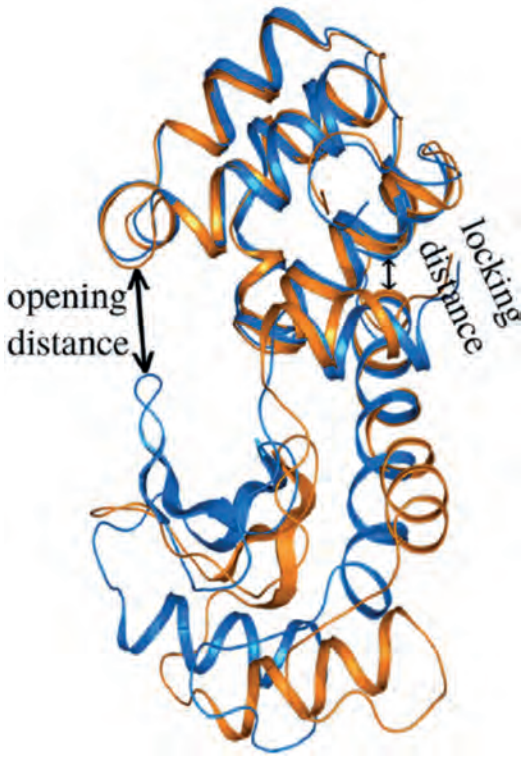

Figure 9. Structure of T4 lysozyme in the open (orange) and closed (blue) state, indicating opening and locking of the molecule (Ref. [44]). Reproduced with permission from *J. Phys. Chem. Lett.*

We do not doubt that we have missed other real examples of new chemistry and physics learned via AI, new "laws" of nature that can be taught, that can enter the creative toolbox of the scientist. People will let us know about them. For now, there is much hype.[45,46]

B6. Complexity, Utility

Does the quantity of information to be processed lead to a qualitative change in what understanding means? Utility and evolution, a lovely example

An interesting question that runs through philosophical discussions of machine learning and simulation is the following: When the explanation of some physical phenomenon becomes so complex, because of many competing influences, that no human being can see his or her way through the welter of data, would that be a place for machine learning? The point is made, for example, in a paper by Bartók et al.[47] We would argue that one should still try and understand the basic physics, and then the different factors that go into an observable can be weighed. That we cannot see our way out of a complexity is not a good argument, someone else—a patterner of chaos—will come in time to do it. Onsager and Woodward did the unimaginable.

There is no doubt that evolution engenders variety (with no attendant implication of utility to us). The beautiful and terrible world of nature is daily evidence of this. Machine learning and neural networks may be seen as products of cultural evolution, as much as the "classical" theory the authors practice. The developing combination of computer tools and evolution may lead to quite incredible outcomes. We mention one here.

Frances Arnold's group at CalTech uses the diversity of heme-binding proteins as the basis for evolving under laboratory conditions new enzymes. These catalyze non-biological reactions, prospectively ones useful for forming some molecules, some bonds that are normally difficult to form.[48,49] Consider, for instance the formation of a C–Si bond by the reaction of Figure 10.

Specific C–Si bonds are difficult to form. And biological activity often is highly specific—one enantiomer (mirror-image environment of a carbon atom) may be active, the other not. The Arnold group has combined machine learning and directed evolution to evolve enzymes that do this reaction, in one case with a yield of 93% "enantiomeric excess" of one chiral isomer, in another case with 73% of its mirror image.[50] Pretty incredible!

No question as to the utility of this process. But does it lead to an increase in understanding? The question of utility as a criterion of value, aesthetic, ethical, or epistemological,

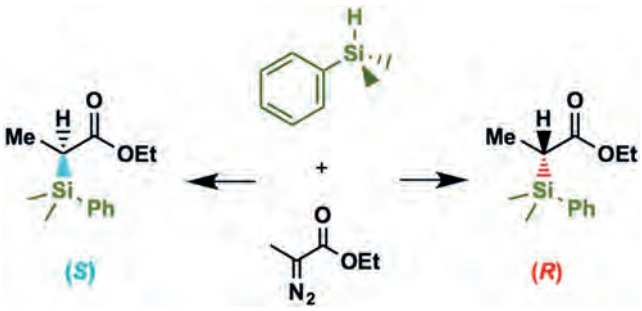

Figure 10. Carbon-silicon bond formation catalyzed by heme-containing enzymes. The products at left and right have opposite chirality (*R*,*S*) at carbon.

has been argued in philosophy for ages.[51,52] Our tentative position is that utility can certainly form value, not only in benefitting human beings but also in furthering knowledge. Utility may also mean destruction, as we sadly know. Utility is not intrinsic, it matters who is acquiring that knowledge, for what purpose, and what they do with it.

B7. And in the World at Large

A collage of simulation/AI uses in society; from funny to scary

Simulation, big data, machine learning are all around us, intruding into our lives. And helping us. One can be a curmudgeon and complain that our ability to read maps has atrophied in the age of the GPS, but one has to realize that maps were once an invention, and hardly available to all. And when one is lost in a tangle of one-way streets always going the wrong way, we grow grateful for this incredible programming and geolocation invention.

Let us provide here a potpourri of ways that IT and AI have penetrated our lives.

1. High-frequency traders find microwaves suit their need for speed

"An 800-foot microwave tower in a Belgian cow pasture transmitted messages for the U.S. armed forces during the Cold War. Now it has been enlisted in financial combat, as high-frequency traders fight to shave microseconds off transmission times. "[53]

Michael Lewis, in his book "Flash Boys,"[54] says high-frequency traders are willing to go to extraordinary lengths to gain this speed advantage—including laying the shortest, and therefore straightest, possible fiber-optic cable between the Chicago stock exchange and the New York one (based in New Jersey), a distance of 827 miles.

We suspect that our retirement funds, public or private, are being traded today over just such networks, with decisions being made not by the quality of the company, its performance, or social consequence, but based on algorithms that make near instantaneous decisions based on trends, or on small fluctuations in stock prices. It is hard to find a reliable estimate of the percentage of security trading done by algorithms, but we have not seen a number below 70% of all stocks. Some so-called "hedge funds" trade only through algorithms.

The advantage of algorithms is given as:

Algorithmic trading eliminates human emotions that prevent investors' behavioral problems in holding losses for a longer time and selling profitable securities too early. It also tests trade ideas on historical data to eliminate poor trading ideas and retain the good ones.[55]

The algorithms may be set by human beings (an investor together with a consultant), but increasingly they are set by automatic programs or robots. Notice, however, that in this case that speed does not create wealth, only acts on its distribution. From the same website:

In future, machine learning will shape algorithms that can pick the techniques by themselves.[56]

2. Buying for the baby

Andrew Pole had just started working as a statistician for Target in 2002, when two colleagues from the marketing department stopped by his desk to ask an odd question: "If we wanted to Figure out if a customer is pregnant, even if she didn't want us to know, can you do that?

We knew that if we could identify them in their second trimester, there's a good chance we could capture them for years," Pole told me. "As soon as we get them buying diapers from us, they're going to start buying everything else too. If you're rushing through the store, looking for bottles, and you pass orange juice, you'll grab a carton. Oh, and there's that new DVD I want. Soon, you'll be buying cereal and paper towels from us, and keep coming back."[56]

Target's analysis was so good that it sent coupons to a young customer before she told her father she was pregnant.

3. The joy of skiing

"Ski resorts are even using data to understand and target their patrons. RFID tags inserted into lift tickets can cut back on fraud and wait times at the lifts, as well as help ski resorts understand traffic patterns, which lifts and runs are most popular at which times of day, and even help track the movements of an individual skier if he were to become lost.

Imagine being an avid skier and receiving customized invitations from your favorite resort when there's fresh powder on your favorite run, or text alerts letting you know when the lift lines are shortest. They've also taken the data to the people, providing websites and apps that will display your day's stats, from how many runs you slalomed to how many vertical feet you traversed, which you can then share on social media or use to compete with family and friends."[57]

4. Not all computers are equal

Orbitz Worldwide Inc. (a travel website) has found that people who use Apple Inc.'s Mac computers spend as much as 30% more a night on hotels, so the online travel agency is starting to show them different, and sometimes costlier, travel options than Windows visitors see.[58]

5. Sexual orientation

"Kosinski first mined 200,000 publicly posted dating profiles, complete with pictures and information ranging from personality to political views. Then he poured that data into an open-source facial-recognition algorithm—a so-called deep neural network, built by researchers at Oxford University—and asked it to find correlations between people's faces and the

information in their profiles. The algorithm failed to turn up much, until, on a lark, Kosinski turned its attention to sexual orientation. The results almost defied belief. In previous research, the best any human had done at guessing sexual orientation from a profile picture was about 60 percent—slightly better than a coin flip. Given five pictures of a man, the deep neural net could predict his sexuality with as much as 91 percent accuracy. For women, that Figure was lower but still remarkable: 83 percent."[59]

The article by Cliff Kuang from which this passage is quoted says that as researchers in artificial intelligence see the remarkable outcomes of their programs, they are increasingly puzzled by what they find and how the programs reach their conclusions.[60]

6. Predicting recidivism

The reference here is to the likelihood of a convicted criminal repeating his or her legal offense to society. In an attempt to reach fairness in sentencing, a number of criminal justice systems in the USA use an "assessment tool" called COMPAS, (which stands for Correctional Offender Management Profiling for Alternative Sanctions). This program is provided (sold) by Northpointe, which changed its name to "equivant" in 2017.

Here is a rationale of what *equivant* offers:

Whether through personalized dashboards, access to offender risk and need assessments, criminal history snapshots, calendar views, access to important documents, or the ability to identify and mitigate potential bottlenecks, it all comes down to having the right tools at the right time to make "data-smart decisions".[61]

There has been substantial debate in the US (and elsewhere) on the judicial system being prejudiced against black offenders.[62] Dressel and Farid recently looked at the accuracy and fairness of COMPAS predictions of recidivism. They concluded:

We have shown that commercial software that is widely used to predict recidivism is no more accurate or fair than the predictions of people with little to no criminal justice expertise who responded to an online survey….When considering using software such as COMPAS in making decisions that will significantly affect the lives and well-being of criminal defendants, it is valuable to ask whether we would put these decisions in the hands of random people who respond to an online survey because, in the end, the results from these two approaches appear to be indistinguishable.[63]

Our astute friend, Paul B. Kantor, remarks here: "*I think it is fair to mention that our system of trial by jury is based on the random selection of citizens to make life or death decisions about other citizens.*"

7. The arrival of AI on the world art scene

On October 25th, an AI-made portrait was sold for USD 432,500 by Christie's. The authors of the underlying algorithm are 3 young French persons, working under the collective name "Obvious". One of the members of the group, Hugo Caselles-Dupré, is a Ph.D candidate in machine learning. The process is fed by a set of 15,000 portraits, and may, of course, produce an infinity of items.[64] There is a human selection step, in the application of the algorithm (called Generative Adversarial Networks). This is not the first creation of art by algorithms. Aside from what the unexpected price (Christie's estimate was $8,000 to $11,500) reached by this "portrait" says about the modern art market, the comments about the event are interesting.

Figure 11. The three principals in "Obvious," the team which produces art using artificial intelligence, stand next to one of their works, "Le Comte de Belamy."[65]

Thus Richard Lloyd, the International Head of Department at Christie's, is sure that this type of creation will proliferate. And maybe everyone will be able to produce his own art works by furnishing his set of preferred paintings to the algorithm. This will be the end of "a privilege yesterday reserved to the very rich people" (coming from the Christie's staff, this invocation of economic democratization through sophisticated technologies is rather amusing). However important questions remain hanging, he says, "Who is the author, the group or the algorithm? Is it necessary to pay copyrights for reproduction of such works?"

The "Obvious" publicity stunt is actually the tip of an iceberg—computer scientists, psychologists and artists have been exploring the potential of computers "making art" for decades, Ahmed Elgammal, a leading figure in the field and director of Rutgers University's Art and AI lab, tells in a recent article some of the fascinating history of the enterprise, going back to a 1973 program of artist Harold Cohen. Critical to recent work in the field is AICAN (artificial intelligence adversarial network), "a program that could be thought of as a nearly autonomous artist that has learned existing styles and aesthetics and can generate innovative images of its own."[65]

8. The right to kill, an enemy or the bad driver

The connections between science and technology on one hand, and military power on the other, are old, strong, and well-documented. AI evidently is of direct and immediate use for armies, both to gather information on the enemy's activities, and in the deployment on the potential battlefield of sophisticated weapons. The US Defense Agencies set up in 2018 a Joint Artificial Intelligence Center, for integrating 600 AI projects.[66] Their budget is not disclosed, but individual projects are in the ten to hundred million dollar range. The contracted work is related to the social control of populations as well as more direct military missions, such as autonomous weapons. In battle, speed of decision is crucial, as illustrated by this example: the ALPHA code, a new AI flight combat

system, consistently defeats a top US combat pilot. Col. Gene Lee was quoted as saying:

"I was surprised at how aware and reactive it [ALPHA] was. It seemed to be aware of my intentions and reacting instantly to my changes in flight and my missile deployment. It knew how to defeat the shot I was taking. It moved instantly between defensive and offensive actions as needed." [67]

The decision to fire and kill may eventually be delegated to the AI-assisted fighter plane. Bill Geertz writes in an article of "*…the growing importance Beijing places on rapidly building autonomous weapons—robotic arms capable of thinking and acting at the speed of light.*"[68] And General John Allen speaks of a "hyperwar,"[69] free from human decision. The Economist, in a recent article says "*The line between human and inhuman weapons is fuzzy, important and breaking down.*"[70]

AI offers a temptation to act quickly, in order to take benefit of a supposedly massive technical superiority. This supposed superiority is not necessarily real nor decisive (as seen 40 years ago in Vietnam, and these days in Mali) but it represents the potential acceleration of violent measures.

Figure 12. A drone operator from the Mosul Brigade of the Iraqi Special Operations Force 2 releases a drone during a military operation to retake parts of Mosul from the Islamic State on Dec. 5, 2016. Achilleas Zavallis-AFP/Getty Images.

B8. Danger. Mortal

Issues of life and death should not be left to computers

In the last section, we have given a range of contemporary applications of big data sets and simulation. These range from innocently ludicrous (what an advertiser sees in the data possibilities of skiing excursions) to downright scary (the social scientist's experiment to judge sexual preferences from a few images. And presumably use them). Our newspapers and media are just full of such frightening applications. Zamyatin ("We"), Orwell ("Nineteen Eighty-four") and Aldous Huxley ("Brave New World") saw it. One is led to opposing perspectives on the future of human beings and AI/simulation out there. It is there in a multitude of recent movies, novels, and nonfiction books; we cannot match a succinct and readable summary in Tad Friend's essay on "Superior Intelligence."[71]

Let us face the strongest moral problem, the matter of life or death. The moral problem of killing in time of war has without doubt already been distanced in the past century by the interposition of layers of technology between the initiator of the action, and the victim. Massive aerial bombing of cities in time of conflict is an example, from World War II on. The problem paradoxically returns in the debate on killing drones, employed in the "fight against terrorism": must we give to the drone the right to fire, or to wait for an order to fire, with the risk that it will be destroyed? If we program it to kill, what will be the acceptable error bar, the number of children that might die, if the target be an important enemy leader?

The fascinating thing is that this question will return soon, has returned, to all of us with the advent of AI-driven cars. The governing algorithms will have to decide the car's behavior in situations where the survival of another car or of pedestrians is pitted against damage for the AI-driven car and its passengers. Can one imagine the number of cases to consider, the weight given in the decision to the fault of the possible victims (who are likely engaged in one or another illegal action, since the automatically driven car obeys the law), the lives of the outsiders and insiders, their number, their ages? Not to speak of the legal responsibility, of the car owner, the vehicle's users, constructor, algorithm developer? It will be worked out in the courts, to be sure, creating employment for lawyers.

It is important, very important, that the designers of AI-driven innovations think about ethics. We note recognition of this obvious idea—so at Harvard a course on "Intelligent Systems Design and Ethical Challenges," introduced by Barbara Grosz, has proven very popular, and with time ethical reasoning has become embedded in a number of computer science courses.[72]

In an excellent article on "Pros and Cons of Autonomous Weapons Systems, Amitai Etzioni and Oren Etzioni summarize the currents situation and arguments on both sides. Remarkably, the pros include not only the expected military but moral justifications:

"Several military experts and roboticists have argued that autonomous weapons systems should not only be regarded as morally acceptable but also that they would in fact be ethically preferable to human fighters. For example, roboticist Ronald C. Arkin believes autonomous robots in the future will be able to act more "humanely" on the battlefield for a number of reasons, including that they do not need to be programmed with a self-preservation instinct, potentially eliminating the need for a "shoot-first, ask questions later" attitude. The judgments of autonomous weapons systems will not be clouded by emotions such as fear or hysteria, and the systems will be able to process much more incoming sensory information than humans without discarding or distorting it to fit preconceived notions. Finally, per Arkin, in teams comprised of human and robot soldiers, the robots could be more relied upon to report ethical infractions they observed than would a team of humans who might close ranks".[73]

Among other arguments in opposition:

"In July 2015, an open letter … notes that AI has the potential to benefit humanity, but that if a military AI arms race ensues, AI's reputation could be tarnished, and a public backlash might curtail future benefits of AI. The letter has an impressive list of signatories, including Elon Musk (inventor and founder of Tesla), Steve Wozniak (cofounder of Apple), physicist Stephen Hawking (University of Cambridge), and Noam Chomsky (Massachusetts Institute of Technology), among others…The open letter simply calls for "a ban on offensive autonomous weapons beyond meaningful human control."[74]

More importantly than the tarnishing the reputation of AI, we do not think that the "moral neutrality" of machines prevents any excess in the behavior of combatants at war. Quite to the contrary, the machine has no chance to feel compassion, to be hurt by the job it does, while soldiers may (not without difficulty) object or refuse. And the soldier at least has a chance to let the public know the human consequences of the operation—no drone will do that.

The loss of life, the taking of a life, is certainly the heaviest moral responsibility of human beings. Delegating this responsibility to algorithms built by some unknown code designer may be comfortable for the user (reduced to his position of consumer). But it is an ethical defeat of the society, and of the rights and privileges of an individual, as it delegates the most sacred decision to an algorithm.[75]

B9. Surveillance and Other Perturbations of the Social Fabric

Costs to society

Turning to "lesser" issues, there is a growing concern, with much public discussion, on government surveillance of normal activities of its citizens. The clash here is between privacy (what's left of it, seemingly well on the way out with the advent of social media), and public security in the age of terrorism. We tend to temper the fear by situating the excesses elsewhere—it is the Chinese government that perfects surveillance in the Xinjiang region.[76] But the number of public video cameras per person (1 camera per 22 people) is large in London as well as Urumqi.

Figure 13. Surveillance, by now antiquated. Original image from Politis magazine, https://www.politis.fr/, used by permission.

It is claimed by some that the direct contacts between individuals that computers and social media offer, brings about the self-assembly (to use a chemical concept) of horizontal networks. And, with this, a new, enhanced chance for democracy. Supporters of a positive role for the new technologies evoke the (generally crushed) Arab Spring revolutions, and demonstrations against oppression around the world as examples. Others insist on the enormous inequality created by the same technologies between the central powers (political or economic) in society, and their citizens, in collecting and disseminating information. The above-evoked example of repression of the Uigur population in western China supports the second thesis. There are tremendous asymmetries of knowledge that the collection of seemingly innocent data generates.[77]

Democracy has always been a fragile construction, whether in its Athenian experiment[78] or in modern times around the world. The impact of AI on this delicate structure, the dream of personal and societal liberty, equality, and comradeship it embodies, remains a major, we would say political, issue.[79,80]

One does not at all need to be a modern Luddite to see that the enabled, shared data future will bring with it massive perturbations in society that no one has thought through. Human tasks of value (yes, there is value in weeding the garden, and sewing on a button, as much as in writing a scientific article) will be reduced. Inequality, and we mean inequality in society, and between poor and rich countries looks to us to be on the increase; and centralization of control is readily abused by the forces of dictatorship and economic exploitation.

B10. Environmental Cost

Uncertainties

There is conflicting evidence on whether the increased use of computers and electronic devices in homes presents a major drain of electricity in developed countries. One study indicates a small perturbation on the scale of other uses in normal life—so air conditioning and television use much more power.[81] The electricity consumption by our tribe—quantum mechanical calculations, biomolecular simulations, other heavy computation—appears not to add much. Another study (from Huawei) on global electricity usages of communication technology reaches a more pessimistic conclusion.[82] It extrapolates to a best case 8%, to a worst case 51% consumption of world electricity by communication technology.

We note a precarious and curious perturbation in the world's romance with cryptocurrencies—Bitcoin "mining" has been using energy at the rate of a smaller developed country.[83]

Not evaluated in the above is the social cost of computing and communication (contributing to global heating), embodied most directly in the manufacture of the devices that have changed our lives. Rare earth element extraction—those elements are needed for IT—turns out to be so polluting. On

the positive side, we have seen a motion to renewable resources in the generation of ever-so-portable electricity, the life-blood of electronics. As solar and wind conversion into electricity grow cheaper, there is in the US, the largest consumer, little incentive to institute practices of conserving energy. One may fear that more available electricity from renewable resources will just lead to greater waste.

B11. Exponential Growth

A social uncertainty principle

Speaking of the future is risky, no less so of the future impact of AI techniques. AI is seen by many as an empowerment, and the future of empowering techniques is supposed to be evident, always increasing our well-being and choices. In this domain extrapolations seem intuitively relevant, and the satisfaction conferred by seeing Moore's law regarding the growth of computational capacities (a purely phenomenological law) is palpable,

Of course, exponential growth of a segment of any system is a recipe for eventual catastrophe—one needs the other pieces of our society, bakers, toilet-cleaners, even reviewers.

Technologies are embedded in societies, issue from them, act on them, for better or worse, depending on factors which are not technology-driven. AI may reduce if not suppress many repetitive activities now pursued by moderately educated people. But the way the benefit of this liberation of time will be used, shared or not, does not depend on the technology itself. The inequalities between qualified and less-qualified people, or between technology-mastering countries and others, may become explosive and make the extrapolations of the techno-prophets obsolete. The reality of what has happened to the World Wide Web's promise with respect to ease and openness to communication, in the age of trolls, is sobering. So is the abuse of social media. The impact of uncontrolled climate changes, in countries and between countries, may lead to major shocks and drive our societies out of the envisioned optimistic trajectories.

We think it important to voice this "social uncertainty principle" before speculating on the future of Science in age of AI.

B12. Correlations and Causes

Back to some philosophy, the pitfall of hidden factors

Perhaps a good starting point here is Thom's statement again, "To predict is not to explain", "Prédire n'est pas expliquer." His point is evident without being explicit: One does not have an explanation or true understanding when a prediction is only based on an empirically verified correlation, in the absence of any explicit causal chain between the stimulus and the issue, the cause(s) and their consequences. No question about it, the reality of the practice of science is that correlations, even sheer numerology, play a role—firmly established correlations have frequently been the first step to real scientific understanding. Examples abound—the Rydberg series that Bohr explained is a good one, as is the roughly contemporaneous introduction of atomic number by Henry Moseley. And don't forget the Periodic Table, *ante* Bohr, or Lewis' pair-wise distribution of electrons in bonds and lone pairs, before its quantum mechanical formulation and the identification of spin.

So, correlations are just fine, provided that a causal link is eventually sought, that explication is part of the design. What has troubled us about most simulations of the modern kind, from routine computational chemistry through machine learning, is just that, that no cause is sought. We can understand that the factors entering are surely complex, that many competitive influences may create an ever-shifting balance seemingly beyond human comprehension. But to abdicate the search? To end a paper without hazarding an explanation?

Modern information technologies offer access to huge data sets, and, with that, the possibility to establish many new and possibly unimagined correlations between variables. Under the name of "Big Data", this collective (and centralized) tool is frequently presented as the enabler of a forthcoming revolution of knowledge. The reality is seen in the story cited of Target's targeted sales to expectant mothers. One cannot deny the interest of seeing unexpected correlations, but science is not a collection of correlations, even of firmly established, strong (in the sense of statistical validity) ones. If these correlations are really surprising they should advance to the status of an enigma. They should turn into an intellectual challenge to our current understanding, call for an explanation, find their place in a consistent chain of implications.

Simply from a pragmatic point of view, one may doubt whether our individual lives and the political choices we make can be, or should be, guided by just correlations. It is not only inefficient but dangerous to act on a symptom that is a side-effect. The Big Data program should not claim to be an ideology-free political guide, nor a substitute for science.

A common noun, with two distinct meanings, appears in politics and in science: namely the word "cause". In the social sphere, it is an ideal, a target—peaceful relations, justice and freedom for instance. The search for causes, in the other sense of the word, is the heart of scientific practice, the ultimate pleasuring of the human mind, dare we say "soul"? Neither of these meanings of cause can be reduced to the maximization of efficiency.

There are well-known pitfalls in the search for causes, aside from the overly seductive pull of simplicity, that flash of Ockham's razor in the sun. Or the Goldilocks hypothesis. Or teleological explanations.

As scientists, we learn how to marshal real or theoretical evidence to make sense. But we need to be aware of still another dangerous shoal on the journey to *Ithaka.* One must consider the possibility that an initially obscure underlying cause may have as its consequences two quite independent phenomena, the so-called prime symptom and another, often tantalizingly close-seeming, issue. B may be correlated to C because a hidden factor A induces both B and C along two orthogonal chains of causality. In this case one may consider B

as a "side-effect" or "side-symptom". With the potential for being identified (fallaciously) as a cause.[84] This is a well-known problem in the social sciences: the percentage of racial minorities in the jails of developed countries may be due to social poverty and the inherited cultural handicaps of the families, not to the color of their skin or racial inequalities.

We did not end up with a social misinterpretation of causality by chance. For we think it is more from the social sciences than the natural ones that this fallacy of reasoning, which Aristotle knew, has come to be understood.

The pitfalls of attributing intelligence to procedures that explicitly eschew considering causality are apparent to most. We mentioned in part A a study that tries to look at how docking or binding models that are successful in drug design work. Here is what the authors say at the end of their paper, in a small section headed "Thoughts for Practitioners:"

The recent machine learning revolution has led to great excitement regarding the use of neural networks in chemistry. Given a large dataset of molecules and quantitative measurements of their properties, a neural network can learn/regress the relationship between features of the molecules and their measured properties. The resulting model can have the power to predict properties of molecules in a held-out test set, and, indeed, can be used to find other molecules with these properties. Despite this promise, an abundance of caution is warranted: It is dangerous to trust a model whose predictions one does not understand. A serious issue with neural networks is that, although a held-out test set may suggest that the model has learned to predict perfectly, there is no guarantee that the predictions are made for the right reason.[85]

B13. The Psychology of Human–Machine Interaction

So complicated that it needs a computer. And so can't have an explanation

We have already hinted at a psychological factor that operates in the community where human–machine interactions are necessary. Whatever program one writes, it is inherently complex, with thousands of lines of code. It never works the first time, giving nonsense, caught in loops. You curse its unresponsive inhumanity, even as you know you have yourself to blame for commanding the undoable. One is fortunate enough to have checks, of symmetry, of zeros.

The laborious act of writing and debugging of a program, tends to prejudice the simulator against the possibility of any "explanation." If it took all that work to write a program to get a number, it surely cannot be an easy number to get. And an order of magnitude estimate just won't do. The author of a complex program is the least likely person to believe that one could build a serviceable simpler model for the phenomenon. And while there is a way, perhaps a variety of ways, to get the program to give a reproducible number, people have not yet invented programming languages that build plain language models.

Certainly the world of science is full of "just-so" stories, teleological pseudoexplanations. One could imagine that the simulator wants to defend him- or herself against that universe. But Roald thinks there is more attitude-shaping at root here, through the psychological consequences of the process of extensive calculation, of programming, of simulation.

B14. Isn't it Time to Take Off Those Dark Glasses, in Theoretical Chemistry?

An alternative, positive view, of simulation in theory as infinite enhancement. The oracle

The authors of this paper have given too much room to their own perspective on the dangers of unthinking simulation, to understanding and society. So let Aspuru-Guzik, Lindh and Reiher, three leading figures in our profession, speak for the alternative view. They also look at the social effects of AI, and see something very different from what we point to above:

Figure 14. Taking off the dark glasses. Image by Vlue; reproduced by permission from *Shutterstock*.

The connection between science and the current drivers for society is deep and cannot be ignored. This century poses several severe challenges that range from the rapid rise of income inequality and the apparent cracks of the neoliberal structure to the stresses on the environment due to industrialization. The work of simulation scientists therefore is linked directly or indirectly to this societal context. In particular, the solutions to many of the challenges related to this century, ranging from the discovery of novel materials for renewable energy to that of environmentally friendly pesticides or next-generation antibiotics, require tools to be developed by our field.[86]

Their optimism on the fruits of simulation extends also to a vision of chemical knowledge:

The new goal of theoretical chemistry should be that of providing access to a chemical "oracle": an AI environment which can help humans solve problems, associated with the fundamental chemical questions of the fourth industrial revolution (clean energy, efficient drugs, smart materials, green

chemistry, etc.), in a way such that the human cannot distinguish between this and communicating with a human expert.[87]

In another recent paper, A. O. von Lilienfeld also makes a utilitarian and educational argument for AI techniques, as follows:

…QML [Quantum Machine Learning] modeling capabilities could then assist with experimental design questions required to resolve many of the outstanding materials and molecular design challenges, possibly alleviating some of today's pressing problems due to lack of new antibiotics, energy conversion and storage, water purification, or superior catalysts, to name a few. Through early and appropriate adaptation of chemistry education, reliable QML methods could also help to attract next generation chemists through cost-effective yet more versatile experimentation throughout the curriculum, using modern immersive virtual reality equipment.[88]

He supplements this with a philosophical case for valuing QML:

According to another line of thought one could argue that inductive reasoning is as applicable to scientific problems as deductive reasoning, or possibly even more powerful since also deductive methods rest on sets of approximations which were inferred at some point. It should not be necessary to remark that any new model, inductive or not, should be subjected to the same amount of skepticism and fact checking as the deductive approaches had to undergo. Since falsifiable predictions are being generated, QML clearly meets Karl Popper's criterion of a scientific method. Richard Feynman's way of how physics is done is also consistent with QML: "In general, we look for a new law by the following process. First, we guess it. Then we compute the consequences of the guess, to see … what it would imply and then we compare the computation results to nature … If it disagrees with experiment, it's wrong".[ref] More provocatively, however, one could even argue that the current state-of-the-art of solving the chemically relevant equations of quantum and statistical mechanics is not much more insightful.[88]

We disagree, naturally—we think the way theory has come to be done is literally insightful. In the body of his paper (not in these quotations), von Lilienfeld actually argues for a reasonable conjoined approach of what we have called theory and AI methods to theoretical problems in chemistry.

The rising tide of papers claiming to explain chemistry via neural network or machine learning processes joins the optimistic tone of the passages cited. We will return to a reasoned argument against this view, then work our way to a future that comes to peace with artificial intelligence.

B15. In Quest of Neutrality: the Ascetic (Ahuman)[89] Dimension of Science

Maybe neutrality is a better word than bias. The return of the observer in quantum mechanics

The hypemasters of the simulated chemical future brand as biased what is taught in the undergraduate and graduate courses across the world. Advocates of machine learning and other methods of simulation claim that they hold the (computerized) keys to the "unbiased" world in the offing. If, less confrontationally, we label what they proffer as neutrality—that one should not necessarily accept as truth and wisdom the good stories that theories tell—then actually the proponents of simulation are situated very much along the path that science has taken. The desire for objectivity, the wish to suppress the specificity, prejudices, and personality of the researcher, appear to be intrinsic to the hope of universality of the reliable knowledge we seek.

This is the ascetic dimension of the western science, that the subject who reaches what he/she thinks to be the truth, should aspire to disappear in the formulation of his/her understanding. Scientistic nirvana! In this process, the side story which tells the fortuitous circumstances through which the scientist reached the shards of the truth granted to him or her, may at best be viewed as a recounting of path-dependence, or a pedagogical crutch—on the margin, no more than "truth construction."

It was not always this way; in the early days of the Royal Society, direct first-person witness to a phenomenon, an observation by an honest human being, was the testimony valued.[90] A plague we owe to the subsequent triumph of the neutralist construction of science is the takeover of scientific language by a matching third person neutered discourse, thought to be most consistent with eliminating the person. Should we then be surprised that the appeal to neutrality, voiced in such language, might be read by the public at large as dehumanization of scientific knowledge? We have a problem.

There is an interesting turn in contemporary discussions of the foundations of quantum mechanics, one that signals a return of the individual. *Gedanken* and real experiments have focused on questions of nonlocality and action at a distance. It's not just animal lovers upset with the fate of Schrödinger's cat—it's thoughtful physicists disagreeing about basic interpretations. As Steven Weinberg writes:[91]

"it is a bad sign that those physicists today who are most comfortable with quantum mechanics do not agree with one another about what it all means"

Weinberg is quite negative on the views of people who bring the observer back into a central position in quantum mechanics.[92] One of these, David Mermin, responds:

In explaining why he finds untenable what he calls "the instrumentalist approach," Weinberg gives voice to just such a widespread prejudice: "Humans are brought into the laws of nature at the most fundamental level." Weinberg is not ready to give up the goal of understanding the relation of humans to nature by deducing it "from laws that make no explicit reference to humans." And so he endorses, with a touch of pessimism, a long-term goal of seeking modifications of quantum mechanics that "are not only speculative but also vague." He embraces this bleak prospect because he cannot accept incorporating the relation between people and nature into "what we suppose are nature's fundamental laws."[93]

In his recent book, *Third Thoughts*, Weinberg voices a hope for a theory that would explain

"what happens when people make measurements from impersonal laws that apply to everything, without giving any special status to people in these laws."[94]

Mermin criticizes this view

"Here he unwittingly puts his finger on what I believe is the actual source of the near-century of discomfort and disagreement. There is an implicit assumption, shared by almost all physicists, that the scientist must be separated from the science. The usual appeals to measurement with classical outcomes, it seems to me, are unsuccessful attempts to objectify and impersonalize processes in which an individual scientist acts on and is reacted upon by the world. The collapse of the wavefunction after measurement represents nothing more than the updating of that scientist's expectations, based on his or her experience of the world's response to the measurement. Weinberg hopes to keep the scientist out of the laws of nature, but our chronic failure to agree on the meaning of quantum mechanics demonstrates the futility of his hope."[95]

B16. The Dubious Attraction of Black Boxes

How theoretical chemistry went down the road; the dialogue with numbers. Why people seem to want omnipotent black boxes

The new waves of machine learning and neural networks propose for quantum chemistry an unbiased future of a black box that is an oracle. Actually, even before the New Waves, computational chemists were already well on the way to that future. In an earlier section, we described, in some detail particular to theoretical chemistry, how this came about. Briefly: we wanted to solve Schrödinger's equation, but the means to do so were lacking. So we invented wonderful models (say those of Hückel, or Pariser–Parr–Pople). In time, the computer gave us the capability of doing substantially more accurate calculations. Of course, we took that path; few remembered the models.

The dialogue with numbers, pre-AI, has a way of drawing you in. Modern computing offers the possibility of reducing as much as possible the number of invoked, qualitative approximations, or preliminary representations. There is no need to call on intermediate knowledge or concepts, be they steric effects, aromaticity and so on. All those fuzzy ideas that gave us trouble in chemistry courses as undergraduates, for which there was a never a simple yes or no answer. Scrap them! Just apply Schrödinger equation in the Born–Oppenheimer approximation, project it on the largest vectorial space of mono- and N-electronic functions, and let the computer give you the most reliable numbers. Then you feel sure, comfortable. In time, many quantum chemists became adepts of black boxes. That serve to avoid thinking.

The road to simulation in our field took only sixty years, very much our lifetime. It did not wait for a well-thought-through strategy or philosophical considerations, but took a convoluted track as the computing power available to quantum chemists grew in its unpredictable way—from mechanical calculators used by James and Coolidge to the cluster arrays and graphic processing units (GPUs) in common use today.

Actually, it is not so easy to root out thinking in a theoretical science. What transpired was more like the first steps in a dance—periods of sheer manipulation of numbers, facilitated by ever-increasing computer speed and architecture, alternating with the working through of ideas that simplify, categorize, interpret. Let us describe one such sequence, perforce in technical language.

Even with the potential of carrying through the heaviest calculations, some people keep thinking of other ways to do it. We might, for instance, identify a subset of mono-electronic functions and a reduced number of electrons which play the leading role in the phenomenon we are considering, which defines an entry into the problem, and which we call the "Active Space." There is real physics behind the singling out of such a reduction.

The AI aficionado feels uncomfortable with this step. In the case at hand, instead of defining an active space, and carrying out a level of configuration interaction in it, the aim would be to conceive and implement a code which bypasses the "entrance door" of the active space concept, and apply a black box which will… do better, either avoid the determination of an active space, or define it through an optimization process, supposed to be neutral and deliver a unique choice. Actually, unthinking optimizations may lead to bad surprises: an example is provided by cutting the triple bond of N_2, which, in principle, requires only 6 active Molecular Orbitals (MOs). If, on the road to improvement, one chooses 10 active MOs, introducing additional MOs which do not have the same physical role at short and large interatomic distances, strange potential energy curves result.[96]

Why do people want black boxes? It's not just in chemistry that we seek them—one can also point to politics and our response to men in white coats. The phenomenon—longing for someone who understands, for a simple solution, for the healing potion—is ultimately psychological. The world out there is multivalent, if not messy. We desperately desire simplicity and certainty. And politicians give it to us every election.

In our context, of chemistry and computations, adopting confidence in black boxes leads us back to Searle's room. The

Figure 15. From an installation by Danae Stratou in Athens, 2012: www.danaestratou.com/site/portfolio/its-time-to-open-the-black-boxes/.

black box is newer, fancier—it is fashionable, embedded in the computer. It caters to a simplistic view of science as omnipotent knowledge, knowledge that is neutral and independent of the observer. The black box generally does what it was designed to do very, very well. And knows no physics or chemistry. Or knows all that a chemist or physicist might want to know, depending on your point of view.

B17. Numbers and Images

The special place of images in theoretical chemistry. And their possible abuse

We want to take a digression next, on pictorial depictions of orbitals and densities. The connection to AI techniques is loose here, but computers have changed the way these images are used, and how theory interacts with them.

A paradoxical effect of the easy access to computers (inherently digital) is the reign of images in scientific communication, at least in theoretical chemistry. A primary consequence of the IT revolution has been representational—programs such as ChemDraw[97] have allowed even the novice to draw 2-dimensional molecular structures perfectly. But the real revolution has been in the 3-dimensional depiction of complex molecules This luxury (or so it seems for those of us brought up in another time, when faithful representation was laborious) is especially evident for complex biochemical molecules. Wonderful software allows the schematization of ribbons and strings in peptides and nucleotides (Figure 16 left), aiding us in the visualization of the biomolecular architectures, enabling us to guess the kind of collective movements molecules may achieve in biochemical processes.

Chemistry is as close as a science gets to Roland Barthes' "An Empire of Signs."[98,99]

Moving closer to theoretical chemistry, a popular tendency today is to draw electron densities or molecular orbital amplitudes, with great precision. The calculation at each point in space of, say, the spin density of a free radical, requires the computation of the amplitudes of all the atomic orbitals, the coefficients of these AOs in the molecular orbitals, and the coefficients of the multitude of determinants involving these MOs. This is obviously fodder for the computer, unfazed by the amount of information required. The way to display the immense information calculated for wavefunctions, with some semblance of three-dimensionality, is by drawing an isosurface, connecting points of the same value of whatever is being plotted. The outcome: a wonderful plasticky image of deformed balloons of two colors (indicating the phase of the amplitude).[100] The rendering, miracle of computer graphics, is certainly useful in establishing three-dimensionality. But sometimes the shininess seems like aesthetic affectation (as will be seen in time, we have nothing against art), perhaps even with erotic connotations—orbitals as lip gloss.

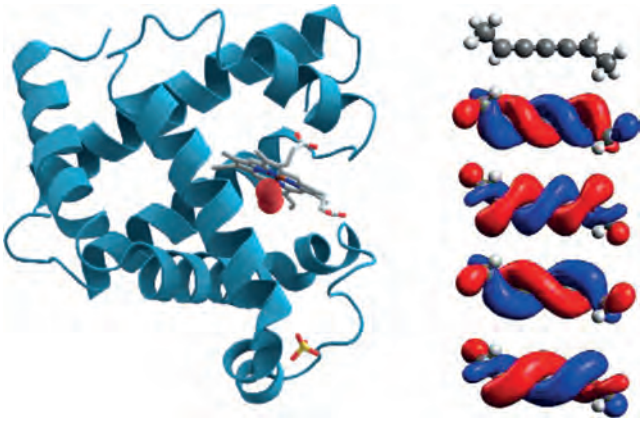

Figure 16. A ribbon representation of myoglobin, and some of the molecular orbitals of a dimethylpentatetraene. The orbitals at right show the inherent helicity of the MOs of this molecule:"Coarctate and Möbius—The Helical Orbitals of Allene and Other Cumulenes," M. H. Garner, R. Hoffmann, S. Rettrup, G. C. Solomon, *ACS Cent. Sci.* **2018**, *4*, 688–700.

In the old days one could also have done this, albeit much, much more laboriously. Also one could—and often did—take an information-reducing step along the way, and draw (sometimes using a template in the shape of an orbital) the major contributing atomic orbital(s). It may happen that the sophisticated information, once reduced to its core, confirms the crudest picture. As an example let us call up the distribution of the unpaired electron in conjugated free radicals, specifically for benzyl $C_7H_7 = (CH)_5CH_2$. Predicted by the topological Hückel Hamiltonian, they may be obtained directly without any matrix diagonalization, as 4/7 on the external carbon and 1/7 on three of the ring atoms. Those predicted from the variational Hartree–Fock calculation are very different, while a sophisticated treatment (full π CASSCF) returns to the Hückel estimate.[101] And one may understand why the Hartree -Fock approximation is in error, giving full privilege to the leading configuration (the left valence structure in Figure 17) at the expense of the other three.

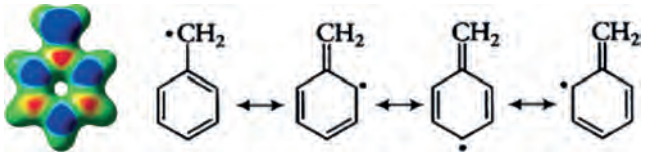

Figure 17. Spin distribution and four resonance structures for the benzyl radical.

One lost information in the old days, and was in danger of losing some essence. But one gained focus, and portability in the structures. So that an explanation, in terms of these simplified MOs, could be sketched for others, thereby transforming numbers into an explanation, maybe even a theory. What we have today is a graphically rich 3D rendering of the contour for one precise (and arbitrary, in its chosen value, and in its dependence on the underlying methodology) value of the electron density. Which can only be admired, but you cannot introduce it in a reasoning process. Worse. One gets the feeling in many papers that a button generating the graph has been pushed too many times. As if more such uninformative orbitals would impress!

We have before us a situation where the "numerism" made possible by the computer's power effectively kills the numbers, in service of supposedly richer pictures. Absolutely nothing has been gained in the process. The numbers are lost, and understanding does not replace them.

To return to our main point: The pretty orbital image, in the service of more faithful representation, in fact kills the Scheme, whether it is the idealized orbital lobes Roald has used, or the Feynman diagrams with which Jean-Paul thinks through the electron correlation problem. These schematic visualizations do not require the assistance of a computer, but help you to build and transmit in an elementary pictorial manner an interpretation. Even as they are technically deficient.

B18. A Science of Many Tongues

The polyglot nature of quantum chemistry; room for many ways to approach a problem

We may wonder whether the search for the omniscient black box has an element of aversion to variety, to there being many doors in to reliable knowledge. Quantum Chemistry today speaks several languages, it may speak in terms of atomic orbitals, as does orthodox Valence Bond theory, or think about whether we might give those orbitals little tails (so as to avoid ionic structures).[102] It also speaks the tongues of localized molecular orbitals, and of canonical symmetry-adapted delocalized MOs (see Figure 18). Quantum chemistry is rich in dialects, expressing the same phenomenon in different idioms. And it gives trouble to the person who fails to learn the underlying equivalence of the dialects.

Or to one who just has an aversion to the fact that a description claiming to be scientific is not unique. This is a variant of the objection that Primo Levi, in a rare moment of naiveté at one point in his education, voices: "Did chemistry theorems exist? No."[103]

One or another of these dialects may be more suited to a given problem, much as seemingly distinct wave and particle pictures of light (that give a modern physicist no trouble at all). So symmetry-adapted MOs for instance enable one to formulate most economically the Woodward–Hoffmann rules for the stereospecificity of electrocyclizations, compared to a VB approach. But describing the dynamics of a molecular excitation in a crystal, or the way an electric field affects a chemical reaction, might come more easily in VB language. Some properties may be equally well described from different entry points, for instance the geometries of conjugated hydrocarbons from Hückel theory (which ignores the electron -electron repulsion), and from a Heisenberg model (which assume this repulsion to be dominant and reduces the electrons to their spins.) The different languages actually serve a positive function—they give us new ways of thinking.

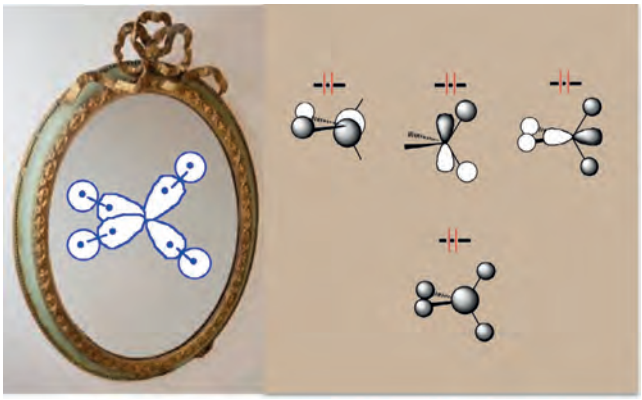

Figure 18. Localized and delocalized perspectives on the molecular orbitals of methane. The graphic is assembled by Philippe Hiberty.

Let's put it another way, in the context of the complementarity principle.[104] Two or more views of a phenomenon are not a sign of weakness for a science. Physicists were not set back by the particle-wave duality. Or the effectiveness of both matrix and wave mechanics. A unique representation is never attainable. And the dream of one separated from the "bias" of its human shapers is just that… a dream. This is going to be the fun of meeting alien civilizations—they are certain to see and express the same chemical and physical reality differently.

The polyglot nature of Quantum Chemistry is to us hardly a weakness, or a sign of immaturity, or something to cure. We view the existence of alternative doors as a spur to intellectual creativity, a prospect of deeper understanding, a source of pleasure for the practitioner and… possibly, a passage to beauty.

B19. Comfort

Providing a way out of black boxes

It is clear that we do not follow the colleagues who, proposing a black-box algorithm to define a Complete Active Space (which may be useful in some cases), speaks of the choice of this space as featuring an element of ambiguity, quoting others as the task being a challenge, and highly subjective. The choice is painted in negative hues.[105]

That's not how it feels to us. The concept that appeals to us is that of *comfort.* From its early conceptions and uses, Technique (and thus Science, behind most of modern technological changes) has been employed to gain better efficiency, security and comfort. Comfort is not just an armchair in front of a large screen; it is also the amelioration of human pain, which has to be, and is, a prime motive force of science. Probably theoretical chemists, of either our old kind or machine learning adepts, have not done so well here. The comfort we have sought and will describe in detail resides in the emotion of satisfaction—yes, call it joy—of grasping understanding.[106]

The quest for comfort, physical and mental, is recognizable in all historical advances of technology, including modern AI. It might seem that the black-box decision-making we tilt against also represents comfort. Bah, the comfort to not think. The calling on previous knowledge on similar systems may be a mental effort, but this effort is also a pleasure: The contentment of a journey (full of detours) through the elements of our knowledge, the byways of unexpected

connections gleaned, the pleasure of constructing a risky prediction, even the enlivening satisfaction of a challenge, to be confirmed or rejected. Even if predictive tools can be automated.

Comfort is not easy to achieve. First, if one admits the importance of its mental and emotional aspect, it is clear that modern science and technology may not be doing so well. Life is in a myriad ways better, longer. But depression and anxiety mark our society. For which pharmacological fixes are sought.

Second, AI clearly raises the comfort level—be it in the ease of finding your way through a maze of one-way streets with GPS (the Global Positioning System), or the Shazam App that identifies remarkably well an obscure rendition of a snippet of a song.[107] Yet so many other uses, some of which we have listed, serve less worthy impulses. We admit there is comfort in not worrying whether one has reached the global minimum in the structure of a molecule.

Even as we seek physical comforts for this world, and not only for humans but the biosphere, we need to save the basic ludic and aesthetic aspects of science.[108] Playing with models, allowing the choice of a representation among several, trying out diverse explanations—these are the elements of the great game on which we have embarked.

B20. Looking Ahead

Numerism and a search for understanding can work harmoniously together. Yet keep an eye on hybrids

A critic of our tilting with the windmills inside "artificial intelligence" machinery might advise us to relax, and not only come to peace with, but make use of AI's empowering, often transformative nature. Haven't we learned to get chemistry out of complicated quantum mechanical calculations? To use another metaphor, we are already in the skin, so-to-speak of elaborate computations—why not welcome the world they open for us?

As an example of what computational chemistry can do today is provided by the detailed theoretical analysis of some enzymatic reactions. Quantum mechanical treatment of the whole enzyme is impossible (and may not be productive). Intelligent strategies have been developed by the community to identify the core biochemical reaction, to treat a sizable model at the highest accuracy, the steric and electrostatic effects of the enzymatic environment perhaps simulated in a classical mode. One takes advantage of the structural information from crystallography, of course, but also that from a variety of spectroscopies.

Theory is then able to identify active sites, to follow the steps of the reactions, and even their dynamics. Once the reliability of the calculations is established, one can begin to believe the fleeting intermediates theory proposes, and design experiments to stabilize or intercept them. It's a beautiful playground. Among the impressive work in the field is the study of the MPnS enzyme by S. Shaik and co-workers,[109] of O_2 in photosystem II, by P.E.M. Siegbahn[110] and the group of F. Neese and co-workers,[111] and the work of the K. Yoshizawa group on dioxygen activation and methane hydroxylation.[112]

Notice how far these studies are from "brute force" approaches. In them enters much knowledge of biochemistry, the weighing of sometimes contradictory experimental results, and the design of an appropriate computational strategy. This is real science. Even as we worry about what the tools of AI will do the future, and to the grand enterprise of understanding on which our Greek, Arab and Chinese forefathers embarked, we revel in what we (or at least our students, or given our age, their students) can do.

And… chess did not end when *Deep Blue* defeated Garry Kasparov in 1987. Kasparov himself, a thoughtful observer of computers and humans,[113] invented "Advanced Chess," which came to be called "cyborg" or "centaur" chess, in which the competition was between human–machine teams, the human participants using whatever AI assistance desired.[114] The intent was to learn, both of the game, and of the strategies. The results are impressive.[115]

There is now a name for the field of activity by human–machine teams, "multi-agent intelligence research."[116] And the military is naturally interested. Here is a quote from a US Defense Dept agency soliciting proposals in the area:

The inability of artificial intelligence (AI) to represent and model human partners is the single biggest challenge preventing effective human–machine teaming today. Current AI agents are able to respond to commands and follow through on instructions that are within their training, but are unable to understand intentions, expectations, emotions, and other aspects of social intelligence that are inherent to their human counterparts. This lack of understanding stymies efforts to create safe, efficient, and productive human–machine collaboration.[117]

This military-oriented call for research makes it sound like much work remains. Maybe we should add "Fortunately." For we enter a danger zone, that of machine–man hybridization. The line from Icarus to post-humanism[118] is involuted, and explored in imaginative writing more than by scientists. It has never been that far from hybridization to hubris, even as the words' etymologies (roots of the former in the interbreeding of species, the latter in the Greek υβρις, excessiveness) differ.

It seems to us that in theoretical chemistry we have already found that hybrid strategy, a natural way, as the biomolecular calculations cited above show.

Onward

Does our position on simulation vs understanding seem Quixotian to the reader? They should know Jean-Paul lives in a house built by a miller, close to its two-century-old windmill.

One has to find a place between a *mauvais coucheur* ~ *kvetch*—and the eternal optimist crossed with a hypemaster. In-between is good place to be, because at the extremes the capacity to change is severely restricted. And change there will be, in this most Heraclitean of sciences.

In the third part of our Essay we will sketch our conception of that in-between-land, where theory, under-

standing, and simulation coexist. Where chemists remain important.

Acknowledgements

See Part A of this Essay.

Conflict of interest

The authors declare no conflict of interest.

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	External C	ortho C	para C
Hückel	0.571	0.143	0.143
ROHF	0.803	0.062	0.050
CASSCF (7,7)	0.591	0.117	0.142

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