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Computational Molecular Spectroscopy

- 2
- ³ Vincenzo Barone¹, Silvia Alessandrini¹
- 4 Malgorzata Biczysko²
- ⁵ James R. Cheeseman³
- 6 David C. Clary⁴
- 7 Anne B. McCoy⁵, Ryan DiRisio⁵
- 8 Frank Neese⁶
- 9 Mattia Melosso⁷, Cristina Puzzarini^{7,*}
- 10

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- ¹¹ ¹ Scuola Normale Superiore, Piazza dei Cavalieri 7, Pisa, 56126, Italy
- ² International Centre for Quantum and Molecular Structures, Physics Department, Shanghai
 ¹³ University, 99 Shangda Road, Shanghai, 200444 China
- ¹⁴ ³ Gaussian Inc., 340 Quinnipiac St., Bldg. 40, Wallingford, Connecticut 06492-4050, United States
- ⁴ Physical and Theoretical Chemical Laboratory, University of Oxford, Oxford OX1 3QZ, United
 Kingdom
- ¹⁷ ⁵ Department of Chemistry, University of Washington, Seattle, Washington 98195, United States
- ⁶ Max-Planck-Institut für Kohlenforschung, Kaiser Wilhelm-Platz-1, Mülheim an der Ruhr, Germany
- ⁷ Department of Chemistry "Giacomo Ciamician", University of Bologna, Via F. Selmi 2, 40126
 Bologna, Italy
 - *Corresponding author: cristina.puzzarini@unibo.it

27 Abstract

Molecular spectroscopy techniques are unique tools to probe molecular systems non-invasively and investigate their structure, 28 29 properties, and dynamics in different environments and physicochemical conditions. Different spectroscopic techniques and their combination can lead to a more comprehensive picture of investigated systems. However, the increasing sophistication of these 30 experimental techniques makes it more and more complex and difficult to interpret the results without the help of computational 31 chemistry. As a consequence, computational molecular spectroscopy has progressively changed from a highly specialized field to a 32 general tool also employed by experimentally-oriented researchers. Computational spectroscopy, born as a branch of quantum 33 34 chemistry for providing predictions of spectroscopic properties and features, evolved as an independent field. In this Primer, we 35 focus on the characterization of medium-sized molecular systems by means of different spectroscopic techniques. We first provide 36 essential information about the characteristics, accuracy and limitations of the available computational approaches, and select 37 examples with the aim of illustrating general trends, that is outcomes of general validity that can be used for modeling spectroscopic phenomena. We emphasize the need for estimating error bars and limitations, coupling accuracy with interpretability, and discuss 38 39 the results in terms of widely recognized chemical concepts.

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- 43 [H1] 1. Introduction
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Spectroscopy is the experimental way to study the electronic structure of a system, which is 45 intimately connected to its molecular structure, chemical linkages, and reactivity. Molecular 46 spectroscopy can probe any system in a non-invasive way, thus allowing the investigation of 47 structure and properties in different environments and/or physicochemical conditions. The 48 molecules addressed in this Primer fall into the category of medium-sized systems, which range in 49 dimension from a dozen atoms (such as the smallest amino acid, glycine) to several tens of atoms 50 (e.g. chlorophyll). Almost all possible environments will be considered: from gas phase to solution, 51 to crystals. 52

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Among the various spectroscopic techniques,¹⁻⁵ rotational spectroscopy is the most accurate and 54 reliable source for structural information and dynamics of gas-phase molecules.⁶⁻¹² Similarly, 55 vibrational spectroscopy permits the characterization of molecules in terms of conformation, 56 chemical linkage, and mutual interactions among atoms and atomic charges modulated by the 57 temperature and environmental effects. Indeed, while rotational spectroscopy is limited to the gas 58 phase, vibrational spectroscopic techniques can also investigate condensed phases. For these 59 reasons, vibrational spectroscopies (infrared, Raman, as well as their chiral counterparts) are 60 commonly employed for characterizing the structure and dynamical behavior of molecular systems. 61 Electronic spectroscopic techniques, in gas or condensed phases, deal with transitions between 62 different electronic states, thus giving access to the characterization of the molecular system in 63 excited electronic states. 64

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Modern high-resolution experimental spectroscopy may involve the acquisition of spectra resolving 66 hundreds, if not thousands of peaks, which is the case, for example, of rotational [G] and ro-67 vibrational [G] spectra of polyatomic, asymmetric molecules as well as electron spin resonance (ESR 68 **[G]**) spectra of metalorganic complexes. This spectral overcrowding means the interpretation of 69 high-resolution spectra without the help of quantum chemistry (QC) is a daunting if not impossible 70 task. Indeed, computational spectroscopy, born as a branch of quantum chemistry for providing 71 predictions of spectroscopic properties and features, evolved as an independent field. Currently, 72 theoretical studies in the field of molecular spectroscopy play three roles: interpretation, 73 complementarity, and prediction and support of experimental results. Computational spectroscopy 74 exploits theoretical models, provides tools and computer codes, and validates procedures for the 75 prediction, analysis, interpretation, and understanding of spectroscopic features, properties and/or 76 phenomena. There are several aspects and reasons that contribute to make computational 77 spectroscopy an unavoidable tool in the field of molecular spectroscopy. While there is no room for 78 addressing them in all detail¹³⁻¹⁸, in the following we emphasize the topics we consider of primary 79 importance. 80

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In terms of spectral interpretation, spectroscopic experiments often need a broad computational 82 investigation. For example, in order to analyze a recorded rotational or vibrational spectrum of 83 flexible molecular systems, a computational conformational analysis as well as subsequent spectral 84 predictions and simulations are necessary to understand which conformers [G] contribute and how. 85 QC also helps identify which aspects of a given structure are responsible for a specific spectroscopic 86 property. Computational studies can establish structure/property relationships as they allow the on 87 or off switching of specific effects and the analysis of the impact of these changes on the simulated 88 spectrum. To give an example, in organometallic complexes, there is a strong relationship between 89 metal-ligand bond distances and Mössbauer isomer shifts [G]. Combining broad computational 90

studies with a focus on structure-property relationships can, for example, identify short-lived and unstable species (in either ground or excited states).

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In terms of complementarity, one of the goals of experimental spectroscopy is to understand the 94 structure and bonding in molecule, although what is actually measured are the frequencies of light 95 that are absorbed. Computational spectroscopy can act as a bridge between experiments and 96 underlying physical properties, as it provides the theoretical expressions linking observable 97 measurements and molecular properties. Computational and experimental spectroscopy can also 98 be used to benchmark each other.¹⁹ Experimental spectroscopy is extremely sensitive to the 99 electronic structure of a given system, and it is one of the best ways to verify the reliability and 100 accuracy of theoretical predictions and validate QC calculation results. In parallel, experimentally 101 accessible spectroscopic properties may be much more sensitive to molecular structure than total 102 energies, which are often not experimentally measurable. 103

In terms of prediction and support, the combination of theory and experiment provides 105 experimentally calibrated or experimentally guided insights into electronic structure and, hence, 106 can serve as a guide to the reactivity of systems. The prediction and interpretation of structural 107 properties and dynamic behavior of molecules is at the heart of a deeper understanding of their 108 stability and chemical reactivity. Furthermore, understanding electronic structure and how is 109 reflected in the spectroscopic properties can give insights into entire classes of compounds, rather 110 than only for individual molecules. Computational spectroscopy can also act as the link between 111 different experimental techniques that traditionally were analyzed separately, such as, for example, 112 infrared (IR), Raman, Resonance Raman, ultraviolet-visible absorption or fluorescence (as well as 113 their chiral counterparts), and electron magnetic resonance. QC computations yield direct 114 information on many properties of molecular systems, which can link the molecular properties 115 measured using different experimental techniques. Finally, while peak positions and intensities 116 provide information on the structure of the system, the spectral line-shape is related to dynamical 117 (e.g. fluctuation) aspects. As a consequence, vis-à-vis comparison between simulated and 118 experimental spectra also gives access to these features. 119

Figure 1 provides a schematic representation of the types of transitions involved in the 121 spectroscopies addressed in this Primer: rotational, vibrational and vibronic spectroscopy. These 122 techniques investigate the transitions between the corresponding energy levels. Together with 123 them, their chiral counterparts, the alternative approach for rotational and vibrational 124 spectroscopies denoted Diffusion Monte Carlo (DMC), and magnetic resonance spectroscopies will 125 be also considered. Figure 1 also allows us to point out the physical aspects underlying each 126 spectroscopic technique. For instance, rotational spectroscopy is related to the rotational motion 127 of the molecular system under consideration, and it can thus be carried out experimentally only in 128 the gas phase. Vibrational spectroscopy describes instead vibrational motion of the atoms within the molecule, and it can be therefore exploited also in condensed phases. The approach mainly 130 followed in this Primer for obtaining the energy levels (DMC being the major exception) is based on 131 effective Hamiltonians and the resolution of the corresponding Schrödinger equation. 132

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Figure 1. Schematic representation of the energy levels, obtained from the resolution of the opportune Schrödinger equation, and the types of possible transitions. Blue arrows denote the transitions involving a change in the electronic state (from left to right: from thicker to thinner, electronic, vibronic and rovibronic transitions). Red arrows denote the transitions involving different vibrational states (from left to right: vibrational and ro-vibrational transitions). Green arrows denote the transitions only involving rotational energy levels. Dark grey arrows denote the transitions between energy levels obtained from magnetic field splitting.

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This Primer is organized as follows. The next section, titled Experimentation, provides the 135 theoretical foundations and computational requirements of the spectroscopic techniques 136 mentioned above. In the subsequent section, some specific results for these spectroscopic 137 techniques are presented, like e.g. the derivation of structural information and the determination 138 of the absolute configuration (AC) [G] of chiral molecules. The fourth section, devoted to 139 applications, reports a selection of significant examples such as Astrochemical studies and the 140 characterization of biomolecules and transition metal complexes. In the next two sections the issues 141 of reproducibility and data deposition, and limitations and optimizations will be addressed, 142 respectively. Finally, outlook and perspectives will be provided. 143

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[H1] 2. Experimentation

In the framework of a Primer dedicated to computational spectroscopy, we translate the 149 instrumentation, experimental design, and equipment to the language of the computational world 150 and discuss the theoretical foundations, computational requirements, and codes. In this section, we 151 start with the theory underlying the spectroscopic phenomena associated with molecular systems, 152 attempting to keep the treatment of mathematical expressions as simple as possible. We then move 153 to the computational requirements needed to reach the desired accuracy. We conclude the section 154 with a schematic presentation of some representative computer codes that are currently employed 155 in the field of computational spectroscopy. 156

[H2] 2.1. Theoretical foundations

The goal of computational spectroscopy is to couple accurate theoretical results with the interpretation of the experimental outcomes by using well-defined models. Theoretical analysis of spectroscopic phenomena is related to the transitions between the energy levels [G] (E_{mol}) of a given molecule (see Figure 1), which can be obtained from the solution of the corresponding Schrödinger equation:

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$$\widehat{H}_{mol}(\boldsymbol{r}, \boldsymbol{R}) | \Psi(\boldsymbol{r}, \boldsymbol{R}) \rangle = E_{mol} | \Psi(\boldsymbol{r}, \boldsymbol{R}) \rangle$$
 (Equation 1)

where $\widehat{H}_{mol}(\mathbf{r}, \mathbf{R})$ is the molecular Hamiltonian [G] (that is the Hamiltonian associated to the 167 molecular system under consideration), with **R** and **r** being the position arrays [G] of the nuclei and 168 electrons, respectively; $|\Psi(r, R)\rangle$ is the wave function [G] denoting the state of the molecule. As 169 Equation 1 is unsolvable for the majority of the molecular systems, approximations must be 170 introduced in order to obtain energy levels. The Born-Oppenheimer (BO) [G] approximation²⁰ 171 permits the separation of nuclei and electrons motions, thus leading to electronic and nuclear 172 Schrödinger equations. Once nuclear and electronic motions are separated, a further approximation 173 is required to simplify the nuclear Schrödinger equation. This is provided by the Eckart-Sayvetz 174 conditions,^{21,22} which factors out the translational motion and minimizes the couplings between 175 vibrations and rotations. One of the major consequences of the BO approximation is the definition 176 of the concept of potential energy surface (PES) [G], which is a function of the nuclear coordinates 177 and provides the relationship between the electronic energy of a molecule (from the resolution of 178 the electronic Schrödinger equation) and its geometry. Stable molecular structures (equilibrium 179 structures) are minima on the PES. A mathematical description of the PES enters the Hamiltonian of 180 the nuclear Schrödinger equation and, to simplify the treatment, it is often expressed in terms of 181 force constants, which are the derivatives of the electronic energies with respect to nuclear 182 coordinates evaluated at the minimum. 183

Here, we focus on the nuclear Schrödinger equation and, in the following, its resolution by means of perturbation theory techniques is presented. The advantage of perturbation theory is that it is generally accurate, and it is a powerful interpretative tool allowing a direct connection with the parameters that are used by experimentalists to fit their spectra. The most common approach for considering nuclear quantum effects and obtaining the energies and wave functions needed to study spectroscopic properties involves solving the time-independent Schrödinger equation:

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$$\widehat{H}_{vr}(\mathbf{R})|\Psi_{vr}(\mathbf{R})\rangle = E_{vr}|\Psi_{vr}(\mathbf{R})\rangle \quad \text{(Equation 2)}$$

with the Watson Hamiltonian²³ \hat{H}_{vr} being the most widely used Hamiltonian for the description of the vibro-rotational motion of semi-rigid molecular systems. The Watson Hamiltonian is expressed in terms of the dimensionless normal coordinates **[G]** (*q*) and their conjugate momenta (\hat{p}) referred to the equilibrium geometry of the system within a reference frame (principal inertia system) centered in the center of mass and oriented in order to diagonalize the equilibrium inertia tensor **[G]** (Eckart-Seyvetz conditions):

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$$\widehat{H}_{\nu r} = \frac{1}{2} \sum_{\alpha,\beta} \left(\widehat{f}_{\alpha} - \widehat{\pi}_{\alpha} \right) \mu_{\alpha\beta} \left(\widehat{f}_{\beta} - \widehat{\pi}_{\beta} \right) + \frac{1}{2} \sum_{r} \omega_{r} \, \widehat{p}_{r}^{2} + V(q) - \frac{1}{2} \sum_{\alpha} \mu_{\alpha\alpha}$$
(Equation 3)

where the q are linear combinations of the displacements of the Cartesian coordinates of the atoms. The harmonic wavenumber associated to the *r*-th normal coordinate is denoted by ω_r , and $\mu_{\alpha\beta}$ denotes an element of the inverse inertia tensor. \hat{J}_{α} is the rotational angular-momentum operator about axis α , and $\hat{\pi}_{\alpha}$ represents the α -th component of vibrational angular momentum. Since the exact form of the inverse molecular inertia tensor μ and the potential energy V are unknown, they are expanded as Taylor series with respect to q. A detailed account can be found in refs. ^{23,24}.

A different procedure is offered by a Hamiltonian-independent approach based on inverting the 210 information contained in the experimental spectroscopic transitions [G] in order to derive the 211 corresponding energy levels. After collecting all available (experimentally) measured transitions and 212 selecting the most accurate data (i.e. those affected by the low errors), and compiling them into a 213 database, spectroscopic networks are established in order to interconnect the energy levels. A 214 spectroscopic network is a graph where the nodes are the energy levels and the links are the 215 transitions. Inversion of the transitions through a weighted least-squares-type procedure results in 216 the energy levels and associated uncertainties. The MARVEL (Measured Active Rotational-217 Vibrational Energy Levels) protocol in the field of ro-vibrational spectroscopy^{25,26} provides an 218 illustrative example. 219

[H3] 2.1.1. Rotational Spectroscopy

To address rotational spectroscopy, the first step is the definition of a suitable Hamiltonian. The 223 starting point is the Watson Hamiltonian, from which the rotational part should be extracted. To 224 accomplish this, a contact transformation [G] is applied to the vibro-rotational Hamiltonian in 225 Equation 2, and this leads to a block-diagonal effective Hamiltonian.²⁷ Each of these blocks is 226 labelled in terms of the powers of q and \hat{p} , and powers of \hat{J} : the power of the former (vibrational) is 227 referred to as *n* and that of the latter (rotational) to *l*. Thus, the vibro-rotational Hamiltonian is now 228 indicated as \hat{H}_{nl} . By retaining the pure rotational and centrifugal-distortion terms (i.e. all 229 Hamiltonian terms with n = 0), the rotational Hamiltonian is obtained: 230

$$\widetilde{H}_{rot} = H_{02} + \widetilde{H}_{04} + \widetilde{H}_{06}$$
 (Equation 4)

where \tilde{H}_{04} and \tilde{H}_{06} are the quartic and sextic centrifugal-distortion terms, and H_{02} is the rigid-rotor Hamiltonian:

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$$H_{02} = \sum_{i} B_{i}^{eq} \hat{f}_{i}^{2}$$
 (Equation 5)

where \hat{J}_i is the projection of the rotational angular momentum operator along the *i*-th inertial axis, and the B_i^{eq} terms represent the equilibrium rotational constants, which are inversely proportional to the corresponding components of the inertia tensor (diagonal in the principal inertia system), which in turn only depends on the equilibrium structure and the isotopic masses of the molecule under consideration.²⁸ From a computational point of view, equilibrium rotational constants are derived from geometry optimization, the computational procedure that leads to the identification of the equilibrium structure. The accuracy of the equilibrium rotational constants therefore depends on the accuracy of this procedure.

To provide a description of the rotational motion that adheres to the real world, it is mandatory to 248 go beyond the rigid-rotor approximation and include centrifugal distortion (\tilde{H}_{04} , \tilde{H}_{06} , and even 249 higher-order terms)^{27,28} in the treatment. In the expression of the centrifugal-distortion terms, the 250 opportune power of the rotational angular momentum operator (which is expressed by the 251 subscript of H) multiplies the centrifugal distortion constants. For the computational determination 252 of the latter, different approximations of the PES entering the Hamiltonian are required: the 253 harmonic [G] part for the quartics (\tilde{H}_{04}) and an anharmonic description [G] for the sextics (\tilde{H}_{06}). 254 The tilde-sign denotes the result from a Hamiltonian reduction (interested readers are referred 255 to^{27,29}). It has to be noted that the Hamiltonian of Eq. 4 applies to the semirigid-rotor approximation 256 case (where the term "semirigid" implies the treatment of centrifugal distortion) and do not take 257 the effect of molecular vibrations into account. For a more accurate and realistic treatment, the 258 terms describing the vibration-rotation interaction need to be incorporated. These lead to the 259 description of the dependence of the rotational and centrifugal constants on the vibrational 260 quantum numbers. 261

The interactions of the molecular electric and/or magnetic fields with the nuclear or electron (for open-shell species) moments introduce additional terms in the rotational Hamiltonian,²⁸ and are responsible for the hyperfine structure in rotational spectra (these aspects are detailed later in the text). It should be noted that some of these hyperfine interactions are at the basis of magnetic spectroscopies such as nuclear magnetic resonance (NMR [G])³⁰ and ESR^{30,31} for interaction with nuclear and electron moments, respectively. Although a detailed analysis of those spectroscopies is outside the scope of the present primer, they play a central role in the study of biological molecules and transition metal complexes in condensed phases.^{32,33}

[H3] 2.1.2. Vibrational and Vibronic Spectroscopy

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²⁷³ The terms of the vibro-rotational Hamiltonian of concern to vibrational spectroscopy are

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$$\widetilde{H}_{vib} = H_{20} + \widetilde{H}_{30} + \widetilde{H}_{40} + D$$
 (Equation 6)

where the last term *D* incorporates high-order pure vibrational terms as well as those representing the interaction with the rotational motion (the so-called Coriolis couplings appearing among the latter terms).^{23,34} The rigid-rotor harmonic-oscillator model [G] corresponds to the first term (H_{20}), and allows to compute wavenumbers (ω) and intensities of the fundamental bands [G] (one-quanta transitions from the vibrational ground state) based on second (quadratic) derivatives of energy (quadratic force constants) and first derivatives of properties (e.g. dipole moment for IR spectra or scalar product of electric and magnetic moment for vibrational circular dichroism, VCD³⁵ [G]).

While a harmonic description of the PES entering the vibro-rotational Hamiltonian allows for a simplified description of the vibrational motion, a more realistic picture of the PES requires including anharmonic corrections. However, this complicates the resolution of the corresponding Schrödinger equation, thereby often resorting to perturbation theory. Vibrational perturbation theory to the second order [G] (VPT2)^{36,37} offers a very effective solution since the energy levels for all vibrational states can be computed from well-defined combinations of Coriolis couplings together with third and semi-diagonal fourth energy derivatives with respect to normal modes [G] (χ_{ii} and χ_{ij}), leading to the anharmonic wavenumbers for fundamentals, overtones [G], and combination bands [G]:³⁸

294	$\Delta E_{i}(0-1) = v_{i} = \omega_{i} + 2\chi_{ii} + \frac{1}{2}\sum_{i \neq j}\chi_{ij}$	(Equation 7)
295	$\Delta E_{i}(0-2) = 2\omega_{i} + 6\chi_{ii} + \sum_{i \neq j} \chi_{ij} = 2\nu_{i} + 2\chi_{ij}$	(Equation 8)
296	$\Delta E_{ij}(0 - 1, 0 - 1) = \omega_i + \omega_j + 2\chi_{ii} + 2\chi_{jj} + 2\chi_{ij}$	$+\frac{1}{2}\sum_{k\neq i,j}(\chi_{ik}+\chi_{jk})=\nu_i+\nu_j+\chi_{ij}$
297	(Equation 9)	-

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In analogy, anharmonic intensities can be obtained by a double-perturbative approach [G] in which, for both energy and property, the terms beyond the second and first derivatives, respectively, are treated as perturbations, with the unperturbed reference being the harmonic oscillator Hamiltonian. Computationally, this model requires second- and semi-diagonal third derivatives of the suitable property, with appropriate equations being derived up to three-quanta transitions.^{35,39-}

The most common way to derive the anharmonic PES and property surface (PS [G]) required for 306 VPT2 computations is based on numerical differentiation of the analytical second derivatives of the 307 energy and the first derivatives of the properties.^{34,42,43} However, energies and/or gradients can be 308 employed in numerical procedures⁴² and, for some electronic structure methods, fully analytical^{44,45} 309 derivations have also been reported. When taking into account resonance effects and/or decoupled 310 large amplitude motions by reduced-dimensionality variational approaches, this model is a very 311 effective working-horse for spectroscopic studies, in particular when dealing with medium- to large-312 sized molecules.^{34,35,39} The more so as vibro-rotational couplings can also be written in terms of 313 energy and rotational constant derivatives, without any additional electronic energy computation.⁴⁶ 314 In this connection, effective analytical first and second derivatives of methods rooted into the 315 density functional theory (DFT [G]) together with general purpose vibrational perturbation 316 implementations and reduced dimensionality models are allowing for reliable yet feasible 317 anharmonic computations of vibrational (IR, Raman) spectra of large systems and also of their chiral 318 counterparts (for example VCD). Noted is that semi-diagonal third-energy derivatives with respect 319 to normal modes are sufficient to evaluate also first-order vibrational modulation effects on other 320 spectroscopic parameters (e.g. optical activity, hyperfine tensors, etc.). 321

Together with perturbative approaches, alternative methodologies are possible such as, e.g. 323 vibrational self-consistent field (VSCF),⁴⁷ vibrational configuration interaction (VCI),⁴⁸ or vibrational 324 coupled clusters (VCC).⁴⁹ However, despite recent efforts,⁵⁰ they remain much more difficult to 325 translate into black-box procedures be also to used by non-specialists. 326 327

Moving to vibronic spectroscopy (vibrational transitions between different electronic states, see 328 Figure 1), vibrational signatures of one-photon absorption (OPA [G]) and one-photon emission (OPE 329 [G]) spectra including chiroptical ones (e.g. electronic circular dichroism, ECD [G]) and resonance 330 regimes (Resonance Raman) are defined by the overlaps between vibrational wavefunctions of the 331 initial (I) and final (F) electronic states $(\langle \Psi_F(\tau) | \Psi_I(\tau) \rangle)$.⁵¹ Small amplitude vibrations can be 332 effectively analyzed by harmonic models, ^{52,53} which take into account the difference between the 333 normal modes description in the initial (q_i) and final (q_f) states by using the Shift vector, K, and the 334 Duschinsky rotation matrix, 54 J): 335

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$$q_I = \boldsymbol{I} q_F + \boldsymbol{K} \qquad (\text{Equation 10})$$

Strong, bright electronic transitions can be simulated in terms of equilibrium transition dipole moments, d_{IF} (Franck-Condon approach^{55,56}), whereas inclusion of the transition dipole moment first derivatives with respect to normal coordinates becomes mandatory for forbidden or weaklyallowed transitions (Herzberg-Teller term⁵⁷):

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$$\left[d_{IF}^{eq}\langle\Psi_F(\tau)|\Psi_I(\tau)\rangle\right]^{FC} + \left[\sum_n \frac{\delta d_{IF}^n}{\delta q} \langle\Psi_F(\tau)|\Psi_I(\tau)\rangle\right]^{HT}$$
(Equation 11)

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with the sum over *n* (in the second term) running over the 3N-6 normal coordinates (3N-5 for linear molecules, N being the number of atoms of the molecule). Finally, for flexible molecular systems internal (in place of cartesian) coordinates must be employed whenever curvilinear effects cannot be neglected (as it is usually the case for low-frequency modes like, e.g., torsions, inversions or ring puckerings),^{58,59} and possibly also integrated with one-dimensional variational models for decoupled large amplitude motions⁶⁰. The considerations above are limited to those cases where the BO approximation applies. More advanced treatments, also including non-adiabatic contributions, are needed for more involved situations (e.g. near conical intersections).

A sketch of the main spectroscopic techniques, which can be reliably simulated in this framework is given in Figure 2, while for additional tutorial and review see refs.^{34,61,62}



Figure 2. General theoretical framework for vibrational and vibronic spectroscopies, and their chiral counterparts. Panel (a): schematic representation of the ground (red) and excited (blue) electronic state PESs, vibrational energy levels and wavefunctions. The energy scale underestimate gap between the two electronic states. Straight arrows represent transitions from the vibrational ground state: vibrational (red; IR and Raman) and vibronic (involving both states, blue; OPA). Circled arrows stand for the interaction with circularly polarized light corresponding to VCD (red), ROA (red) and ECD (blue) spectroscopies. Panel (b): schematic representation of resulting vibrational and vibronic line positions and corresponding intensities. Panel (c): examples of simulated and experimental spectra from refs^{17,35}.

356 [H3] 2.1.3. Chiral Spectroscopy

The chiral spectroscopic techniques addressed in this Primer are limited to optical rotation (OR), 357 ECD and VCD, as well as Raman optical activity (ROA [G]). OR and ECD arise from the differential 358 refraction and absorption, respectively, for left and right circularly polarized light and are associated 359 with electronic transitions. Optical rotatory dispersion (ORD [G]) is the wavelength dependence of 360 the OR. VCD and ROA arise from the differential absorption and scattering, respectively, for left and 361 right circularly polarized light and are associated with vibrational transitions. The approximations 362 and models related to the vibrational wavefunctions and their overlaps are the same as described 363 in the previous section (2.1.2). 364

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ORD is determined by the electric dipole – magnetic dipole polarizability, which is computed using 366 linear response methods as implemented in different QC software packages.⁶³⁻⁶⁵ Specifically, QC 367 programs report the specific rotation at each incident frequency in units of degrees dm⁻¹ (g/mL)⁻¹, 368 which can then be compared directly with the experiment. ECD and VCD are determined by the 369 dipole and rotational strengths of electronic or vibrational transitions, respectively, which are 370 related to the scalar products of the electric dipole and magnetic dipole transition moments. For 371 VCD, these are computed using linear response methods at either the harmonic^{1,66,67} or 372 anharmonic³⁵ level. The experiments measure the differential absorbance for left and right circularly 373 polarized light, which is typically converted to the differential molar extinction coefficient $\Delta\epsilon$ (in 374 units of M^{-1} cm⁻¹), which is related to the absorbance through Beer's Law⁶⁸. Since experimental 375 band-shapes of VCD spectra are most frequently Lorentzian while the experimental band-shapes of 376 ECD spectra tend to be Gaussian, the appropriate line-shape function [G] is added to the calculated 377 $\Delta\epsilon$. For more detail and the relevant conversions, the reader is referred to ^{1,66,69} for VCD and ^{69,70} 378 for ECD. 379

ROA is determined by electric, magnetic, and quadrupole polarizability transition moments of 381 vibrational transitions that are computed using linear response methods at either the 382 harmonic^{67,71,72} or anharmonic³⁵ level. In the far-from-resonance theory, where the exciting laser 383 radiation is far from the lowest allowed electronic excited state, ROA intensity differences are 384 determined by three tensor invariants constructed as linear combinations of products of these 385 polarizability tensors.^{1,69,73,74} Depending on the choice of polarization modulation and scattering 386 geometry, several forms of ROA are obtained, although the most common is back scattered circular 387 polarization denoted as SCP(180). QC programs report the ROA scattering activities for a particular 388 experimental setup, which are then converted to a differential scattering cross section which 389 includes a factor of $(v_{inc} - v_i)^4$, where v_{inc} and v_i are the wavenumbers for the incident frequency 390 and mode *i*, respectively^{69,75,76} Since experimental band shapes are typically Lorentzian, calculated 391 spectra are plotted using the Lorentzian line-shape function. As absolute ROA intensities are not 392 typically measured, it is common practice to label the intensity differences as $I_R - I_L$, as is done for 393 the experimental spectra. 394

[H3] 2.1.4. Diffusion Monte Carlo (DMC)

An alternative to conventional time-independent computational approaches to rotational and vibrational spectroscopy is offered by propagation of the time-dependent Schrödinger Equation as

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$$|\Psi(\tau)\rangle = \sum_{n} c_{n} e_{n}^{-\tau(E_{n}-V_{\text{ref}})} |\phi_{n}\rangle$$
 (Equation 12)
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where $|\phi_n\rangle$ is an eigenstate of the Hamiltonian, with energy E_n^{77-86} and $\tau = it/\hbar$. When we propagate an arbitrary wave function in imaginary time, at long times the leading contribution to

the wave function will be the ground state. Further, if $V_{ref} = E_0$, the amplitude of the wave function 404 will remain constant. The advantage of DMC approaches over conventional approaches comes in 405 the representation of the wave function. In the simplest implementation of diffusion Monte Carlo, 406 $|\Psi(\tau)\rangle$ is represented by an ensemble of localized functions, $g(\mathbf{x} - \mathbf{x}_i)$, 407

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 $\langle \boldsymbol{x} | \Psi(\tau) \rangle = \sum_{i} w_{i}(\tau) g(\boldsymbol{x} - \boldsymbol{x}_{i})$ (Equation 13)

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At each time step in the simulation, each of the components of each of the x_i is displaced by a random value based on Gauss-random distributions, where the distribution for the jth atom has a width of $\sqrt{\frac{\Delta \tau}{m_j}}$, where m_j represents the corresponding mass. After the atoms are displaced, the potential energy is evaluated, and the weight $w_i(\tau)$ is adjusted according to

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$$w_i(\tau + \Delta \tau) = e^{(V(x_i) - V_{ref})\Delta \tau} w_i(\tau)$$
 (Equation 14)

This relatively simple algorithm provides a Monte Carlo sampling of the ground state wave function 418 for the molecule of interest based on the provided potential surface as well as the ground state 419 energy. By propagating the ensemble forward in time we can obtain the information required to 420 generate the ground state probability amplitude.^{84,87} Such information allows us to explore how the 421 molecule samples the potential and evaluate, for example, rotational constants for obtaining 422 rotational spectra. Finally, energies and wave functions for rotation or vibrationally excited states 423 can be obtained using this approach by imposing a nodal structure for these states.^{86,88,89} The major 424 advantage of DMC over more conventional approaches is that it allows a way to explore the role of 425 nuclear quantum effects in systems where the ground state wave function is delocalized among 426 multiple local minima on the potential surface. These are situations where approaches, like 427 perturbation theory, become less effective. 428

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[H2] 2.2. Software for computational spectroscopy 431

Some available QC packages together with their potentialities and main features are provided in 432 Table 1. 433

Table 1. Selection of common soft	ware packages for computational spect	troscopy applications: QC methodologies and main	
spectroscopic features.			
Software package	Methodology	Spectroscopic applications	
CFOUR	CC theory / MP2	Rotational spectroscopy: all parameters	
http://www.cfour.de/	(analytic 2 nd derivatives)	Vibrational spectroscopy: VPT2	
[academic]	CC composite schemes	NMR/ESR spectroscopies: all parameters	
Gaussian	DFT/TD-DFT/MP2	Rotational spectroscopy: all parameters	
https://gaussian.com/	(analytic Hessians)	Vibr. Spectroscopy: IR, Raman, VCD, ROA	
[commercial]	CCSD(T) energies	Electr. Spectroscopy: UV-Vis, ECD, RR, RROA	
	QM/QM'/MM/PCM	NMR/ESR spectroscopies: all parameters	
Molpro	CC and explicitly correlated CC	Rot. Spectroscopy: equilibrium rot. constants	
https://www.molpro.net/	Multireference methods	Vibrational Spectroscopy: VSCF/VCI	
[commercial]	DFT/TD-DFT		
NWCHEM	CC theory energies	Rot. spectroscopy: equilibrium rot. constants	
https://nwchemgit.github.io/	MP2 analytical gradients	Vibration spectroscopy: VSCF energies	
[academic]	DFT/TD-DFT	Electr. Spectroscopy: UV-Vis	
	QM/MM	NMR: shielding tensors and indirect spin-spin	
	COSMO/SMD/VEM	coupling	

OPCA	CC and explicitly correlated CC	Pot Spoctroscopy: aquilibrium rat constants	
		Rot. Spectroscopy. equilibrium rot. constants	
https://orcaforum.kofo.mpg.de/	Local correlation methods	Vibr. Spectrosc.: IR, Raman, res. Raman, NRVS	
app.php/portal	Multireference methods	Electr. Spectroscopy: UV-Vis, ECD, MCD,	
[academic]	DFT/TD-DFT	Fluorescence, Phosphoresence, Band shapes	
	QM/MM, Embedding schemes	NMR/ESR spectroscopies: all parameters	
	Implicit solvation	X-ray absorption/emission, RIXS, Mössbauer	
QChem	CC theory (ground and excited	Rot. spectroscopy: equilibrium rot. constants	
http://www.q-chem.com/	states, spin-flip methods), MP2/ADC	Vibrational spectroscopy: IR/Raman, anharmonic	
[commercial]	schemes	energies TOSH, VPT2, VCI	
	(energies and gradients)	Electronic Spectroscopy: UV-Vis, RR	
	DFT/TD-DFT		
	QM/MM		
	PCM		
PSI4	CC /MP2	Spectrosc. constants for diatomics from PES fit	
http://www.psicode.org	CCSD(T) gradients	Rot. spectroscopy: equilibrium rot. constants	
[academic]	CC/MP2 composite schemes for	Vibrational spectroscopy: harmonic models,	
	energies, gradients and Hessians	Electronic Spectroscopy: UV-Vis, OR	
	DFT/TD-DFT		
	Solvent via external codes		

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[H2] 2.3. Computational requirements

The computational requirements strongly depend on the type of spectroscopic technique under

437 consideration and the accuracy specifically required.

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In the case of rotational and vibrational spectroscopies, the leading properties to be accurately 439 computed are the equilibrium rotational constants (which means equilibrium structure 440 determinations) and the harmonic frequencies (which implies harmonic force-field evaluations), 441 respectively. To obtain accurate results, one has to put effort on the electronic structure 442 calculations, the key point being to reduce as much as possible the errors due to the truncation of 443 both basis set (one-electron error) and wavefunction (N-electron error). To achieve this goal, 444 composite schemes have been set up: these evaluate the contributions important to reach high 445 accuracy at the best possible level and then combine them through the additivity approximation 446 (see, e.g., refs. ⁹⁰⁻¹⁰²). These usually involve the coupled-cluster (CC) theory [G] ¹⁰³ and in particular 447 the CC single and double excitations and a perturbative treatment of triples (CCSD(T)) [G] 448 method¹⁰⁴, which is often denoted as the "gold standard" for accurate calculations. On the other 449 hand, the introduction of explicitly-correlated (F12) treatments¹⁰⁵ allows for partially recovering the 450 one-electron error without extrapolation techniques. The development of local-correlation 451 treatments based on pair natural orbital (PNO [G])^{106,107} allows instead for improving the scaling of 452 coupled cluster treatments with the number of electrons. 453

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From a computational point of view, going beyond the rigid-rotor harmonic-oscillator 455 approximation increases the complexity and the cost of electronic structure calculations, thus 456 requiring a reduction of the level of theory for the electronic computations as well as the 457 introduction of approximations for the solution of the nuclear problem. Concerning the former 458 issue, global-hybrid or double-hybrid density functionals¹⁰⁸⁻¹¹⁰ [G] provide an optimal alternative to 459 low-cost ab initio methodologies such as the Møller-Plesset theory to second order (MP2)¹¹¹, while 460 VPT2 offers a powerful tool for the latter. The definition of hybrid coupled cluster/density functional 461 theory (CC/DFT) models, employing anharmonic corrections and/or property predictions beyond 462 the electric dipole moment from DFT, have been shown to represent nearly optimal compromises 463 between feasibility and accuracy.^{35,112,113} 464

However, application of DFT approaches to computational spectroscopy studies requires careful 466 benchmarking of all the required properties. Unfortunately, most of the benchmark studies 467 reported so far have been focused on the accuracy of energetic properties, for selected equilibrium 468 structures, ¹¹⁴⁻¹¹⁷ whose conclusions cannot be directly transferred to assess the accuracy of wider 469 regions of the PES (1) or other properties (2).^{62,118-120} Concerning the issue 1, flexible systems (like, 470 e.g., most biomolecules) are governed by flat potential energy surfaces, whose behavior cannot be 471 described in terms of the well-separated energy minima within nearly-harmonic basins, which have 472 been considered in most benchmarks. Focusing on point 2, the interpretation of important 473 spectroscopic techniques requires properties (e.g. magnetic dipole moments for chiroptical 474 techniques), whose computation has -however- not yet been validated in a comprehensive way. 475 Moreover, often second and higher analytical derivatives (of energy and properties) are not 476 implemented for some of DFT models, hampering their application in computational spectroscopy 477 studies. As a matter of fact, only a limited number of functionals and basis sets have been 478 benchmarked for geometric structures, ¹²⁰⁻¹²⁶ anharmonic vibrational frequencies, ^{62,118,119,126,127} and 479 other spectroscopic properties.^{119,126} The situation is less advanced for excited electronic states, but 480 the first benchmark studies going beyond vertical excitation energies have been reported^{128,129}. 481 Moreover, the recent implementation of analytical TD-DFT Hessians allows more efficient VPT2 482 computations for excited electronic states of medium- to large-sized molecules.¹³⁰ A more reliable, 483 but much more computational expensive alternative to DFT is offered by highly accurate Equation-484 of-Motion-CC (EOM-CC [G])¹³¹. Nevertheless, despite the successful applications of these 485 approaches, multireference (MR) methods¹³² cannot be avoided whenever nondynamic (static) 486 correlation [G] is important. Indeed, MR methods being based on wave functions described by the 487 linear combination of several electronic configuration are able to well address strong correlation 488 effects. We note in passing that modern linear or low-order scaling local correlation methods (based 489 on MP2 or CCSD(T)) have found increasing use in quantum chemistry and also in theoretical 490 spectroscopy¹³³⁻¹³⁵ However, a more detailed description of these aspects is out of the scope of this 491 Primer. 492

493 The most generally applicable methods in transition-element theoretical spectroscopy (see section 494 4.3) are based on traditional¹⁸ or more recent (e.g. density matrix renormalization group [G], 495 DMRG¹³⁶) multireference wavefunction based theories. These methods can now be routinely 496 applied to larger molecules (100-200 atoms). While they have been used extensively in form of, for 497 example, complete active space perturbation theory to second order (CASPT2 [G])^{137,138} or N-498 electron valence state perturbation theory to second-order (NEVPT2 [G])¹³⁹, severe limitations still 499 exist that will provide incentive for method developers for decades to come. A more thorough 500 description of these approaches and their strengths and weaknesses is outside the scope of this 501 Primer. 502

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A non-exhaustive summary of the computational evaluation of spectroscopic parameters is provided in Table 2, where - for each spectroscopic technique considered in this Primer - the (best) accuracy obtainable, the type of computation required as well as the level of theory and the affordable dimension of the system are collected. Noted is that this table is based on analytical derivative techniques, which means that further extensions in terms of properties and levels of theory can be reported.

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[bH1] Table 2. QC methodologies for the evaluation of spectroscopic parameters and associated accuracy.					
Spectroscopy	Spectroscopic parameters	Accuracy	QC calculations	QC methodology & feasible	number of atoms
				Wave function	DFT
Magnetic	 Chemical Shifts Spin-Spin Coupling g-tensor Zero-Field splitting Hyperfine coupling Quadrupole coupling Magnetizability 	Moderate; Variable for different nuclei	Response property calculation for imaginary and triplet perturbations	CCSD(T) < 10 Local CCSD(T) <200 (Local) MP2 < 200 HF < 1000	GGA < 2000 Hybrid < 1000 Double hybrid < 100
Nuclear	Mössbauer NRVS	10 ⁻⁹ eV <10%	Isomer shift, Quadrupole splittings, low-energy vibrational modes	CCSD <10 DLPNO-CCSD < 100	DFT < 1000
Rotational	Rotational constants Equilibrium Vibrationally corrected	<0.1% - 0.5% 0.1% - 2%	Geometry optimization (minimum of the PES) Anharmonic force field (2 nd and 3 rd energy deriv.)	Composite schemes < 30 MP2 < 20 CCSD(T) < 10	Hybrid > 100 Double-hybrid < 100 Hybrid < 100 Double-hybrid < 20
	Centrifugal (quartic) distortion constants	<1%	Harmonic force field	Composite schemes < 15	Hybrid <30 Double-hybrid < 20
Vibrational	 Vibrational freq. Harmonic Anharmonic 	1-20 cm ⁻¹ 1-10 cm ⁻¹	Harmonic force field Anharmonic contributions	Composite schemes < 15 MP2 < 20 CCSD(T) < 10	Hybrid < 400 Double-hybrid < 50 Hybrid < 50
	(VSCF/ VCI/ VPT2)		(3 rd + 4 th energy derivatives)		Double-hybrid < 20
	IR/Raman intensities Harmonic	10 km mol ⁻¹	dipole mom./polarizability: 1 st der. wrt to nucl. coord.	Composite schemes < 15 MP2 < 20	Hybrid < 100 Double-hybrid < 50
	Anharmonic	5 km mol ⁻¹	dipole mom./ polarizability: 2/3 der. wrt to nucl. Coord	CCSD(T) < 10	Hybrid < 50 Double hybrid < 20
	 VCD/ROA intensities Harmonic Anharmonic 	10-30%	Magnetic moments: 1 st der. wrt to nucl. coord. Magnetic moments: 2/3 der. wrt to nucl. coord		Hybrid < 100 Hybrid < 50
Vibronic	Electronic energy	0.1 -0.5 eV	Initial - final state energy difference between	MRCI, ADC EOM-CCSD <50 DLPNO-STEOM-CCSD < 150	TD-DFT < 200 TDA < 2000
	 Ground state equilibrium structure, normal modes and frequencies 	(see Rotation	al and Vibrational)		
	• Excited electronic state equilibrium structure	0.02-0.1 Å	Geometry optimization (minimum of the PES)	ADC(2) <50 EOM-CCSD,CC3 <15	TD-DFT < 100 TDA < 200
	Excited electronic state normal modes and Harmonic frequencies	30 cm ⁻¹	Harmonic force field (analytical or numerical differentiation of analytical gradient)	EOM-CCSD < 20	TD-DFT < 100 TDA < 200
	frequencies	10 cm ⁻¹	Anharmonic contributions (3 rd + semi-diag. 4 th deriv.)	MRCI, EOM-CCSD < 6	TD-DF T <20
	OPA/OPE/ECD	0.2 eV	Electric and/or magnetic transition moment	EOM-CCSD, CC3 < 15	TD-DFT < 100 TDA < 200
	• FC/HT	0.05 eV	Transition moment derivatives		TD-DFT < 100
X-ray	 K-edge absorption L-edge absorption K-beta emission RIXS 	1 eV 10% relative intensity	Excitation energies Multipole transition moments	EOM-CCSD < 20 MRCI < 10 NEVPT2 < 200 (RO-)CIS < 1000	TD-DFT < 1000

514 [H1] 3. Results

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In this section a few spectroscopic techniques have been selected to provide examples of how to
 process, treat and interpret spectroscopic data, specifically for spectroscopies involving rotational
 and vibrational motions.

[H2] 3.1. Rotational Spectroscopy for structural information

Despite the fact that rotational spectroscopy is the technique of choice for structural determinations, such derivations are seldom straightforward. Indeed, extracting geometrical parameters from the experimental information (rotational constants) is hampered by the number of data (rotational constants) actually available and vibrational effects.⁶ The fruitful interplay of high-resolution spectroscopy and QC allows for overcoming such difficulties, thereby exploiting a semiexperimental approach.

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The semiexperimental approach leads to equilibrium structures (i.e., by definition, the geometries corresponding to minima on the PES) by least-squares fitting the structural parameters to the semiexperimental equilibrium rotational constants $(B_{i,e}^{SE})$, which are determined by subtracting the computed vibrational corrections $(\Delta B_{i,0}^{calc})$ from the experimental (vibrational) ground-state rotational constants $(B_{i,0}^{exp})$:⁶

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 $B_{i,e}^{SE} = B_{i,0}^{exp} - \Delta B_{i,0}^{calc} = B_{i,0}^{exp} + \frac{1}{2} \sum_{n} \alpha_i^n$ (Equation 15)

where *i* denotes the principal inertial axis (a, b or c; so that $B_{i=a} = A$); the α_i^r are the so-called 536 vibration-rotation interaction constants and the sum is taken over all fundamental vibrational 537 modes n.²⁸ As evident from Eq. 15, resorting to equilibrium rotational constants allows to get rid of 538 vibrational effects (via the subtraction of the vibrational corrections). To overcome the limitation of 539 the number of experimental data (for a given isotopologue, there are at most three rotational 540 constants), different isotopic species are considered. In fact, these share the same equilibrium 541 structure because, within the BO approximation, the PES of a given molecule is isotope 542 independent. At the same time, they have different equilibrium rotational constants (because they 543 depend on the equilibrium structure and on the isotopic masses), thus increasing the amount of 544 experimental data. A sufficient number of isotopic species is required to have enough information 545 for a complete structural determination (i.e. to have more data than geometrical parameters). This 546 procedure is graphically described in Figure 3. Vice versa, high-level QC calculations allow accurate 547 predictions of the rotational parameters¹⁴⁰ to be used for planning, guiding, and interpreting 548 experiment.³⁴ Such an interplay can be enhanced by exploiting graphical tools able to visualize, 549 compare and manipulate spectra as well as to handle their assignment.¹⁴¹ 550

While these accomplishments are well established for small to medium-sized, semi-rigid molecules 552 (such as those shown in Figure 3), the situation is more involved for larger (and usually less rigid) 553 molecular systems. In recent years, thanks to the introduction of laser ablation vaporization¹⁴² and 554 broadband⁹ techniques, the targets of spectroscopic studies have been shifting towards flexible 555 molecules as well as non-covalent molecular complexes involving more than two molecules, both 556 categories being characterized by a large number of closely spaced energy minima (conformers or 557 isomers), all contributing to the overall spectrum. Therefore, a correct analysis of the latter requires 558 the knowledge of the rotational spectra of all isomers and/or conformers present in the gas-phase 559 mixture. Then, by weighting each contribution according to its population, the overall rotational 560

spectrum is obtained. Therefore, an incomplete account of conformers [G] can easily generate an unsatisfactory modeling; the situation is similar to the case of a wrong equilibrium structure determination when considering a semi-rigid molecule. To overcome these difficulties, powerful unsupervised techniques (such as machine learning algorithms) for the exploration of the degrees of freedom associated to the large amplitude motions are required.¹⁴³



Figure 3. Schematic representation of the interplay of experiment and theory in rotational spectroscopy for the determination of molecular structure. Experimental vibrational ground-state rotational constants are computationally corrected for vibrational effects. The resulting semi-experimental equilibrium rotational constants for different isotopic species allow for the determination of the equilibrium structure.

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[H2] 3.2. Vibrational/vibronic spectroscopy of flexible systems

The simplest approach to vibrational spectroscopy is based on the double harmonic approximation, 570 which employs quadratic and linear approximations for the PES (for transition frequency) and PS 571 (for intensity), respectively. This tool is available in several electronic structure QM codes, and it 572 becomes extremely efficient whenever analytical energy second derivatives and property gradients 573 are available. Mechanical (PES) and electric/magnetic (PS) anharmonicities can be introduced by 574 means of perturbative^{34,35,39-41,43} or variational^{34,47,48,144-146} time-independent (TI) approaches. The 575 first route, despite some limitations (e.g. the proper treatment of large amplitude motions, LAMs 576 [G]), allows for a general and robust simulation of spectral line-shapes and vis-á-vis comparisons 577 with experimental outcomes.^{35,39-41,61} Integration of both models within a general platform 578 simultaneously allows the correct treatment of small amplitude motions [G] (SAMs) and LAMs¹⁴² 579 Spectral simulation, analysis, and comparison with experiment can be greatly facilitated by 580 dedicated graphical tools like, e.g., the Virtual Multifrequency Spectrometer (VMS).⁶¹ 581

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In TI models, structures and properties of energy minima and their local environments are employed in variational or perturbative formalisms mostly exploiting the Watson Hamiltonian³⁴ (given in Equation 3 and discussed in section 2.1). In time-dependent (TD) approaches, classical or semiclassical dynamics simulations are performed over the whole PES and the corresponding PS.¹⁴⁷⁻¹⁴⁹ The two approaches (TI and TD) offer complementary information and the selection of the most appropriate strategy depends on several factors, including the environment (e.g. TI models are more

suitable for isolated molecules and TD ones for condensed phases), the effective mass governing 589 the motion (e.g. classical TD models are more effective for large masses), and other effects. For 590 flexible molecular systems, harmonic models based on curvilinear coordinates⁵⁸ should be used; for 591 systems with several low-lying conformers/tautomers, appropriate averaging of individual spectra 592 must be performed. Analogously to rotational spectroscopy, the presence of several low-lying 593 conformers/tautomers can tune the overall spectrum, thus requiring appropriate conformational 594 searches and weighting of the spectra of the most stable structures by the corresponding Boltzmann 595 populations.¹⁵⁰ In the case of solutions, for innocent solvents (that is solvents that do not establish 596 specific interactions like, e.g., hydrogen bonds), solvatochromic effects can be incorporated at a 597 negligible cost by means of the polarizable continuum model (PCM [G])³⁴, while - in more complex 598 cases - at least solvent molecules in the cybotactic [G] region must be explicitly included.¹⁵¹ 599

Moving to vibronic spectroscopy, absorption or emission electronic spectra are the envelopes of 601 specific vibrational levels of the initial and final electronic states. However, most of the current 602 computations still employ rough phenomenological models in which vertical transition energies are 603 broadened by empirical Gaussian or Lorentzian functions. Moreover, the analysis of experimental 604 data is often based on the assumption that the peak maxima are related to the so-called 0-0 605 transition (transition between vibrational ground states of initial and final electronic state). 606 However, it is impossible to know a priori which vibronic transition will be most intense, as it 607 depends on the largest overlap of vibrational wavefunctions. Therefore, realistic simulations must 608 take into account vibrational effects. In the Franck-Condon approximation the transition dipole 609 moment (Eq. 11) is considered constant (i.e. nuclear-coordinate independent) in harmonic TI (sum-610 of-state)⁵² or TD (path-integral)⁵³ approaches. The simplest formulation, based on one-dimensional 611 vibrational overlaps between (a possibly reduced number of) identical normal modes for the 612 different electronic states, is still employed in several studies and is also exploited in the 613 prescreening procedure for more sophisticated TI computations.⁵¹ While more accurate, direct 614 nuclear dynamics simulations are prohibitive for large systems and, as such, the most advanced 615 models employing highly accurate potential energy and property surfaces (PES and PS) can only be 616 applied to small-sized molecules.¹⁴⁴⁻¹⁴⁶ Integration of TI and TD models within a general platform 617 allows at the same time simulations of highly resolved spectra (including band assignments) and full 618 convergence of spectra at finite temperatures. For more complex, flexible systems several 619 approximate yet sufficiently accurate approaches have been proposed^{34,152-154} for both vibrational 620 and vibrationally-resolved electronic spectra. 621

[H3] **3.2.1** The MI-IR spectrum of glycine

A step-by-step route from the starting harmonic computations to the final realistic simulated 624 spectra is presented in Figure 4 for glycine (H₂NCH₂COOH), the simplest amino acid. Glycine is 625 characterized by conformational flexibility due to the rotation along three single bonds: N-C, C-C 626 and C-O. The small size of the molecule allows for a full theoretical exploration of its conformational 627 space, which confirmed the presence of eight local minima,^{113,120,155} labelled by roman numbers 628 referring to their stability order, with "p,n" describing the planarity or non-planarity of the 629 backbone, and "c,g,t" the cis, gauche or trans orientation of the lone-pair(N)-N-C-C, N-C-C-O, and C-630 C-O-H dihedrals. 631

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The six most stable conformers have been studied by means of Fourier transform infrared (FTIR) spectroscopy with three of them detected under the same experimental conditions.¹⁵⁶⁻¹⁵⁸ Figure 4 compares the computed spectra with FTIR results for glycine deposited in a low-temperature matrix. The most intense experimental bands can be identified based on the harmonic spectrum of the most stable conformer Ip. An improvement (a more realistic spectrum) is obtained by including anharmonic corrections to band positions and intensities, with the consequent appearance of several new bands (non-fundamental transitions). The best agreement with experiment is obtained once the contributions from IIn and IIIp conformers, weighted for their Boltzmann populations, are added. Fully anharmonic spectra allow to distinguish between low-intensity bands related to nonfundamental transitions of the most abundant conformer (not present at harmonic level) and the fundamental transitions of the less abundant ones (see ref. ¹¹³ for detailed discussion and analysis).





Figure 4. Computed¹¹³ and experimental¹⁵⁷ MI-IR spectra of glycine. Simulated harmonic and anharmonic theoretical spectrum of the most stable Ip conformer together with the final spectrum resulting from the sum of the contributions of Ip/ttt, IIn/ccc and IIIp/tct conformers, weighted for their relative abundances, at 410 K (temperature of the sample preparation), also assuming the conformational cooling of less stable conformers.

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[H3] 3.2.2 Vibronic spectrum of chlorophyll-a

In general terms, vibronic spectra simulations are necessary to distinguish different contributions to the spectrum line-shape from different electronic transitions, conformers, or other species possibly present in the experimental mixture, for instance as photoproducts.¹⁵⁹ As an example, the UV-vis spectrum of chlorophyll-a in methanol solution (Figure 5) has been simulated considering environmental effects by means of hybrid implicit/explicit solvent model with the two methanol molecules coordinating the Mg ion and the bulk solvent effects accounted for using the PCM (see ref. ¹⁶⁰ for the details, and ref. ¹³⁵ for the gas-phase spectrum simulation).

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The spectra of chlorophylls are traditionally described in terms of four bands, based on the simplified four-orbital Gouterman model:¹⁶¹ two low-energy Q-bands and two high energy Soret (B) bands. The additional x/y labeling, according to the direction of their polarization within a macrocycle plane,¹⁶² can also (as in this case) be used. The top panel demonstrates how the set of

vibronic transitions defines the asymmetric shape of the lowest energy $S_1 \leftarrow S_0$ transition, which 659 cannot be well described by the simplest vertical energy approach, irrespective of the applied 660 broadening. This transition dominates the Qy band, but gives also a significant contribution to the 661 Qx one. The final spectrum, which can be directly compared with the experimental one in the whole 662 UV-vis range, is obtained from the single $S_x \leftarrow S_0$ (x=1-8) transition contributions. Simulation of 663 vibronic spectra allows for the unequivocal assignment of the main spectral features, showing that 664 the line shape is dominated by two pairs of overlapping transitions: $S_1 \leftarrow S_0$ and $S_2 \leftarrow S_0$ being the first 665 pair and $S_3 \leftarrow S_0$ $S_4 \leftarrow S_0$ the second one. These pairs give rise to the Qy/Qx and By/Bx bands, 666 respectively. 667 668



Figure 5. Computed¹⁶⁰ and experimental¹⁶³ UV-vis spectrum of chlorophyll-a in methanol. Simulated theoretical spectra: (top panel) $S_1 \leftarrow S_0$ (Q_y) transition simulated by the vertical approximation (VE) and vibronic spectrum; (bottom panel): absorption spectrum in the 250-700 nm range obtained as sum of vibronic spectra of the first 8 lowest single electronic transitions. All theoretical spectra are red-shifted by 450 cm⁻¹ (about 20 nm). Theoretical stick spectra have been convoluted by Gaussian functions with a half-width at half maximum (HWHM) of 500cm⁻¹ (VE) or Lorentzian functions with a HWHM of 250 cm⁻¹ (Vibronic).

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[H2] 3.3. Molecular vibrations from diffusion Monte Carlo

For molecules that undergo large amplitude vibrations, many insights can be obtained from knowledge of how the ground state wave function samples the potential surface, and how this is affected by isotopic substitution. DMC provides an approach that is well-suited to exploring ground

state properties of molecules showing LAMs. The power of the DMC approach comes from the fact that the wave function is represented by an ensemble of localized functions (or walkers [G]) as described by Eq. (12). This allows for studies of systems that are not well-approximated by a simple zero-order (harmonic) description (like, e.g., torsions around simple bonds or ring puckerings). This comes at the cost that, generally, only one state can be calculated at a time, making the approach well-suited for studies that focus on the ground state wave function and associated properties including vibrationally averaged rotational constants.

In DMC, at each step in the simulation, a reference energy is evaluated using⁸⁶

 $V_{ref} = \overline{V}(\tau) - \alpha \left(\frac{N_w(\tau)}{N_w(0)} \right)$ (Equation 16)

where the first term provides the ensemble average of the potential energy, and the second term adjusts the value of V_{ref} to ensure a nearly constant ensemble size throughout the simulation. Once the ensemble has equilibrated, the time averaged value of V_{ref} provides the zero-point energy of the system of interest.

It is important to recognize that this value fluctuates throughout the simulation, as is illustrated for 692 $H^{+}(H_{2}O)_{2}^{164}$ in panels A-C in Figure 6. These plots show the evolution of V_{ref} for three different 693 combinations of time increments ($\Delta \tau$) and ensemble sizes (N_w), where all simulations are 694 propagated over the same total time. Generally, the size of the fluctuations of V_{ref} decreases as N_w 695 or $\Delta \tau$ increases, thus improving the quality of the results, but also increasing the computational 696 time. Additionally, the size of these fluctuations can be tuned by changing the value of α . For the 697 plots shown in black in panels A-C of Figure 6, α = 0.5/ $\Delta \tau$. In panel C, we explore how the value of α 698 affects the sizes of the fluctuations in V_{ref}. As is seen, when α = 0.5, the fluctuations are largest, and 699 as α is decreased to 0.1 or smaller, the size of these fluctuations remains roughly the same on the 700 scale of this plot. On the other hand, if we focus on a smaller range of propagation times, we find 701 that decreasing α removes the highest frequency fluctuations, while a low-frequency oscillation of 702 V_{ref} remains (see lower panel of Supplementary Figure 2 in the Supplementary Information). In 703 selecting α , one strives to identify a value where the high frequency oscillations of V_{ref} occur 704 between roughly three and ten time steps. This choice lessens the correlation of V_{ref} between 705 subsequent time steps without increasing the magnitude of the fluctuations of V_{ref}- Several tests 706 confirmed that $\alpha = 0.5/\Delta\tau$ generally yields good results in this regard.^{84,165,166} 707

The numbers shown in panel B provide the zero-point energy [G] that is obtained by averaging V_{ref} 709 over different ranges of τ . The numbers in parentheses represent the standard deviation among 710 five independent simulations that were performed using these parameters. As seen, the evaluated 711 energy is relatively insensitive to how long the averaging is over, but the standard deviations are 712 about half as large when $V_{
m ref}$ is averaged over more than 10 000 a.u. of time. The evaluated zero-713 point energies for nine different combinations of ensemble sizes and time increments are compared 714 in panel D. We note that the smallest N_w has the greatest uncertainty in its zero-point energy, and 715 when one uses both the smallest N_w and the largest $\Delta \tau$, the simulation yields a zero-point energy 716 that is inconsistent with the benchmark calculation (dotted line with grey shading). The larger 717 ensembles provide zero-point energies that agree with the benchmark results for all three time 718 increments. However, as with the fluctuations of V_{ref}, the statistical uncertainties in the reported 719 zero-point energies decrease for smaller $\Delta \tau$ and for larger ensembles, so a compromise must be 720 made between accuracy and computational time. 721

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In addition to the zero-point energies, DMC provides a powerful tool for obtaining projections of 723 the ground state probability amplitude onto a desired coordinate. This is achieved by propagating 724 the ensemble of walkers over a short period of imaginary time [G], τ_{DW} , and identifying the fraction 725 of the ensemble at τ + τ_{DW} that is traced to a particular walker in the ensemble at τ . This number 726 is proportional to the value of the wave function at the coordinates of the walker at τ ,^{84,87} allowing 727 us to use Monte Carlo integration to generate the desired projection of the probability amplitude, 728 Ψ^2 . This approach is used to obtain the projection of the ground state probability amplitude onto 729 the Δr (see inset in panel E), and the resulting distributions are shown in the panel E of Figure R4 730 for several values of τ_{DW} . As it is hard to differentiate among these results, the mean values of Δr , 731 along with the standard deviation, are shown as functions of au_{DW} in panel F. The convergence of 732 the results can be estimated by the results reported in this panel, which compares the computed 733 values against independently obtained values of these quantities based on symmetry ($\langle \Delta r \rangle$, black 734 dotted line) or an alternative way to obtain expectation values ($\sigma_{\Delta r}$, green dotted line).^{83,167} 735 736

Extensions to DMC that enable the study of excited state energies and wave functions have been
 developed,^{86,168-170} although a discussion of these is beyond the scope of the present Primer.



Figure 6: (A)-(C) The value of V_{ref} plotted as a function of imaginary time, obtained from DMC simulations using (A) N_w=4000 and $\Delta\tau$ =10 a.u.; (B) N_w = 16 000 and $\Delta\tau$ =5 a.u.; and (C) N_w = 32 000 and $\Delta\tau$ =1 a.u.. In panel B, we also show how the evaluated zero-point energy depends on how long V_{ref} is averaged. These values are also tabulated in the Supplementary Information (Supplementary Tables 1 to 3). In Panel C, we also explore how the size of the α -parameter (see equation above) affects the magnitude of the fluctuations in V_{ref}. (D) The calculated zero-point energy is plotted as a function of the time increment for ensemble sizes ranging from 4000 (red) to 3200 (green) walkers, and compared to the results obtained using N_w = 20 000 and a time increment of 10 a.u. (black line, where grey shading indicates a 5 cm⁻¹ uncertainty in that value). (E) Projections of Ψ^2 onto Δr (see inset) as a function of ensemble size based on a calculation where the number of descendants is evaluated after τ_{DW} = 520 a.u. (F) The expectation value (grey) and standard deviation of Δr , plotted as a function of τ_{DW} . The dotted grey and green lines provide reference values of 0 Å for the average and 0.240 Å for the standard deviation. While the average value of of Δr can be determined by symmetry, the standard deviation is obtained using an adiabatic DMC calculation.^{83,167} All error bars and uncertainties reflect the standard deviations among five independent DMC simulations.

[H2] 3.4. Determination of absolute configurations

The chiral spectroscopic techniques considered here (ORD, ECD, VCD and ROA) play a fundamental 742 role in the determination of absolute configuration (AC) [G]. As spectra for enantiomers are mirror 743 images, the AC can be determined by comparing the calculated spectra with the experimental ones. 744 In the simplest case, in order to determine the AC using the methods mentioned above, the spectra 745 of the two enantiomers are calculated and compared to the experimental spectrum of one of the 746 enantiomers, (+) or (-). The calculated spectrum in best agreement with the experimental spectrum 747 defines the AC of the experimental enantiomer. As an example, the experimental and calculated 748 VCD spectra for (+)-camphor and (1R,4R)-camphor are shown in Figure 7a. Given the quantitative 749 agreement between the calculated and experimental spectra, the AC of (+)-camphor is assigned to 750 be 1R,4R. Since these are enantiomers, it follows that (-)-camphor is (1S,4S). 751

Each of these chiral spectroscopies can be applied individually or in combination.¹⁷¹⁻¹⁷⁶ The 753 advantage of using multiple methods is that they provide complementary information, which is 754 useful in distinguishing diastereomers with multiple chiral centers, as one method may not be able 755 to distinguish particular stereocenters. Specifically, Polavarapu et al.¹⁷¹ found that ORD, ECD and 756 VCD were individually unable to unambiguously assign the AC of Hibiscus and Garcinia acids, each 757 containing two chiral centers. However, a combination of VCD with either ECD or ORD was able to 758 correctly assign the AC of both molecules. Similarly, Hopman et al.¹⁷⁶ found that VCD and ROA, but 759 not ECD, were able to correctly assign the AC of Synoxazolidinone, a marine antibiotic compound 760 containing two chiral centers and one asymmetrically substituted double bond, resulting in a total 761 of eight possible stereoisomers. A recent study by Bogaerts et al.¹⁷⁴ on Artemisinin, an anti-malaria 762 drug containing seven chiral centers, found that even though ROA and VCD could independently 763 assign the correct stereochemistry, the combination of these two methods resulted in an even 764 stronger unambiguous AC assignment (VCD and ROA spectra shown in Figure 7b,d). 765

For molecules containing multiple chiral centers and whose diastereomers predict similar spectra, 767 the harmonic approximation, which is routinely used for VCD and ROA, may not be sufficient in 768 providing a reliable AC assignment. This is the case for Diplopyrone, a phytotoxic monosubstituted 769 tetrahydropyranpyran-2-one, containing four chiral centers, two of which were previously 770 unassigned.¹⁷³ In addition, this molecule possesses several low-energy conformers, further 771 complicating the analysis of the spectra as discussed in section 3.2. In this case, ECD was not able to 772 distinguish between the four possible diastereomers and the diastereomers predicted very similar 773 harmonic VCD spectra. However, VCD spectra computed at the anharmonic level (Figure 7f) were 774 sufficiently close to experiment to allow for a confident assignment of the two unknown chiral 775 centers. 776

The comparison of calculated and experimental spectra is an important part of the assignment of 778 AC. Although this comparison can be performed visually, different approaches exist to remove bias 779 and to quantify the degree of similarity. All of these methods rely on the calculation of a spectral 780 overlap between the experimental and predicted spectra.^{172,174} Another approach involves the 781 analysis of the dissymmetry factor, the ratio of $\varDelta\epsilon$ and $\epsilon.^{69,175,177}$ Another measure of the reliability 782 of the calculated vibrational spectra is the concept of robust modes, first developed for VCD¹⁷⁸ and 783 later extended to ROA.¹⁷⁹ In this approach, a mode is determined to be robust if the rotational 784 strength or scattering activity will not change sign due to small perturbations in either experiment 785 or calculation. 786

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Although the primary utility of the chiroptical vibrational methods is to produce the spectra shown in Figure 7, additional information can be extracted which can help in the analysis and interpretation of the results. These include examining the vibrational transition current density associated with a molecular vibration^{180,181} for VCD and computing atomic contribution patterns and group coupling matrices¹⁸² for ROA.

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Figure 7: Computed and experimental VCD and ROA spectra for the determination of AC. (a) Comparison of calculated and experimental VCD spectra for (1R,4R)-camphor and (+)-camphor, respectively. Calculated spectra are plotted using the Lorentzian lineshape function using a HWHM of 4 cm¹. Experimental data, originally from ref ⁶⁶, kindly provided by Frank Devlin (USC). (b-e) Comparison of calculated and experimental VCD (b) and IR (c) and ROA (d) and Raman (e) spectra for artemisinin. Calculated spectra are plotted using the Lorentzian lineshape function using a HWHM of 5 cm⁻¹ for VCD/IR and 8 cm⁻¹ for ROA/Raman. Figure taken from ¹⁷⁶. For a molecule containing seven chiral centers there would, in principle, be $2^7 = 128$ diastereomers, but since two of the chiral centers are fixed (via the endoperoxide bridge) this number is reduced to $2^6 = 64$. However, half of these are enantiomers so that conformational analysis and spectra calculations were performed for a total of 32 diastereomers. (f-g). Comparison of calculated anharmonic and experimental VCD (f) and IR (g) spectra for (+)-diplopyrone ((+)-6-[(1R)-1-hydroxyethyl] 2,4a(S),6(S),8a(S) tetrahydropyran[3,2-b]pyran-2-one). Calculated spectra are plotted using the Lorentzian lineshape function, using a HWHM of 8 cm⁻¹. Figure taken from ¹⁷³.

796 [H1] 4. Applications

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As done for the results section, a limited selection of possible applications is reported to provide significant examples of the potential of computational molecular spectroscopy, the examples being selected from the spectroscopies addressed in this Primer. However, the list of possible applications is too long for being even simply enumerated here.

[H2] 4.1. Astrochemistry

The role of spectroscopic techniques in the study of the interstellar medium (ISM) has grown rapidly 804 in the last few decades, with rotational spectroscopy playing a critical role. Most of the 805 understanding of the ISM – the gas and dust existing in the space between the stars of a galaxy – 806 comes from Earth-based spectroscopic observations. Atoms and molecules in the gas phase 807 constitute 99% of the ISM's mass, while the remaining mass is composed of silicate and carbonate 808 grains.¹⁸³ At the low temperatures of the ISM, gas-phase particles emit radiation whose frequency 809 spans from the gigahertz to the terahertz domains. Physically, the quanta emitted corresponds to 810 the transitions between rotational energy levels of molecules. Thus, each molecule can be identified 811 through its peculiar fingerprints - i.e., its rotational transitions.¹⁸³ With these molecules being 812 ubiquitous in the ISM, the chemical composition - as well as the physical properties and the 813 evolutionary stage of interstellar objects - can be derived from radioastronomical observations.¹⁸⁴ 814 The laboratory data needed to guide the latter and to discover new interstellar species are provided 815 by rotational-spectroscopy laboratory studies,¹⁸⁵ which are increasingly supported and 816 complemented by QC computations.¹⁴⁰ 817

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The search for interstellar complex organic molecules (i-COMs, i.e. species containing at least six 819 atoms and composed of carbon, hydrogen, oxygen, and/or nitrogen¹⁸⁶ can be assisted by the 820 Minimum Energy Principle (MEP), which states that "the most stable isomer of a given chemical 821 formula is always the most abundant in the ISM".¹⁸⁷ A computational study of the relative stability 822 of different isomeric (structural or conformational) species allows the screening of potentially 823 observable molecules. In the case of conformers, the energy difference among the various 824 conformers can be as small as a few kJ/mol, and the size of the electric dipole moment becomes an 825 important parameter worth computing (the intensity of rotational transitions scales with the square 826 of the dipole moment component that allows the transition). The combination of the MEP and the 827 magnitude of the electric dipole moment enables the straightforward identification of the most 828 likely detectable i-COMs. 829

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Once the species of interest is recognized, computational spectroscopy guides the experimental 831 study by providing accurate predictions of the rotational parameters to be used for simulating their 832 spectra.^{141,188} Despite the potential accuracy that can be reached by such calculations,¹⁴⁰ this is 833 generally insufficient for directly guiding astronomical searches and/or assignments. However, in 834 some cases, QC predictions can assess the detection of new astrochemical species, as is the case 835 with the cyanobutadiynyl anion, C₅N⁻.¹⁸⁹ Due to the difficulty of producing this species, no laboratory 836 study of its rotational spectrum has been reported to date. Nonetheless, C₅N⁻ has been discovered 837 in the envelope of a carbon-rich star thanks to the pinpoint match between astronomical 838 observations and predictions based on high-level coupled-cluster calculations.¹⁹⁰ 839

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The analysis of astronomical spectra can provide new information; however, the help of QC calculations is often needed. To give a specific example, the investigation of the hyperfine structure of the rotational spectrum is fundamental to gaining information on column densities, which provide

a measure for molecular abundances. The hyperfine structure in rotational spectra is due to 844 interactions between the molecular electric and/or magnetic fields and the nuclear moments. The 845 most important of these interactions is that between the molecular electric-field gradient and the 846 electric quadrupole moment of nuclei (with the latter being present when the nuclear spin is greater 847 than 1/2). Among the magnetic interactions, the weak magnetic field generated by the end-over-848 end rotation of a molecule interacts with the nuclear magnetic moments, thus producing a slight 849 magnetic split or shift of the lines (with nuclear magnetic moments being present when the nuclear 850 spin is non-null). These two interactions are referred to as nuclear quadrupole coupling and spin-851 rotation interaction, respectively; in addition, dipolar spin-spin interactions among different nuclear 852 spins may also arise. In the case of molecular ions, the resolution of experiment is usually limited by 853 the impossibility of reducing the working pressure inside the cell (because of the ion-production 854 process),¹⁹¹ thus leading to the partial or even non-resolution of hyperfine structures, as shown in 855 Figure 8. Interstellar lines are instead very narrow. Therefore, when required, one can resort to QC 856 calculations to accurately predict the hyperfine structure of astronomical spectra: the quantitative 857 accuracy obtainable with state-of-the-art QC calculations is demonstrated in Figure 8. Another 858 significant example is offered by CF⁺,¹⁹² for which the hyperfine structure of the astronomical 859 (rotational) spectrum was assigned using the computed hyperfine parameters. 860



Figure 8. Comparison of a portion of the laboratory $(LAB)^{191}$ and astronomical (ASTRO, low-mass cloud core L1512 in Taurus¹⁹³) spectrum of the first rotational transition (J = 1 - 0, with J being the rotational quantum number) of the diazenylium cation (N_2H^+). The actual comparison is between the red LAB spectrum (resulting from the line profile analysis of recorded spectrum in black, with the green trace being the corresponding residual) and the ASTRO counterpart, with the hyperfine splittings also reported. These are compared with the computed (QC) values.

The hyperfine structure is due to the presence of two nuclear quadrupolar nuclei, the nitrogens. The quantum numbers F_1 and F arise from the coupling schemes $F_1 = J + I_{N1}$ and $F = F_1 + I_{N2}$, respectively, with I being the nuclear spin quantum number (=1 for nitrogen).

Finally, an appropriate modeling of the ISM demands the computation of collisional rate coefficients 863 for interstellar molecules by the most abundant species, i.e. hydrogen and helium (denoted as 864 collider). Interstellar species are often far from a local thermodynamic equilibrium (LTE) condition. 865 Therefore, the collisions occurring between the molecule under consideration and molecular 866 hydrogen (or atomic helium) significantly affect the population of rotational levels of the former 867 and thus have an impact on the rotational transitions observed with radioastronomy.¹⁹⁴ In turn, the 868 derivation of collisional data requires the computation of the PES of the molecule-collider with high 869 accuracy. 870

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[H2] 4.2. Weakly bound clusters and biomolecules

A wide and expanding application of computational spectroscopy is the calculation of spectra for weakly bound clusters and biomolecules. In its broadest sense this includes magnetic and electronic spectroscopy^{195,196} but here we will confine comments to vibrational spectroscopy with applications mainly to the near and far infrared region of the spectrum.

Advances in high resolution infrared spectroscopy of small van der Waals molecules have stimulated 878 very good agreement between theory and experiment.¹⁹⁷ This work started with rare gas atoms 879 attached to diatomic molecules¹⁹⁸ but has been extended to larger weakly bound clusters involving 880 polyatomic molecules¹⁹⁹. Clusters involving water molecules have received particular attention due 881 to the importance of water throughout the sciences.²⁰⁰ Water dimer is a key system and highly 882 accurate fully dimensional potential energy surfaces have been produced from sophisticated ab 883 *initio* procedures.²⁰¹ These potentials have been used in converged calculations of vibrational states 884 using appropriate basis functions for the different degrees of freedom and full-dimensional 885 Hamiltonians with variational procedures. This has led to excellent agreement between theory and 886 experiment for the spectra in the far infrared region of the water dimer.²⁰² 887

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This advance is important as the PES for water dimer forms the main component of potentials for 889 larger water clusters, as the only supplements needed are fairly simple three- and four-body 890 interactions between the different water molecules.²⁰³ More challenging is the accurate calculation 891 of the ro-vibrational states of water clusters larger than the dimer, as conventional basis set 892 methods with variational procedures then quickly become unwieldy. However, alternative 893 procedures have been applied for larger water clusters that can calculate quite accurately some 894 parameters of experimental interest, such as the rotational constants of the lowest vibrational 895 states of clusters of different geometries, and tunneling splittings of vibrational states arising from 896 identical minima on the potential energy surfaces. In this way diffusion DMC,²⁰⁴⁻²⁰⁶ instanton,²⁰⁷ and 897 path integral²⁰⁸ procedures have been applied effectively on clusters up to (H₂O)₈ and have allowed 898 detailed comparison with far infrared and microwave experiments. 899

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The general importance of water in biology has meant that clusters of water with molecules of biological interest have been the subject of numerous calculations.²⁰⁹ Methods such as DMC can also be applied to calculate structures of geometric isomers of biomolecules and the associated rotational constants.²¹⁰ QC calculations of infrared spectra for complexes such as uracil-water have shown the importance of hydrogen bonding and anharmonic effects in these systems.²¹¹



Figure 9. Experimental and calculated near infrared spectra of crystalline (A) adenine; (B) cytosine; (C) guanine; (D) thymine in the 4000–7500 cm⁻¹ region.²¹²

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For more complicated biomolecules the whole plethora of quantum chemistry, DFT and more approximate procedures such as QM/MM and semiempirical force fields have been applied.²¹³ In the simplest approaches just the harmonic frequencies are calculated but anharmonic aspects have also been considered using a variety of quantum mechanical (QM) procedures including VPT2 and VSCF.²¹⁴

A good example of a recent study is a calculation²¹² of the near infrared spectra of the crystalline structures of DNA bases in which results from Deperturbed VPT2 (DVPT2) calculations were compared in detail with experiment (see Figure 9). Calculations such as those shown in Figure 9 demonstrate the power of computations in predicting and interpreting the vibrational spectra of molecules of biological interest. Indeed, assignment of the different overtones and combination bands found in this high-energy region (4000-7500 cm⁻¹) and their interpretation in terms of structural motifs would be very difficult (and questionable) without the help of QC computations.

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[H2] 4.3. Spectroscopy of d- and f-elements

The spectroscopy of *d*- and *f*-elements introduces new experimental and theoretical challenges that are not easily met. At the heart of the challenges associated with these elements is the fact that they can exist in a variety of oxidation states that lead to spectroscopically well-defined d^n and f^n configurations (*n*=number of electrons in the *d*- or *f*-shell).

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Given the high effective nuclear charge experienced by the *d*- or *f*-electrons, the corresponding orbitals are compact. Hence, compared to the strong bonds formed between main group elements, the *d*- and *f*-elements bind comparatively weakly through their orbitals to the surrounding ligands. Thus, the ligand environment induces limited orbital splittings [G]. This has been exploited very fruitfully in the phenomenological model of crystal field theory [G] (CFT²¹⁵). In CFT, the *d*- or *f*electrons are treated as free ions perturbed by an electrostatic field created by the surrounding ligands. While quantitatively unrealistic, the theory captures essentials of *d*-(*f*-) element electronic

structure. Thus, the combination of a partially filled d- or f-shell and limited ligand field splittings 935 leads to a series of low-lying electronic states formed from distributing *n*-electrons between the 936 available orbitals and at the same time couples their spins in all possible ways to a resulting net total 937 spin. On top of the complexity arising from a large variety of multiplets [G] comes the fact that d-938 and *f*-elements are heavy. Hence, the effects of relativity become much more prominent in these 939 compounds and whenever there are unpaired electrons, a treatment of the spin-orbit-coupling (SOC 940 [G]) becomes mandatory for theoretical spectroscopy.¹³ The electronic complexity is necessarily 941 also reflected in the observed spectra. Throughout the range of available techniques ranging from 942 hard X-rays (10⁴ eV) down to microwaves and radiowaves (10⁻¹¹-10⁻⁹ eV)) the spectra typically show 943 a high amount of spectral crowding due to the multitude of final states that can be reached in the 944 respective spectroscopic transitions. In addition, the spectra are difficult to interpret because of the 945 complexity of the electronic states that are involved and consequently, they require a high amount 946 of expertise to be interpreted correctly. 947

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Figure 10. The complex arrangements of electrons in partially filled *d*- and *f*-shells give rise to a wide variety of spectroscopic phenomena that are challenging to model with high-accuracy by quantum chemistry. The geometric structure (panel **a**: left, grey=carbon, white=hydrogen, blue nitrogen, brown=transition metal) imposes a distinctive splitting of the molecular orbitals that are based on the transition metal d-orbitals (panel **a**: right). The distribution of the n electrons in a dⁿ configuration gives rise to a multitude of electronic states that can be probed with optical or magnetic spectroscopy (panels **b**-**d**). Among these, the most prominent ones are EPR (**b**), absorption (**c**) and X-ray absorption (**d**) spectra. EPR spectroscopy probes the net electron spin caused by the unpaired electrons of the electronic ground state. ABS probes transitions of electrons between valence orbitals, including the metal d-based orbitals. X-ray spectroscopy probes excitations from deep core electrons on the transition metal center(s) into the empty or half-filled valence orbitals. Since the core levels vary systematically along the periodic table, this provides a highly sensitive element specific probe of the system under investigation.

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The complex electronic multiplets in the presence of relativistic effects are not easily reproduced even in a semi-quantitative way by the available QC methods.²¹⁶⁻²¹⁸ In those cases where there are

952 (near-) orbital degeneracies (as readily predicted by CFT), there may not be a single Slater

determinant **[G]** that is an appropriate starting point for the description of the electronic ground state. In such a case, all single-reference determinant based methods (including DFT) fail to describe the electronic structure of either the ground or the excited states correctly. Typically, not even the number of reachable final states tend to be correct.^{13,17} Thus, DFT has many serious shortcomings in the field of theoretical *d*- and *f*-element theoretical spectroscopy. These shortcomings were highlighted in some reviews over a decade ago and stand unchanged today.^{13,17,219}

The occurrence of a rich multiplet structure together with the prominence of relativistic effects, 960 opens up rich opportunities for experimental spectroscopy (Figure 10). Magnetic low-energy 961 spectroscopies, such as NMR and ESR, can probe the magnetic sublevels of the electronic ground 962 state multiplets, while modern magnetometry is extensively used to study the magnetic properties 963 of d- and f-elements for molecular magnetism. Electronic spectroscopies including UV/vis, CD and 964 magnetic CD (MCD [G]) or resonance Raman spectroscopies provide in-depth insights into the 965 electronic structure of these species. Finally, since there are typically only a few atoms of a given 966 element present in the compound, element specific techniques like Mössbauer or X-ray 967 absorption/emission spectroscopies are very widely used.¹⁷ All of these methods provide detailed 968 fingerprints of the geometric and electronic structure of the systems under investigation. 969 Importantly, each one of these techniques is sensitive to different geometric and electronic 970 structure details. Thus, there is a host of experimentally available electronic structure information. 971 However, in order to develop the full information content of these spectra, it is inevitable to turn to 972 quantum chemistry for spectral interpretations. A successfully carried out study results in 973 experimentally calibrated electronic structure level insight of the investigated species, be they 974 stable entities or reaction intermediates. As discussed elsewhere, this leads to insights that can not 975 be obtained from the pure calculation of total energies^{220,221} 976

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978 [H3] **4.3.1.** Case study of magnetic Co(II) tetrathiolates

Coordination complexes of Co(II) ions (d⁷ configuration) have been known in coordination chemistry 979 since its cradle days and have been routinely characterized with magnetic measurements like SQUID 980 [G], EPR or MCD spectroscopy. It is well-known that in an approximately tetrahedral environment 981 the ground state has a total spin of S=3/2. A cursory look at the ion [Co(S-Ph)₄]²⁻ also reveals nothing 982 particularly special. However, this changed dramatically when Long and coworkers reported that 983 this ion show slow magnetic relaxation at zero magnetic field. This is the signature of the very 984 thought-after single-molecule magnet (SMM) behaviour.²²² What is particularly exciting is that 985 [Co(S-Ph)₄]²⁻ was the first mononuclear compound to show this behavior where for several decades 986 it was believed that only large, oligonuclear transition metal clusters could show SMM properties 987 (see²²³). 988

A careful study of the magnetic properties of two different salts containing [Co(S-Ph)₄]²⁻ coupled to 990 quantum chemical calculations were subsequently reported.^{224,225} Quite surprisingly, only the [Co(S-991 $Ph_{4}(P(Ph)_{4})_{2}$ was showing SMM behavior, while $[Co(S-Ph)_{4}](N(Et)_{4})_{2}$ did not. The careful 992 experimental investigation showed that this is due to the Co(II) ion P(Ph)₄ having a large and 993 negative zero-field splitting (ZFS [G]), while in the N(Et)₄ salt, the ZFS is small and positive. The 994 magnetic properties of both structures were reproduced with excellent accuracy through 995 CASSCF/NEVPT2 calculation with inclusion of spin-orbit coupling (SOC). Furthermore, the method 996 of Ab Initio Ligand Field Theory (AILFT [G]) allowed for the ligand field parameters to be deduced 997 from the large-scale wavefunction based ab initio calculations. They revealed that the origin of the 998 radically different behavior is a subtle distortion that renders Co(II)-ion in the P(Ph)₄ salt to be in an 999 elongated tetrahedral environment, while in the N(Et)₄ salt, it is in a compressed tetrahedral 1000

structure. The changes in the d-orbital splitting pattern are then sufficient to cause the dramatic switch of magnetic properties, as predicted by ligand field theory. Quite fascinatingly, the origin of the dramatically different behavior can thus be traced back to weak intermolecular interactions in the second coordination sphere of the cobalt. These insights opened up the avenue for many further investigations on Co(II) complexes (e.g. ²²⁶). This study (summarized in Figure 11) is one demonstration that a large body of complex and initially puzzling experimental observations can be quantitatively interpreted in a unified manner through large-scale multireference ab initio calculations. Moreover, the results of these calculations can be translated concisely into a familiar chemical language through the AILFT procedure.



Figure 11. Panels **a,b**: the two structures of $[Co(S-Ph)_4]^{2-}$ found in the $(Et_4N)_2$ and $(Ph_4P)_2$ salts reflecting compressed and elongated tetrahedra respectively. Panels **c,d**: the radically different EPR spectra of the two species demonstrating their very different electronic structures. Panels **e,f**: the effective d-orbital splitting patterns deduced from CASSCF/NEVPT2 calculations for the two structures effectively explaining the origin of the very different D-values. Panel **g**: Potential energy and property surface (ZFS-value) for two key angles describing the distortion into flattened and elongated tetrahedra in $[Co(S-Ph)_4]^{2-}$. There are two shallow minima associated with qualitatively different D-values as reflected in their ESR spectra (**a,b**) and readily understood from quantum chemical calculations (**c,d**).

[H1] 5. Reproducibility and data deposition

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Here we discuss different levels at which the issue of data reproducibility and deposition can be examined.

The first level is the definition of a general standard for the inputs and outputs (I/O) of electronic 1025 structure codes; this was discussed, for instance, in the MOLSSI workshop 1026 (https://molssi.org/2019/08/19/molssi-workshop-rovibrational-molecular-spectroscopy/). Indeed, 1027 we have been witnessing an increasing number of large-scale international and interdisciplinary 1028 collaborations, which often involve shared infrastructures and multi-user facilities, resulting in 1029 massive amounts of data. To enhance these collaborations, there is a strong need to integrate and 1030 standardize computational codes starting from a common syntax and/or language. An example in this direction is provided by the VMS project,⁶¹ which aims at integrating several spectroscopic 1032 techniques and providing a user-friendly interface to different QC programs (see, e.g., the module 1033 dedicated to rotational spectroscopy¹⁴²). 1034

The second level is the compilation and management of highly accurate results for small (2-4 atoms) 1036 molecules, which can rival the corresponding experimental data.³⁴ Outside this narrow size range, 1037 theoretical models and computational procedures for computational spectroscopy are always 1038 based on approximations and assumptions, which need to be correctly recognized in the 1039 applications to realistic systems. Thus, small molecules can represent suitable fragments for 1040 benchmarking less refined methods and defining transferable correction factors for fragments of 1041 larger molecules.²²⁷ The latter paves the way toward the set-up of public databases of molecular 1042 structures and spectroscopic properties. One example is provided by the database of semi-1043 experimental equilibrium structures (derived as described in section 3.1) available at 1044 https://smart.sns.it/molecules/. 1045

The third level concerns the lines to be followed for the spectroscopic characterization of large 1047 systems, which are of increasing interest to different scientific communities. The available results 1048 for an adequate number of medium-sized systems should be organized in sets of comparable 1049 accuracy by clustering techniques employing widely accepted general criteria. For some properties 1050 (essentially energies), the general definition of platinum, gold and silver standards²²⁸ is more or less 1051 accepted. These definitions are based on the accuracy provided. For example, CCSD(T) calculations 1052 1053 extrapolated to the complete basis set limit define the gold standard. The silver standard provides the best approximation to the gold standard at a reduced computational cost, while the platinum 1054 standard improves the gold one by adding further corrections (such as higher-order coupled cluster terms). However, such standards have not been developed for most spectroscopic properties, and 1056 for them the situation is thus more challenging. For instance, fully quantitative results for high-1057 resolution spectroscopic techniques like rotational spectroscopy are still out of reach even for semi-1058 rigid tri- and tetra-atomic systems,²²⁹ the required computations being unaffordable. However, new 1059 methods based on the template approach [G] possibly coupled with the machine-learning appear 1060 quite promising.^{227,230} To give an example, in the field of vibrational spectroscopies, some 1061 methodologies (such as VPT2 treatments based on an anharmonic description of the PES at a 1062 suitable level of theory³⁴) can reach an accuracy within 10 cm⁻¹ and are also applicable to large-sized 1063 systems with the help of linear scaling^{231,232} and reduced dimensionality²³³ techniques. In this 1064 connection, the compilation and management of databases (as mentioned for the second level for 1065 large molecules) is a task of current interest in the field. More work in this direction should be 1066 performed with compilations of spectroscopic parameters for molecules including heavy elements 1067

and for different spectroscopies. The situation is instead more involved for spectroscopic transition intensities, where the definition of widely accepted standards is still missing. Another important issue when dealing with large systems is their flexibility, which requires the implementation of effective approaches to search for the energetically low-lying structures (i.e. conformers or isomers).¹⁵⁰ In fact, a key point toward data/spectra reproducibility is the understanding of which of these conformers or isomers contribute to the overall spectroscopic signal. However, we are still far from any general definition of classes of methods/models achieving a desired accuracy.

Focusing on an integration of the levels 2 and 3, an interesting option would be to simulate and store overall spectra in place of databases collecting lists of spectroscopic parameters. Another step forward would be the set-up of compilations that combine results of different spectroscopies having comparable accuracies in view of their use to assist the experimental work, which more and more rests on the integrated use of different techniques.

A transversal issue is the role of environmental effects (e.g. solvent), which should be analyzed for 1082 different properties and/or solvents, thus allowing for the use of the most appropriate model for 1083 the specific case under consideration. Indeed, when the spectroscopic investigation is carried out in 1084 solution or, more generally, in condensed phase, data reproducibility requires the proper account 1085 of environmental effects. For instance, polarizable continuum models³⁴ can be employed to 1086 describe innocent solvents at a negligible additional cost with respect to the corresponding 1087 simulation in vacuo. Such a model can be improved by incorporating a reduced number of explicit 1088 solvent molecules in the treatment,¹⁵¹ provided that they occupy well-defined positions and are 1089 quite strongly bonded to the solute. In this respect, topological models for the automatic definition 1090 of the number and position of strongly bonded solvent molecules are under active development²³⁴ 1091 and the definition of widely accepted standards would be a very important achievement. 1092

Finally, while the issue of a general standard addressed above (first level) is a basic need for collaborations, a mention to the information accompanying publications is deserved. This does not involve program outputs, the collection (in tables) of spectroscopic parameters being usually exhaustive. However, cartesian coordinates for the molecular systems investigated are generally provided, while more rarely the force constants [G] describing a portion of PES are reported.

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[H1] 6. Limitations and optimisations

Since its very beginning, computational spectroscopy has focused on deriving spectroscopic parameters to support the analysis of experimental spectra. In fact, interpretation of experimental data is often a difficult task. This is due to the fact the observed spectroscopic behavior derives from the interplay of different effects, whose specific roles are difficult to disentangle. Furthermore, the theoretical model used for their interpretation might be oversimplified.

Pushing the treatment of the electronic and nuclear problems to the limit ensures rigorous analyses, 1108 quantitative results, and correct interpretations of the spectroscopic outcomes. However, such 1109 accurate approaches involve high computational costs and efforts and, therefore, they are 1110 restricted to small, isolated molecules (as briefly addressed in section 5). Increasing the size and 1111 complexity of the systems often requires a sacrifice of accuracy for interpretability, thus leading to 1112 qualitative descriptions. In such cases, the main limitation is an oversimplification that might lead 1113 to the right answer for the wrong reason, which means to obtain the correct reproduction of the 1114 spectral features based on wrong spectroscopic parameters. In turn, this might also mean the 1115 derivation of wrong physicochemical properties, or even incorrect interpretation on what molecular 1116 species are actually observed. The only way to mitigate this is to try to apply a physically sounded 1117 model and possibly take corrective actions based on similar (but smaller) systems already 1118 investigated. However, the selection of the fragments and the treatment of the boundary among 1119 them are open questions that require considerable experience, good knowledge of the system to 1120 be investigated and, above all, further algorithmic developments and implementations. 1121

Modern computational spectroscopy aims to bridge the gap between sophisticated experimental techniques and oversimplified analyses, also exploiting visualization and simulation techniques. An interesting example is provided by oxirane derivatives, whose spectral features could not be described by more simplified theoretical models. State-of-the-art simulations of IR, Raman, VCD, ROA, OPA, ECD are in good agreement with their experimental counterparts allowing also to reconcile theory and experiment.^{35,112,235,236}

1129 As mentioned in the previous section and along this primer, accurate methodologies have been 1130 developed for the treatment of small- to medium-sized molecular systems (see e.g. refs. ^{34,150,237}), 1131 linear-scaling and hybrid approaches (that will be addressed later in this section) allowing for their 1132 extension to larger systems. However, a current challenge for computational spectroscopy tools is 1133 provided by large flexible molecules, for which the analysis of the conformational PES is the first 1134 obstacle to be overcome. In fact, in order to correctly interpret their spectroscopic features, the 1135 knowledge of the structures contributing to them is mandatory. In this respect, in the last decade, 1136 significant progress has been made thanks to stochastic (molecular dynamics or Monte Carlo) 1137 techniques¹⁵⁰ and machine-learning algorithms,^{230,234} all of them helping in deriving an exhaustive 1138

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Moving to spectral simulations, the number and types of LAMs are still a strong limitation for accuracy. In fact, while a decoupling (or a minimization of the coupling) between SAMs and LAMs together with a variational treatment of the latter modes can pose the basis for an accurate spectroscopic treatment, this approach is currently effective for dealing with only one LAM.²³⁸ Nevertheless, a further issue is the level of theory employed for the description of the portion of PES (or PESs) required to the spectroscopic technique under consideration. In fact, the scaling of most of the accurate QC models is prohibitive, thus hampering their application already to medium-

account of the number and type of conformers relevant for the spectroscopic analysis.

sized molecular systems. However, for the latter, composite schemes often provide an effective 1148 solution. For larger systems, a possible way-out is offered by fragment-based approaches such the 1149 molecules-in-molecules,²³⁸ which is a multilevel partitioning approach coupled with electronic 1150 structure studies at different levels of theory with the final aim of providing a hierarchical strategy 1151 for systematically improving the computed results. At the same time, further improvements on the 1152 reliability of methods rooted in the density functional theory (e.g. double-hybrid functionals, long 1153 range corrections, etc.)²³⁹ and the development of linear-scaling techniques, especially for the 1154 exact-exchange²⁴⁰ and MP2²⁴¹ parts, paves the route toward more reliable computations for large 1155 systems. In parallel, explicitly-correlated F12 treatments¹⁰⁵ allows the reduction of the basis-set 1156 dimensions in electronic structure computations, thus improving the reachable accuracy. A further 1157 step is provided by local-correlation treatments based on PNO,^{106,107} which - as already mentioned 1158 - allow for improving the scaling of coupled cluster treatments with the number of electrons. 1159

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While being aware that limitations and optimizations in the field of computational molecular 1161 spectroscopy cannot be exhaustively addressed in this section, it should be noted that the accurate 1162 spectroscopic characterization of open-shell species is more challenging than that of their closed-1163 shell counterparts, regardless of the size of the molecular system under consideration.²⁴² The 1164 situation is even more involved for systems showing large static correlation effects (e.g. low-spin 1165 states of most transition metals, see section 4.3), with methods rooted in the DMRG¹³⁶ or quantum 1166 Monte Carlo²⁴³ being good alternatives with respect to multi-reference methods and opening 1167 promising routes toward effective treatments. 1168

1169 **[H1] 7. Outlook**

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The previous sections have shown that the ongoing developments of hardware and software are 1171 allowing the study of the spectroscopic outcomes of several systems and processes of current 1172 scientific and technological interest with an accuracy simply unthinkable even ten years ago. 1173 Furthermore, the range of applications of computational spectroscopy has considerably widened 1174 including now diverse fields as astrochemistry,²⁴⁴ atmospheric chemistry²⁴⁵ or catalysis,²²⁰ just to 1175 mention a few. However, the historical dichotomy between accuracy and interpretability (not to 1176 speak of feasibility and user-friendliness)³⁴ remains one of the hardest obstacles against the 1177 definitive transformation of computational spectroscopy from a highly specialized field to a general-1178 purpose tool aiding both theoretically- and experimentally-oriented scientists in their research 1179 work. This aspect is even more important since state-of-the-art spectroscopic investigations usually 1180 involve the contemporary use of several experimental techniques and new, highly sophisticated 1181 computational tools are constantly proposed and implemented. In this framework, the most needed 1182 developments concern the extension of accurate evaluations of spectroscopic parameters from 1183 small semi-rigid closed-shell systems containing light atoms in the gas phase²³⁷ to a general 1184 workflow for the spectroscopic characterization of large, flexible chromophores in condensed 1185 phases.²⁴⁶ While most of the building blocks of the procedure are already available, their integration 1186 into a robust, general, and user-friendly tool calls for further developments and validations. 1187

One aspect to consider is the extension and validation of composite models for electronic structure calculations to transition metals and heavy atoms, large systems, open-shell species, and excited electronic states. Possible routes to achieve this include explicitly-correlated coupled-cluster approaches,^{105,247} localized treatments of correlation (e.g. local pair natural orbitals, LPNO **[G]**),^{231,232} effective treatment of static correlation,^{136,248} further improvements of density functionals for comprehensive scans of PESs²⁴⁹ as well as reliable structure and force-field evaluations,²³⁹ more effective treatments of excited electronic states.^{250,251}

Another important aspect to take into consideration is the vis-à-vis comparisons between computed and experimental spectra, including positions and heights (i.e. intensities) of band maxima, but also spectral shapes⁶¹ and the extension of such comparisons to all possible spectroscopies. This in turn requires accurate yet effective evaluations of all the parameters needed by different spectroscopic techniques^{133,252} and their post-processing. Indeed, the vis-à-vis comparison is probably the best way to exploit the interplay of experiment and theory.

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To improve the spectroscopic analysis of flexible molecules, in particular in the fields of rotational 1204 and vibrational spectroscopies, general-purpose treatments of their spectra in terms of curvilinear 1205 internal coordinates, possibly coupling the variational treatment of LAMs with the perturbative 1206 treatment of SAMs and couplings, need to be developed and implemented.^{249,253} A promising 1207 alternative is offered by integrated treatments of electronic and high-frequency nuclear motions by 1208 means of nuclear-electronic orbitals.²⁵⁴ In the framework of electronic spectroscopies, the 1209 extension to large chromophores of anharmonic vibronic models²⁵⁵ for absorption and emission 1210 electronic spectroscopy, also including chiroptical spectra, is important to take a step forward in the 1211 characterization of biomolecules. 1212

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Effective coupling between explicit dynamic treatment of soft degrees of freedom (e.g., torsions around single bonds, ring puckerings, and solvent fluctuations) involving large-mass moieties (for which classical equations of motion are fully adequate) and quantum-mechanical treatment of hard degrees of freedom.²⁵⁶ These developments will allow the accurate yet effective treatment of large flexible systems in condensed phases, which is hardly feasible with current software and hardware.

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Integration of the variational (QM, QM/QM' or QM/MM, MM standing for molecular mechanics and
 the "slash" used to denote that two levels of treatments are employed, thus implying a partitioning
 of the system) evaluation of large-scale deformations (e.g. different conformers and/or different
 topologies of solute-solvent interactions in the cybotactic region) with the perturbative (e.g. PMM
 [G]) evaluation of fluctuations within different basins.¹⁵¹ Also in this case, clever coupling of
 variational (QM/QM, etc.) and perturbative (PMM) approaches will strongly reduce the computer
 requirements (both time and memory) without sacrificing the accuracy of the overall computation.

In the framework of ro-vibrational spectroscopy, effective determination of partition functions (and/or density and number of states) beyond the rigid-rotor/harmonic-oscillator model^{257,258} would allow the computation of accurate thermodynamic functions and reaction rates for flexible systems possibly in condensed phases.

Implementation of artificial-intelligence tools for the sampling of PESs after their training with 1233 reference to state-of-the-art QC results paves the route toward very accurate energies, structures 1234 and force fields of both local minima and transition states at a cost comparable to that of inexpensive MM methods.²³⁰ On the other hand, implementation of immersive virtual- and 1236 augmented-reality tools for the effective setup of general spectroscopic studies and the interactive 1237 analysis of the results²⁵⁹ can revolutionize the whole field (as well as many others), thereby changing 1238 the perspective from abstraction to perception by bringing the objects under study to the same spatial-temporal scale of human beings. In a more distant perspective, effective use of quantum 1240 computing will improve the rate of state-of-the-art techniques.²⁶⁰ As a matter of fact, the exact 1241 solution of the Schrödinger equation has an intrinsic exponential scaling with the dimension of the 1242 problem and the most accurate QC techniques scale as high powers (at least 10⁸) of the number of 1243 active particles. In parallel, the speed of traditional computers scales linearly with the number of 1244 cores, whereas the scaling of quantum computers is, in principle, exponential. 1245

In summary, in this Primer --focusing on a selection of molecular spectroscopic techniques-- we have shown how Computational Spectroscopy works, briefly presenting its foundations as well as significant results and applications. Furthermore, along this Primer, the fundamental role of Computational Spectroscopy in supporting and complementing experimental investigations has been addressed. A critical analysis of its current limitations and possible improvements has also been performed, which has been concluded by an exhaustive presentation of future perspectives and needs.

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1256 Glossary (terms in text annotated with [G])

AC	Absolute Configuration: indicates the spatial arrangement of atoms in a chiral system
	Abjinitio ligand field theory: is a method connecting the results of abjinitio calculations
AILFT	with the parameters entering ligand field theory
Anharmonicity	Deviation from the harmonic accillator hebavior
RO (approximation)	The Porp Opportation Approximation: is the assumption that the motion of atomic
BO (approximation)	The Born-Oppennemer Approximation. Is the assumption that the motion of atomic
	nuclei and electrons can be treated separately, based on the much larger mass of
CACDTO	nuclei.
CASPIZ	complete active space perturbation theory to second order: is one specific
	generalization of MP2 (see below) to multiconfigurational reference wave-functions.
CC (theory)	Coupled-cluster (theory): is a hierarchy of electron correlation methods that, by means
	of an exponential Ansatz, systematically converge to the exact solution of the molecular
	Schrödinger equation starting from the independent particle Hartree-Fock model.
CD	Circular Dichroism: is dichroism (splitting of a beam of light into two beams with
	different wavelengths) involving circularly polarized light, i.e., the differential
	absorption of left- and right-handed light.
CCSD(T)	CC method that considers full account of single and double excitations and a
	perturbative treatment of triple excitations.
CFT	Crystal field theory: describes the splitting of the (relativistic) many particle multiplet
	states of an ion in a d" or f" configuration incurred by the electrostatic interaction with
	its coordinating ligands that are treated as point charges.
CIS	Configuration interaction (i.e. mixing of ground and excited electronic states) including
	only single excitations from a reference Slater determinant.
Combination band	A combination band is observed when two or more vibrations are excited
	simultaneously
Conformer	Isomer that can be converted into another one by rotation about a formally single
	bond.
Contact	Unitary transformation with an exponential operator $U = exp(iS)$, where S is Hermitean
transformation	and antisymmetric with respect to time reversal, thus ensuring that U is unitary and
	invariant to time reversal.
Cybotactic (region)	The region around a solute molecule including solvent molecules belonging to the first
	solvation shell, i.e. showing close solute-solvent contacts
DFT	Density functional theory: is a quantum-mechanical method in which the properties of
	a many-electron system are determined using functionals (i.e. functions of another
	function) of the spatially dependent electron density and, possibly, its derivatives.
DMC	Diffusion Monte Carlo: provides a Monte Carlo based approach for obtaining the exact
	ground state solution to Equation 2.
DMRG	Density matrix renormalization group: is a very efficient numerical variational
	technique devised to obtain the lowest-energy wavefunction of a given Hamiltonian
	expressed in terms of a matrix product state.
(DL)PNO	(Domain-based local) pair natural orbitals: are electron pair specific localized natural
	orbitals expanded in a set of local atomic orbitals belonging to pair specific domains.
Double-perturbative	Simultaneous perturbative treatment of the energy and one property (e.g. the electric
approach	dipole moment in infrared spectroscopy) around a stationary point.
ECD	Electronic version of the circular dichroism (see above)
Electron correlation	Electron Correlation: describes the effects of electron-electron interactions beyond the
	mean field Hartree-Fock model.
Electron Correlation:	Electron correlation effects describing the "instantaneous" electron-electron
Dynamic	interaction if groups of electrons approach each other in close proximity.
Electron Correlation:	Electron correlation effects describing the correlated motion of electrons not captured
Static	correctly by the single Slater determinant treatment offered by the Hartree-Fock
	model.
Energy level	According to quantum mechanics (see below), the allowed energy for a system is not

Ensemble of walkers	A large number of virtual copies of a single particle moving randomly over a given
	potential energy surface.
EOM	Equation-of-Motion: in a quantum chemistry context it refers to the coupled cluster treatment of electronically excited or ionized states
FSR	Electron spin resonance: is a spectrosconic techniques equivalent to NMR (see below)
Lon	but dealing with excitation of the electronic spins in open-shell systems
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EPK	Electron paramagnetic resonance: is a synonym of electron spin resonance.
Force constant	Derivative of the potential energy with respect to nuclear coordinates evaluated at the minimum structure (e.g. the quadratic force constant is the second derivative).
Fundamental band	Vibrational transition from the vibrational ground state to the first excited state of a
	given vibrational mode.
FWHM/HWHM	Full/Half width at half maximum: is the width (or half the width) between the two
	points where the value of the function is its half maximum.
Hamiltonian	In quantum mechanics, it is the operator corresponding to the energy of a system.
Harmonic	Model in which the vibrational motion is described in terms of masses attached to a
	spring, whose energy is governed by a quadratic potential.
Hybrid/Double-	Families of density functionals including a percentage of Hartree-Fock exchange
hybrid density	(hybrid) and MP2-type correlation (only double-hybrid).
functional	
Imaginary time	Since the time evolution of a quantum system starting from time to is governed by exp[-
	$(H(t-t0))$ where H is the Hamiltonian operator $\tau = i(t-t0)$ is usually referred to as
	imaginary time
Infrared enastroscopy	Integritary time.
initiated spectroscopy	excitation of the vibrational states of molecules.
IFT	Ligand Field Theory: a semi-empirical "perturbed ion" model, based on CET, that
	describes the electronic structure and properties of transition metal complexes
Line-shape function	A mathematical function (usually Gaussian Lorentzian or a combination of both)
Line-shape function	describing phonomonologically the shape of a spectral hand
	The Circular Dichasian induced hus static lensituding systemal resonatio field
IVICD	The Circular Dichroism induced by a static, longitudinal external magnetic field.
LAM	Large amplitude motion: refers to a molecular vibration whose amplitude is so large that the harmonic oscillator model is no more a reliable zero-order approximation.
Mössbauer isomer	The shift in resonance frequency of the nuclear gamma-ray transition in a Mössbauer
shift	active isotope (e.g. ⁵⁷ Fe) caused by its interaction with the molecular environment.
MM	Molecular mechanics (or force-field methods) uses classical type models to predict the
	energy of a molecule as a function of its conformation.
MP2	Møller-Plesset theory including many-body effects on top of the mean field Hartree-
	Fock reference wavefunction up to the second order of perturbation theory.
MRCI	Multi reference configuration interaction: extends the configuration interaction
	approach to multireference wavefunctions.
Multiplet	The ensemble of many particle states that arise from the distribution of a given number
	of electrons among sets of degenerate atomic or molecular orbitals under the action of
	the electron-electron (and nerhans the spin-orbit coupling) interaction
	N-electron valence state perturbation theory to the second order: is a variant of second
	order multireference perturbation theory similar to CASPT2.
NMR	Nuclear magnetic resonance: is a spectroscopic technique based on the perturbation
	of nuclei in a strong constant magnetic field by a weak oscillating magnetic field (in their
	close environment) which produces an electromagnetic signal with a frequency related
	to the magnetic field at the nucleus
Normal made /	Vibrational mation of the molecules where all stoms vibrate in phase with the same
Normal mode /	for a substantial motion of the molecules where an atoms vibrate in phase with the same
Normal coordinate	requency but with different amplitudes, and the center of mass remains fixed. A
	normal coordinate is a linear combination of Cartesian displacement coordinates. The
	motion described by a normal coordinate is called a normal mode.
OPA	Spectroscopic technique in which one-photon absorption leads from the electronic
	ground state to an excited electronic state.
OPE	Spectroscopic technique in which one-photon emission leads from an excited
	electronic state to a less-excited (lower energy, usually the ground) state.

-	Optical rotation: is the rotation angle of the polarization plane of polarized light issuing
	from its passage through a layer or a liquid and is determined by the concentration of
	chiral molecules and their structure in a substance.
Orbital splitting	Splitting of a specific orbital due to external factors (e.g. electric or magnetic field).
ORD	Optical rotatory dispersion: is the variation of the optical rotation of a substance with
	a change in the wavelength of light.
Overtone	Vibrational transition involving the excitation of two or more quanta of a given
	vibration mode (i.e. the quantum number describing the vibrational energy levels
DCM	Change varies by two o more)
P CIVI	polarizable continuum in which the solute is fully embedded.
PES	Potential energy surface (multi-dimensional, hyper-surface): describes the variations of
-	the electron energy of a system in terms of suitable nuclear coordinates.
PMM	Perturbed matrix method: describes solvent effects on a quantum center in terms of
	CIS, whose elements are the energies of the isolated solute perturbed by the electric
	field produced by the different configurations of the solvent issuing from a molecular
	dynamics simulation.
Position array	Array containing the coordinates of the position of a specific point in a multi-
	dimensional space.
PS	Property surface (multi-dimensional): describes the variations of a property as a
	function of suitable nuclear coordinates.
QC	Quantum chemistry (quantum chemical being the corresponding adjective): refers to
	the application of quantum mechanics to chemistry.
QM	Quantum mechanics (quantum mechanical being the corresponding adjective): is a
	reportion of the matter at the atomic and subatomic level
Paman spectroscony	Properties of the matter at the atomic and subatomic level.
Raman spectroscopy	scattering).
Rigid-rotor harmonic-	A reference model in which a molecular system as a whole is described in terms of a
oscillator model	rigid rotating object and in terms of decoupled harmonic oscillators for its vibrational
	motion.
ROA	motion. Raman optical activity: is a vibrational spectroscopy based on the differential Raman
ROA	motion. Raman optical activity: is a vibrational spectroscopy based on the differential Raman scattering of left and right circularly polarized light due to molecular chirality.
ROA Rotational	motion. Raman optical activity: is a vibrational spectroscopy based on the differential Raman scattering of left and right circularly polarized light due to molecular chirality. Spectroscopy using the microwave region of the electromagnetic field to study the
ROA Rotational Spectroscopy	 motion. Raman optical activity: is a vibrational spectroscopy based on the differential Raman scattering of left and right circularly polarized light due to molecular chirality. Spectroscopy using the microwave region of the electromagnetic field to study the excitation of the rotational states of molecules.
ROA Rotational Spectroscopy Rovibrational	 motion. Raman optical activity: is a vibrational spectroscopy based on the differential Raman scattering of left and right circularly polarized light due to molecular chirality. Spectroscopy using the microwave region of the electromagnetic field to study the excitation of the rotational states of molecules. Spectroscopy dealing with rotational and vibrational states of molecules.
ROA Rotational Spectroscopy Rovibrational Spectroscopy	 motion. Raman optical activity: is a vibrational spectroscopy based on the differential Raman scattering of left and right circularly polarized light due to molecular chirality. Spectroscopy using the microwave region of the electromagnetic field to study the excitation of the rotational states of molecules. Spectroscopy dealing with rotational and vibrational states of molecules.
ROA Rotational Spectroscopy Rovibrational Spectroscopy SAM	 motion. Raman optical activity: is a vibrational spectroscopy based on the differential Raman scattering of left and right circularly polarized light due to molecular chirality. Spectroscopy using the microwave region of the electromagnetic field to study the excitation of the rotational states of molecules. Spectroscopy dealing with rotational and vibrational states of molecules. Small amplitude motion/mode: refers to a molecular vibration whose amplitude is
ROA Rotational Spectroscopy Rovibrational Spectroscopy SAM	 motion. Raman optical activity: is a vibrational spectroscopy based on the differential Raman scattering of left and right circularly polarized light due to molecular chirality. Spectroscopy using the microwave region of the electromagnetic field to study the excitation of the rotational states of molecules. Spectroscopy dealing with rotational and vibrational states of molecules. Small amplitude motion/mode: refers to a molecular vibration whose amplitude is small enough so that the harmonic oscillator is a reliable zero-order approximation.
ROA Rotational Spectroscopy Rovibrational Spectroscopy SAM Schrödinger equation	 motion. Raman optical activity: is a vibrational spectroscopy based on the differential Raman scattering of left and right circularly polarized light due to molecular chirality. Spectroscopy using the microwave region of the electromagnetic field to study the excitation of the rotational states of molecules. Spectroscopy dealing with rotational and vibrational states of molecules. Small amplitude motion/mode: refers to a molecular vibration whose amplitude is small enough so that the harmonic oscillator is a reliable zero-order approximation. Equation associated to the Hamiltonian operator: its resolution provides the allowed enough (signaphuration) and the expresenting (signaphuration).
ROA Rotational Spectroscopy Rovibrational Spectroscopy SAM Schrödinger equation	 motion. Raman optical activity: is a vibrational spectroscopy based on the differential Raman scattering of left and right circularly polarized light due to molecular chirality. Spectroscopy using the microwave region of the electromagnetic field to study the excitation of the rotational states of molecules. Spectroscopy dealing with rotational and vibrational states of molecules. Small amplitude motion/mode: refers to a molecular vibration whose amplitude is small enough so that the harmonic oscillator is a reliable zero-order approximation. Equation associated to the Hamiltonian operator: its resolution provides the allowed energy levels (eigenvalues) and the corresponding wave functions (eigenfunctions).
ROA Rotational Spectroscopy Rovibrational Spectroscopy SAM Schrödinger equation Slater determinant	 motion. Raman optical activity: is a vibrational spectroscopy based on the differential Raman scattering of left and right circularly polarized light due to molecular chirality. Spectroscopy using the microwave region of the electromagnetic field to study the excitation of the rotational states of molecules. Spectroscopy dealing with rotational and vibrational states of molecules. Small amplitude motion/mode: refers to a molecular vibration whose amplitude is small enough so that the harmonic oscillator is a reliable zero-order approximation. Equation associated to the Hamiltonian operator: its resolution provides the allowed energy levels (eigenvalues) and the corresponding wave functions (eigenfunctions). Representation of a many particle 'mean-field' wavefunction in terms of the anticymmetrized products of single electron
ROA Rotational Spectroscopy Rovibrational Spectroscopy SAM Schrödinger equation Slater determinant	 motion. Raman optical activity: is a vibrational spectroscopy based on the differential Raman scattering of left and right circularly polarized light due to molecular chirality. Spectroscopy using the microwave region of the electromagnetic field to study the excitation of the rotational states of molecules. Spectroscopy dealing with rotational and vibrational states of molecules. Small amplitude motion/mode: refers to a molecular vibration whose amplitude is small enough so that the harmonic oscillator is a reliable zero-order approximation. Equation associated to the Hamiltonian operator: its resolution provides the allowed energy levels (eigenvalues) and the corresponding wave functions (eigenfunctions). Representation of a many particle 'mean-field' wavefunction in terms of the antisymmetrized products of single-electron wavefunctions (molecular orbitals). Spin orbit coupling: refers to the coupling between the spin and the orbital angular.
ROA Rotational Spectroscopy Rovibrational Spectroscopy SAM Schrödinger equation Slater determinant SOC	 motion. Raman optical activity: is a vibrational spectroscopy based on the differential Raman scattering of left and right circularly polarized light due to molecular chirality. Spectroscopy using the microwave region of the electromagnetic field to study the excitation of the rotational states of molecules. Spectroscopy dealing with rotational and vibrational states of molecules. Small amplitude motion/mode: refers to a molecular vibration whose amplitude is small enough so that the harmonic oscillator is a reliable zero-order approximation. Equation associated to the Hamiltonian operator: its resolution provides the allowed energy levels (eigenvalues) and the corresponding wave functions (eigenfunctions). Representation of a many particle 'mean-field' wavefunction in terms of the antisymmetrized products of single-electron wavefunctions (molecular orbitals). Spin orbit coupling: refers to the coupling between the spin and the orbital angular momenta
ROA Rotational Spectroscopy Rovibrational Spectroscopy SAM Schrödinger equation Slater determinant SOC	 motion. Raman optical activity: is a vibrational spectroscopy based on the differential Raman scattering of left and right circularly polarized light due to molecular chirality. Spectroscopy using the microwave region of the electromagnetic field to study the excitation of the rotational states of molecules. Spectroscopy dealing with rotational and vibrational states of molecules. Small amplitude motion/mode: refers to a molecular vibration whose amplitude is small enough so that the harmonic oscillator is a reliable zero-order approximation. Equation associated to the Hamiltonian operator: its resolution provides the allowed energy levels (eigenvalues) and the corresponding wave functions (eigenfunctions). Representation of a many particle 'mean-field' wavefunction in terms of the antisymmetrized products of single-electron wavefunctions (molecular orbitals). Spin orbit coupling: refers to the coupling between the spin and the orbital angular momenta.
ROA Rotational Spectroscopy Rovibrational Spectroscopy SAM Schrödinger equation Slater determinant SOC Spectroscopic transition	 motion. Raman optical activity: is a vibrational spectroscopy based on the differential Raman scattering of left and right circularly polarized light due to molecular chirality. Spectroscopy using the microwave region of the electromagnetic field to study the excitation of the rotational states of molecules. Spectroscopy dealing with rotational and vibrational states of molecules. Small amplitude motion/mode: refers to a molecular vibration whose amplitude is small enough so that the harmonic oscillator is a reliable zero-order approximation. Equation associated to the Hamiltonian operator: its resolution provides the allowed energy levels (eigenvalues) and the corresponding wave functions (eigenfunctions). Representation of a many particle 'mean-field' wavefunction in terms of the antisymmetrized products of single-electron wavefunctions (molecular orbitals). Spin orbit coupling: refers to the coupling between the spin and the orbital angular momenta. The passage between two energy levels, i.e. from an initial to a final state, detected by a spectroscopic technique.
ROA Rotational Spectroscopy Rovibrational Spectroscopy SAM Schrödinger equation Slater determinant SOC Spectroscopic transition SQUID	 motion. Raman optical activity: is a vibrational spectroscopy based on the differential Raman scattering of left and right circularly polarized light due to molecular chirality. Spectroscopy using the microwave region of the electromagnetic field to study the excitation of the rotational states of molecules. Spectroscopy dealing with rotational and vibrational states of molecules. Small amplitude motion/mode: refers to a molecular vibration whose amplitude is small enough so that the harmonic oscillator is a reliable zero-order approximation. Equation associated to the Hamiltonian operator: its resolution provides the allowed energy levels (eigenvalues) and the corresponding wave functions (eigenfunctions). Representation of a many particle 'mean-field' wavefunction in terms of the antisymmetrized products of single-electron wavefunctions (molecular orbitals). Spin orbit coupling: refers to the coupling between the spin and the orbital angular momenta. The passage between two energy levels, i.e. from an initial to a final state, detected by a spectroscopic technique. Magnetometer based on superconducting loops used to measure very low magnetic
ROA Rotational Spectroscopy Rovibrational Spectroscopy SAM Schrödinger equation Slater determinant SOC Spectroscopic transition SQUID	 motion. Raman optical activity: is a vibrational spectroscopy based on the differential Raman scattering of left and right circularly polarized light due to molecular chirality. Spectroscopy using the microwave region of the electromagnetic field to study the excitation of the rotational states of molecules. Spectroscopy dealing with rotational and vibrational states of molecules. Small amplitude motion/mode: refers to a molecular vibration whose amplitude is small enough so that the harmonic oscillator is a reliable zero-order approximation. Equation associated to the Hamiltonian operator: its resolution provides the allowed energy levels (eigenvalues) and the corresponding wave functions (eigenfunctions). Representation of a many particle 'mean-field' wavefunction in terms of the antisymmetrized products of single-electron wavefunctions (molecular orbitals). Spin orbit coupling: refers to the coupling between the spin and the orbital angular momenta. The passage between two energy levels, i.e. from an initial to a final state, detected by a spectroscopic technique. Magnetometer based on superconducting loops used to measure very low magnetic fields.
ROA Rotational Spectroscopy Rovibrational Spectroscopy SAM Schrödinger equation Slater determinant SOC Spectroscopic transition SQUID STEOM	 motion. Raman optical activity: is a vibrational spectroscopy based on the differential Raman scattering of left and right circularly polarized light due to molecular chirality. Spectroscopy using the microwave region of the electromagnetic field to study the excitation of the rotational states of molecules. Spectroscopy dealing with rotational and vibrational states of molecules. Small amplitude motion/mode: refers to a molecular vibration whose amplitude is small enough so that the harmonic oscillator is a reliable zero-order approximation. Equation associated to the Hamiltonian operator: its resolution provides the allowed energy levels (eigenvalues) and the corresponding wave functions (eigenfunctions). Representation of a many particle 'mean-field' wavefunction in terms of the antisymmetrized products of single-electron wavefunctions (molecular orbitals). Spin orbit coupling: refers to the coupling between the spin and the orbital angular momenta. The passage between two energy levels, i.e. from an initial to a final state, detected by a spectroscopic technique. Magnetometer based on superconducting loops used to measure very low magnetic fields. Similarity transformed equations of motion (see above).
ROA Rotational Spectroscopy Rovibrational Spectroscopy SAM Schrödinger equation Slater determinant SOC Spectroscopic transition SQUID STEOM TDA	 motion. Raman optical activity: is a vibrational spectroscopy based on the differential Raman scattering of left and right circularly polarized light due to molecular chirality. Spectroscopy using the microwave region of the electromagnetic field to study the excitation of the rotational states of molecules. Spectroscopy dealing with rotational and vibrational states of molecules. Small amplitude motion/mode: refers to a molecular vibration whose amplitude is small enough so that the harmonic oscillator is a reliable zero-order approximation. Equation associated to the Hamiltonian operator: its resolution provides the allowed energy levels (eigenvalues) and the corresponding wave functions (eigenfunctions). Representation of a many particle 'mean-field' wavefunction in terms of the antisymmetrized products of single-electron wavefunctions (molecular orbitals). Spin orbit coupling: refers to the coupling between the spin and the orbital angular momenta. The passage between two energy levels, i.e. from an initial to a final state, detected by a spectroscopic technique. Magnetometer based on superconducting loops used to measure very low magnetic fields. Similarity transformed equations of motion (see above). Tamm Dancoff approximation: is, from a practical point of view, a synonym of CIS.
ROA Rotational Spectroscopy Rovibrational Spectroscopy SAM Schrödinger equation Slater determinant SOC Spectroscopic transition SQUID STEOM TDA Template approach	 motion. Raman optical activity: is a vibrational spectroscopy based on the differential Raman scattering of left and right circularly polarized light due to molecular chirality. Spectroscopy using the microwave region of the electromagnetic field to study the excitation of the rotational states of molecules. Spectroscopy dealing with rotational and vibrational states of molecules. Small amplitude motion/mode: refers to a molecular vibration whose amplitude is small enough so that the harmonic oscillator is a reliable zero-order approximation. Equation associated to the Hamiltonian operator: its resolution provides the allowed energy levels (eigenvalues) and the corresponding wave functions (eigenfunctions). Representation of a many particle 'mean-field' wavefunction in terms of the antisymmetrized products of single-electron wavefunctions (molecular orbitals). Spin orbit coupling: refers to the coupling between the spin and the orbital angular momenta. The passage between two energy levels, i.e. from an initial to a final state, detected by a spectroscopic technique. Magnetometer based on superconducting loops used to measure very low magnetic fields. Similarity transformed equations of motion (see above). Tamm Dancoff approximation: is, from a practical point of view, a synonym of CIS. A model in which the structure of a molecular system is refined with reference to
ROA Rotational Spectroscopy Rovibrational Spectroscopy SAM Schrödinger equation Slater determinant SOC Spectroscopic transition SQUID STEOM TDA Template approach	 motion. Raman optical activity: is a vibrational spectroscopy based on the differential Raman scattering of left and right circularly polarized light due to molecular chirality. Spectroscopy using the microwave region of the electromagnetic field to study the excitation of the rotational states of molecules. Spectroscopy dealing with rotational and vibrational states of molecules. Small amplitude motion/mode: refers to a molecular vibration whose amplitude is small enough so that the harmonic oscillator is a reliable zero-order approximation. Equation associated to the Hamiltonian operator: its resolution provides the allowed energy levels (eigenvalues) and the corresponding wave functions (eigenfunctions). Representation of a many particle 'mean-field' wavefunction in terms of the antisymmetrized products of single-electron wavefunctions (molecular orbitals). Spin orbit coupling: refers to the coupling between the spin and the orbital angular momenta. The passage between two energy levels, i.e. from an initial to a final state, detected by a spectroscopic technique. Magnetometer based on superconducting loops used to measure very low magnetic fields. Similarity transformed equations of motion (see above). Tamm Dancoff approximation: is, from a practical point of view, a synonym of CIS. A model in which the structure of a molecular system is refined with reference to suitable fragments, whose structures are accurately known.
ROA Rotational Spectroscopy Rovibrational Spectroscopy SAM Schrödinger equation Slater determinant SOC Spectroscopic transition SQUID STEOM TDA Template approach VCD	 motion. Raman optical activity: is a vibrational spectroscopy based on the differential Raman scattering of left and right circularly polarized light due to molecular chirality. Spectroscopy using the microwave region of the electromagnetic field to study the excitation of the rotational states of molecules. Spectroscopy dealing with rotational and vibrational states of molecules. Small amplitude motion/mode: refers to a molecular vibration whose amplitude is small enough so that the harmonic oscillator is a reliable zero-order approximation. Equation associated to the Hamiltonian operator: its resolution provides the allowed energy levels (eigenvalues) and the corresponding wave functions (eigenfunctions). Representation of a many particle 'mean-field' wavefunction in terms of the antisymmetrized products of single-electron wavefunctions (molecular orbitals). Spin orbit coupling: refers to the coupling between the spin and the orbital angular momenta. The passage between two energy levels, i.e. from an initial to a final state, detected by a spectroscopic technique. Magnetometer based on superconducting loops used to measure very low magnetic fields. Similarity transformed equations of motion (see above). Tamm Dancoff approximation: is, from a practical point of view, a synonym of CIS. A model in which the structure of a molecular system is refined with reference to suitable fragments, whose structures are accurately known. Vibrational version of the circular dichroism.
ROA Rotational Spectroscopy Rovibrational Spectroscopy SAM Schrödinger equation Slater determinant SOC Spectroscopic transition SQUID STEOM TDA Template approach VCD VCI	 motion. Raman optical activity: is a vibrational spectroscopy based on the differential Raman scattering of left and right circularly polarized light due to molecular chirality. Spectroscopy using the microwave region of the electromagnetic field to study the excitation of the rotational states of molecules. Spectroscopy dealing with rotational and vibrational states of molecules. Small amplitude motion/mode: refers to a molecular vibration whose amplitude is small enough so that the harmonic oscillator is a reliable zero-order approximation. Equation associated to the Hamiltonian operator: its resolution provides the allowed energy levels (eigenvalues) and the corresponding wave functions (eigenfunctions). Representation of a many particle 'mean-field' wavefunction in terms of the antisymmetrized products of single-electron wavefunctions (molecular orbitals). Spin orbit coupling: refers to the coupling between the spin and the orbital angular momenta. The passage between two energy levels, i.e. from an initial to a final state, detected by a spectroscopic technique. Magnetometer based on superconducting loops used to measure very low magnetic fields. Similarity transformed equations of motion (see above). Tamm Dancoff approximation: is, from a practical point of view, a synonym of CIS. A model in which the structure of a molecular system is refined with reference to suitable fragments, whose structures are accurately known. Vibrational version of the circular dichroism. Vibrational configuration interaction: exploits the configuration interaction model to

Vibronic	Spectroscopy involving the simultaneous excitations of vibrational and electronic states
spectroscopy	of molecules.
VPT2	Vibrational perturbation theory to second order: exploits perturbation theory to the
	second order to treat the vibrational motions.
VSCF	Vibrational self-consistent field: exploits the self-consistent model to treat the
	vibrational motion.
Wave function	Mathematical description of the quantum state of an isolated quantum system
	resulting from the corresponding Schrödinger equation.
ZFS	Zero field splitting: describes the lifiting of the degeneracy of the 2S+1 magnetic
	sublevels of a spin multiplet with total spin S in the absence of a magnetic field, caused
	by the effects of SOC and electron-electron spin-spin interactions.
ZPE	Zero-point energy: is the lowest energy that a quantum system may have, which,
	contrary to the classical case, is nonzero due to the Heisenberg uncertainty principle.

1262 Author contributions

- Introduction (V.B., M.B., F.N., C.P.); Experimentation (V.B., M.B., J.R.C., A. B. M., F.N., C.P.); Results
- (M.M., C.P., V.B., M.B., A.B.M., R.D., J.R.C.); Applications (M.M., C.P., D.C.C., F.N.); Reproducibility
- and data deposition (S.A., V.B., M.B., A.M.B., C.P.); Limitations and optimizations (S.A., V.B., M.B.,
- J.R.C., C.P.); Outlook (V.B.); Overview of the Primer (C.P.).

1268 **Competing interests**

1269 All authors declare no competing interests.

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