3
Computational Modeling and Least-Squares Fitting of EPR Spectra

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3.1
Introduction

In EPR (electron paramagnetic resonance) spectroscopy, computer simulation and least-squares fitting are essential in extracting quantitative structural and dynamic parameters from experimental spectra. Without numerical methods, this extraction would be restricted to simple systems. This chapter summarizes simulation and fitting methods that have been proposed in the literature and implemented in software. It includes an extensive, though not complete, list of references.

Emphasis is placed on methods currently implemented in the software package EasySpin [1], which covers EPR simulations in the following regimes: (i) rigid-limit continuous-wave (cw) EPR spectra for arbitrary spin systems, for both powders and single crystals, at various levels of theory including eigenfields, matrix diagonalization, and perturbation theory; (ii) dynamic EPR spectra of tumbling spin centers with one electron spin and several nuclei, implementing stochastic Liouville equation (SLE) solvers and perturbative approaches; (iii) EPR spectra in the fast-motion limit, using either a Breit–Rabi solver or perturbation theory; (iv) dynamic EPR spectra due to chemical exchange in solution, implementing a direct Liouville-space method; (v) solid-state ENDOR (electron nuclear double resonance) spectra based on either matrix diagonalization or perturbation theory; and (vi) pulse EPR spectra for general pulse sequences using the Hilbert-space density matrix formalism in the high-field limit. All these simulation regimes are reviewed in the following.

Similarly to many other programs, EasySpin also provides a range of least-squares fitting algorithms, among them Levenberg–Marquardt (LM), Nelder–Mead simplex, genetic algorithms, particle-swarm optimization, as well as simple Monte Carlo and grid searches. These algorithms, as well as the objective function choice, multicomponent fitting, and error analysis, are discussed below.

This chapter is not intended to be a complete review of all theory underlying EPR simulation methods, which would be utterly impossible. Instead, it summarizes theoretical and algorithmic aspects that are implemented in or are relevant to EasySpin. Applicability and limitations of methods are discussed as well. The

chapter is not concerned with the specifics of usage of software packages. Tutorials and documentation for EasySpin can be found online at *easyspin.org*.

Many reviews have appeared over time that summarize progress in the methodology for EPR spectral simulation and fitting and that describe available simulation programs, starting with very early ones [2–4] up to more recent times [5–8]. A previous *Handbook of ESR* included a review on computer techniques [9]. A very detailed review of simulation methods and programs as of 1992 is contained in the book by Mabbs and Collison [10]. A list of software available in 1993 is published [11].

In the following, after summarizing key aspects of available simulation software packages, we discuss the basic aspects of EPR simulations and then progress to describe methods for static and dynamic cw EPR spectra, pulse EPR, ENDOR, and DEER (double electron–electron resonance) spectra. Subsequently, a section is dedicated to least-squares fitting. After a short section covering topics such as spin quantitation and data formats, we summarize in the conclusion some of the challenges that still lie ahead.

3.2
Software

In this section, we describe a few details about EasySpin and other EPR simulation programs. Some of them are available online, and many others can be obtained from their authors. A few have ceased to be developed and are no longer maintained.

3.2.1
EasySpin

EasySpin, developed by the author, was originally conceived as an in-house simulation program for solid-state cw EPR spectra in the laboratory of Arthur Schweiger at ETH Zurich, with a first public release in 2000. The initial work is documented in a 2003 PhD thesis [12] and, including subsequent extensions, in a 2006 article in *Journal of Magnetic Resonance* [1]. A summary of EasySpin functionality relevant to nitroxides was subsequently published [13].

Since its first publication, EasySpin has advanced on many levels. Thanks to feedback from the worldwide user community, bugs were corrected, algorithms became more robust, implementations became faster, and more regimes and experiments were added. Notably, support for pulse EPR simulations was added in 2009 [14], least-squares fitting was introduced in 2010, and chemical exchange was implemented in 2012.

The program continues to be developed, with the ultimate goal of removing the data analysis and simulation bottleneck from the EPR discovery process. Its core strengths are solid-state cw EPR spectra as well as ENDOR and ESEEM (electron spin echo envelope modulation) spectra, with growing support for slow-motion simulations and other more specialized situations.

3.2.2
Other Software

EasySpin draws substantially from methods implemented in other, mostly older, EPR simulation programs. In the following, we give a partial list. The National Institute of Environmental Health Sciences (NIEHS) maintains a database of EPR simulation programs (electron spin resonance software database, ESDB) [15], including programs of limited availability and dedicated to specific problems.

Bruker ships certain spectrometers with SimFonia, a simulation program developed by Weber at Bruker in the 1990s [16]. Hanson and coworkers have developed Sophe, a widely used simulation program for solid-state EPR spectra [17–23] that has been equipped with a graphical user interface (UI) by Bruker and marketed as XSophe. A more modern UI to Sophe called *Molecular Sophe* (MoSophe) has recently been developed [24].

WinSIM is dedicated to solution spectra of spin traps and was developed at the NIEHS [25]. Hendrich [26] has developed SpinCount, a program that emphasizes spin quantitation. Slow-motion spectra of nitroxide radicals can be simulated and fitted using the suite of highly optimized SLE solvers developed by the Freed group at the ACERT center at Cornell [27–30]. Altenbach has developed a code dedicated to nitroxide labels [31]. Dipolar broadening of cw EPR spectra of nitroxides can be analyzed using DIPFIT [32]. E-SpiReS is a program for slow-motion simulation that also interfaces to quantum chemistry programs [33, 34]. At Manchester, an in-house code has been used to simulate hundreds of spectra in a book about transition metal ion EPR [10]. Weil's program EPRNMR [35] is designed for solid-state EPR and has extensive support for single-crystal spectra. DDPOW supports binuclear complexes [36]. QPOW [37] and SIMPOW6 [38] were developed at the University of Illinois. Sim is a program by Weihe that accepts arbitrary Hamiltonian matrices as input [39, 40]. SPIN, developed at the National High Magnetic Field Laboratory, is tailored toward high-spin systems. Xemr is a general-purpose EPR simulation program [41]. EPRsim32 [42] is a powder cw EPR simulation program that includes genetic fitting algorithms. Rockenbauer and Korecz [43] have developed a general simulation program that includes chemical exchange. Another still popular program for chemical exchange was created by Heinzer in the early 1970s [44, 45]. WinMOMD is a program for simulation of slow-motional nitroxide spectra using the MOMD (microscopic order, macroscopic disorder) model [46]. EWVoigt is geared toward nitroxide spectra in the fast-motion regime and utilizes convolution methods [47]. EPRSIM-C implements a variety of models for nitroxide spectra and includes evolutionary fitting algorithms [48].

Several programs were developed specifically for ENDOR and ESEEM simulations. MAGRES from Nijmegen [49, 50] was an early one. GENDOR is an ENDOR simulation program developed by Hoffman at Northwestern [51–53]. HYSCORE (hyperfine sublevel correlation) simulation programs were pioneered by Goldfarb [54] and Schweiger [55]. Astashkin's program SimBud is equipped with a UI [56]. OPTESIM [57] provides ESEEM simulations and least-squares fitting.

Many simulation programs for NMR spectra have been developed over the years and have been reviewed [58–61]. Among the many programs, SIMPSON [62], SPINEVOLUTION [63], and Spinach [64] are particularly widely used. Spinach is a very general and efficient spin dynamics code that is geared toward large NMR spin systems, but supports EPR experiments as well.

In addition to the programs mentioned, there are many excellent in-house codes developed by various research groups, but are not separately described in literature, and are either not distributed or have not seen widespread use.

3.3
General Principles

3.3.1
Spin Physics

The simulation of EPR spectra is based on a spin Hamiltonian that describes the interactions amongst the spins in the spin system and between the spins and the externally applied magnetic field. The following summarizes the most common terms in the spin Hamiltonian used to model EPR spectra [65]. We do not intend to outline the complete theoretical basis. Instead, the discussion is limited to some aspects that are often overlooked by users and that are important for obtaining correct simulation results. We also summarize the basic quantum dynamic equations needed to compute EPR spectra.

3.3.1.1 Interactions
EPR spectra are generally simulated on the basis of a spin Hamiltonian (sH), an effective Hamiltonian that represents the subset of closely spaced and low-lying energy levels of a spin center that are accessible in EPR experiments as a spin system, a network of coupled (effective) electron spins and nuclear spins [66]. The sH model is not universally valid and becomes inadequate, for example, in the presence of very large spin–orbit coupling or in the gas phase. Essentially all common simulation programs are based on an sH. The sH (often expressed in angular frequency units) consists of a sum of interaction terms

$$H = \sum_i (H_{ez,i} + H_{zf,i}) + \sum_{i,j} H_{ss,i,j} + \sum_{i,k} H_{hf,i,k} + \sum_k (H_{ez,i} + H_{nq,i})$$

where i and j run over the electron spins and k runs over the nuclear spins in the system. In the following, we present the conventional forms of the various terms that mostly utilize Cartesian spin vector operators, $\mathbf{S}^T = (S_x, S_y, S_z)^T$ and $\mathbf{I}^T = (I_x, I_y, I_z)^T$, where T indicates the transpose of the matrix.

The electron Zeeman interaction in angular frequency units is described by

$$H_{ez} = \frac{-\mathbf{B}^T \boldsymbol{\mu}_{el}}{\hbar} = + \left(\frac{\mu_B}{\hbar} \right) \mathbf{B}^T g \mathbf{S}$$

with the 3×3 g-matrix g. The externally applied magnetic field $\boldsymbol{B}$ includes both the static and microwave fields. Another form of the term is $\left(\frac{\mu_B}{\hbar} \right) \boldsymbol{S}^T g \boldsymbol{B}$. Often, it is assumed that g is symmetric, $g = g^T$, since it is not possible to determine the antisymmetric component of g from conventional cw EPR spectra employing linearly polarized microwave [67]. In this case, the two forms are identical. However, g-matrices calculated by quantum chemical programs are generally asymmetric [68]. Then, the two forms are not identical [65] and one has to verify that the quantum chemistry program and the EPR simulation program assume the same form. If the EPR simulation software only supports symmetric g matrices, the effective symmetric matrix g_{sym} corresponding to a given asymmetric g can be obtained from $g_{sym} = (gg^T)^{\frac{1}{2}}$.

Higher order electron Zeeman terms proportional to $\boldsymbol{B}$ and $\boldsymbol{S}^3$ or $\boldsymbol{S}^5$ are in principle possible [66] and have been reported [69–72]. Very few programs, such as EPRNMR [73], have provisions for these terms.

The nuclear Zeeman interaction contribution to the EPR spin Hamiltonian (in angular frequency units) is given by

$$H_{nz} = \frac{-\boldsymbol{B}^T \boldsymbol{\mu}_{nuc}}{\hbar} = -\left(\frac{\mu_N}{\hbar} \right) \boldsymbol{B}^T g_n \boldsymbol{I}$$

where g_n is the isotropic nuclear g-factor and μ_N is the nuclear Bohr magneton. Any anisotropy in g_n (chemical shift anisotropy) is very small compared to g_n itself and is generally neglected in EPR. The pseudo-nuclear Zeeman effect [67, 74] in high-electron-spin systems manifests itself in a significant apparent anisotropy of an effective g_n. It arises naturally when the full spin system is simulated, but can be taken into account explicitly in perturbational treatments with a restricted system.

The hyperfine (hf) interaction (in angular frequency units) between an electron spin $\boldsymbol{S}$ and a nuclear spin $\boldsymbol{I}$ is anisotropic and described by a general 3×3 coupling matrix A

$$H_{hf} = \boldsymbol{S}^T A \boldsymbol{I}$$

Another form of the hf interaction $\boldsymbol{I}^T A \boldsymbol{S}$ is identical to $\boldsymbol{S}^T A \boldsymbol{I}$ only if the hyperfine coupling matrix A is symmetric. In general, there are three contributions to $A : A = a_{iso} + T + A_L$, where a_{iso} is the isotropic Fermi contact term, T is the matrix describing the magnetic dipole–dipole coupling between the electron and nucleus (axially symmetric in the limit of the point-dipole approximation of a completely localized electron spin), and A_L is a generally asymmetric 3×3 matrix describing the orbital contribution [75]. In analogy to the g-matrix, not all programs allow the input of nonsymmetric A matrices.

The interaction energy between the nuclear electric quadrupole moment of a nucleus with $\boldsymbol{I} > \frac{1}{2}$ and the local electric field gradient is described in the sH by

$$H_{nq} = \boldsymbol{I}^T P \boldsymbol{I}$$

where P is the traceless nuclear quadrupole tensor [75]. Although this term can have significant effects on cw EPR spectra (e.g., on Au(II) complexes [76]), it is not implemented in all EPR simulation programs.

The coupling between two electron spins is described by the general form

$$H_{ss} = \boldsymbol{S}_1^T J_{12} \boldsymbol{S}_2$$

with a general 3×3 coupling matrix J_{12} [77]. It can contain three contributions: $J_{12} = J_{ex} + J_{dip} + J_{as}$. The first is the isotropic exchange coupling, J_{ex}. The associated term, called the *Heisenberg–Dirac–van Vleck Hamiltonian*, is encountered in the literature in several different forms ($J_{ex}\boldsymbol{S}_1^T\boldsymbol{S}_2$, $2J_{ex}\boldsymbol{S}_1^T\boldsymbol{S}_2$, $-2J_{ex}\boldsymbol{S}_1^T\boldsymbol{S}_2$), so that care has to be exercised in ensuring correct conversion between the definitions of J_{ex} in the literature and in the simulation program. The second contribution is the symmetric magnetic dipole–dipole coupling, J_{dip}, analogous to T in the hyperfine term. The third contribution, J_{as}, is antisymmetric and describes the Dzyaloshinskii–Moriya interaction [77]. The corresponding term can be written in vector form as $\boldsymbol{J}_{as}^T(\boldsymbol{S}_1 \times \boldsymbol{S}_2)$.

Another term describing electron–electron coupling that is occasionally included in the spin Hamiltonian for transition metal ion dimers is biquadratic exchange [78, 79] of the form $-j(\boldsymbol{S}_1^T\boldsymbol{S}_2)^2$. It is supported by a few programs such as SPIN and EasySpin.

The quadratic zero-field splitting term for an electron spin $S > \frac{1}{2}$ is given by

$$H_{zf} = \boldsymbol{S}^T D \boldsymbol{S}$$

with the (usually made traceless) symmetric 3×3 zero-field tensor D, in angular frequency units [65]. Two common issues with this term are the notational ambiguity of D (it indicates the full tensor as well as the scalar parameter equal to $\frac{3}{2}$ the largest principal value of the tensor) as well as the variety of axis-labeling conventions [80, 81], which determine the values and relative signs of the scalar zero-field parameters D and E.

Beyond the most common quadratic zero-field term, a variety of higher order single-spin terms containing $\boldsymbol{S}^k$ with $k > 2$ are used in the sH for high-spin transition and rare earth ions [66]. These include the two fourth-order terms with the conventional parameters a and F used for Fe(III) and Mn(II) ions [67, 82–85]. They have been included in early simulation programs [86]. Care has to be exercised concerning the correct axis definitions. Beyond these conventional parameters, the general form for the high-order terms is $H = \sum_{k=2}^{2S} \sum_{q=-k}^{+k} B_{kq} O_{kq}(\boldsymbol{S})$, where B_{kq} represents the scalar interaction parameters and $O_{kq}(\boldsymbol{S})$ represents the tensor operator components for an electron spin $\boldsymbol{S}$. There is some degree of arbitrariness in the choice of these tensor components, especially their phases. As a consequence, there are a significant number of inconsistent definitions of O_{kq} in the literature. The most common ones are the extended Stevens operators [87]. The various forms and definitions of high-order terms have been extensively and critically reviewed by Rudowicz [88–90]. A review of such parameters for all 32 point groups has been compiled by Misra *et al.* [91]. The relation between D and E and the parameters B_{2q} has also been discussed [92, 93]. Rudowicz and Chung [94] list explicit expression for operators O_{kq} up to $k = 12$. Efficient methods for the computation of the matrix elements have been published recently [95, 96]. A general method for rotational transformation of these high-order tensor sets is available [97], including tesseral

tensor operators. Utmost care has to be taken with these terms, as definitions and usage in the literature are often not only inconsistent, but sometimes incorrect as well [98, 99].

In the construction of the sH, the evaluation of perturbational expressions and the conversion between various energy and field units, accurate values of fundamental constants are required. The values of these fundamental constants are regularly updated every few years by CODATA based on continuous improvements in their measurements [100]. The same holds for nuclear isotope properties, which were updated last in 2011 [101]. Simulation programs should stay up-to-date in both respects.

3.3.1.2 Quantum States and Spaces

In Hilbert space, a (pure) state of a spin system is described by a state vector, $|k\rangle$. In numerical representation, for an N-level spin system, this is an $N \times 1$ vector. The size of the Hilbert space, N, grows exponentially with the number of spins, $N = \prod_i (2S_i + 1) \cdot \prod_k (2I_k + 1)$. As a consequence, the simulation of large spin systems is challenging. Various basis sets are used to represent spin states, and the best choice depends on the computational problem at hand. The most common basis set for representing these vectors is the uncoupled Zeeman basis, where each basis state is a product of single-spin Zeeman states, $|S, m_S\rangle$ and $|I, m_I\rangle$, with the magnetic projection quantum numbers m_S and m_I. Another basis in Hilbert space is the coupled basis, for example, the singlet–triplet basis for a system of two coupled spins-$\frac{1}{2}$, with the singlet state $|S\rangle$ and the triplet states $|T_{-1}\rangle$, $|T_0\rangle$, and $|T_{+1}\rangle$. Yet another basis is the eigenbasis, where the basis states are the eigenstates of the spin Hamiltonian, H.

State vectors can only represent pure quantum states [102] and are sufficient if only eigenstates of the spin Hamiltonian are required, such as in solid-state cw EPR simulations. For representing mixed quantum states, the density operator is required. It is a statistical state operator, $\sigma = \sum_k p_k |k\rangle\langle k|$, which can describe both pure and mixed quantum states of spin systems and spin system ensembles [102, 103]. When represented in a basis in Hilbert space, the density operator is an $N \times N$ matrix and is called the *density matrix*. It is generally advantageous to use the density matrix for computing the quantum dynamics of spin systems [75, 104, 105].

The space of all operators in Hilbert space constitutes Liouville space. The Liouville space of an N-level spin system is N^2-dimensional. In one basis choice, each Liouville state $|u\rangle|v\rangle$ corresponds to a pair of states $|u\rangle$ and $|v\rangle$, or a "transition" $|u\rangle \leftrightarrow |v\rangle$, in Hilbert space. In Liouville space, the density operator is represented as an $N^2 \times 1$ vector. Operators in Liouville space, acting on Liouville vectors such as the density matrix, are called *superoperators* and are numerically represented by $N^2 \times N^2$ matrices. The Hilbert-space Hamiltonian corresponds to the Liouville-space Hamiltonian commutation superoperator, whose matrix representation is $\hat{\hat{H}} = H \otimes I - I \otimes H$, where $\otimes$ is the Kronecker product. Eigenvalues and eigenvectors of the Hamiltonian superoperator correspond to transition frequencies and transition state pairs. The use of Liouville space was first introduced in NMR by Banwell and Primas [106].

As in Hilbert space, there exist several basis choices in Liouville space [105]. One that is commonly used to derive analytical expressions in NMR and pulse EPR is the Cartesian Zeeman product operator basis [105]. It forms the basis of the intuitive product operator formalism [107]. A basis of irreducible spherical tensor operators (ISTOs) [64, 108–110] or linear combinations thereof [111] is less intuitive, but offers many computational advantages. In EPR, it has first been extensively utilized by Freed and Fraenkel [112]. ISTOs are related to the high-order spin operator sets used in the EPR spin Hamiltonian [72], as discussed above.

The description of systems with sets of equivalent nuclear spins can be simplified by decomposing the associated Hilbert or Liouville space into separate subspaces using the Clebsch–Gordan series of the rotation group by recursively applying $D^{j_1} \otimes D^{j_1} = D^{j_1+j_2} \otimes D^{j_1+j_2-1} \cdots \otimes D^{|j_1-j_2|}$. The sH is block-diagonal in the associated basis. Also, magnetic equivalence of n nuclei means that the sH is invariant under any permutation among the equivalent spins [113–115]. Therefore, the properties of the associated permutation group S_n can be leveraged to gain further insight and to reduce the size of the problem [64, 116, 117]. In EPR, internuclear couplings are generally negligible so that special considerations for the equivalence of spins with $I \geq 1$ and the effect of relaxation, as done in NMR [114, 115, 118], need not be taken fully into account.

3.3.1.3 Equations of Motion

There are several possible equations of motion that can be used to describe the dynamics of spin ensembles. The dynamics of a single spin-$\frac{1}{2}$ can be described classically. For such a system, the classical torque equation that describes the Larmor precession (and nutation) of its magnetic moment vector or of the macroscopic magnetization (magnetic moment per volume) in the external, possibly time-dependent, magnetic field is $\frac{d\boldsymbol{M}}{dt} = \gamma_e \boldsymbol{M} \times \boldsymbol{B}(t)$.

To take spin relaxation into account, Bloch [119] augmented this equation by phenomenological relaxation terms with time constants T_1 and T_2. The resulting Bloch equations in matrix form [120] are

$$
\begin{pmatrix} \frac{dM_x}{dt} \\ \frac{dM_y}{dt} \\ \frac{dM_z}{dt} \end{pmatrix} = \begin{pmatrix} -T_2^{-1} & +\gamma_e B_z & -\gamma_e B_y \\ -\gamma_e B_z & -T_2^{-1} & +\gamma_e B_x \\ +\gamma_e B_y & -\gamma_e B_x & -T_1^{-1} \end{pmatrix} + \begin{pmatrix} 0 \\ 0 \\ \frac{M_z(0)}{T_1} \end{pmatrix}
$$

and can be easily solved numerically.

These classical equations cannot be applied to spin systems with more than one spin-$\frac{1}{2}$. In general, quantum dynamics has to be applied. There are three forms of the quantum equation of motion for an EPR spin system: for states in Hilbert space, for density operators in Hilbert space, and for density operators (which are Liouville-space state vectors) in Liouville space.

The equation of motion for Hilbert-space state vectors $|k\rangle$ is the Schrödinger equation, $\frac{d|k(t)\rangle}{dt} = -iH|k(t)\rangle$. Its integrated form is $|k(t)\rangle = U(t, t_0)|k(t_0)\rangle$, with the time propagation operator U satisfying the Schrödinger equation, $\frac{dU(t,t_0)}{dt} =$

$-\mathrm{i}HU(t, t_0)$. If H is time independent, then U is a simple exponential operator $U(t, t_0) = \exp(-\mathrm{i}H\Delta t)$ with $\Delta t = t - t_0$.

The equation of motion for the density operator $\sigma(t)$ in Hilbert space is the Liouville–von Neumann (LvN) equation, $\frac{\mathrm{d}\sigma(t)}{\mathrm{d}t} = -\mathrm{i}[H, \sigma(t)]$, with the commutator $[H, \sigma] = H\sigma - \sigma H$. In integrated form, it is $\sigma(t) = U(t, t_0)\sigma(t_0)U^\dagger(t, t_0)$, with the same propagator as above. This "sandwich" time propagation product is central in Hilbert-space spin dynamics simulations. In this form, however, it is not possible to incorporate stochastic processes such as rotational diffusion or chemical exchange.

In Liouville space, the LvN equation is $\frac{\mathrm{d}\sigma}{\mathrm{d}t} = -\mathrm{i}\widehat{\widehat{H}}\sigma$, with the Hamiltonian commutation superoperator $\widehat{\widehat{H}}$ and the density operator in vector form, σ [105]. $\widehat{\widehat{H}}$ is often denoted $\widehat{\widehat{L}}$ and called the *Liouville superoperator*. In integrated form, the equation is $\sigma(t) = \widehat{\widehat{U}}(t, t_0)\sigma(t_0)$, with the (super)propagator $\widehat{\widehat{U}}$. In contrast to the sandwich product in Hilbert space, this is a simple matrix–vector product.

To include stochastic processes into the dynamic model, the Liouville-space LvN equation is extended to the SLE [121–123]. In one of its forms, the SLE is

$$\frac{\mathrm{d}}{\mathrm{d}t}\sigma = (-\mathrm{i}\widehat{\widehat{H}} + \widehat{\widehat{\Gamma}} + \widehat{\widehat{X}})\sigma$$

with the stochastic relaxation superoperator $\widehat{\widehat{\Gamma}}$ and the chemical exchange superoperator $\widehat{\widehat{X}}$.

In Hilbert-space representation, the detected EPR signal V is computed from the density operator using $V(t) = \mathrm{trace}(D\,\sigma(t))$, where D is the detection operator representing quadrature detection, usually one of the electron spin ladder operators S_- or S_+. From a Hilbert-space state vector, it can be computed using the expectation value $V = \langle k|D|k\rangle$. In Liouville space, both D and σ are state vectors, and the expectation value is the scalar product $V = \langle D|\sigma\rangle$. All these equations are usually formulated in the rotating frame [75].

The two most common situations for which the above equations of motions are solved in EPR are the $\frac{\pi}{2}$ pulse experiment with FID (free induction decay) acquisition (pulse-acquire) [124] and the unsaturated steady-state limit [125]. Saturation is easily incorporated into the steady-state solution [126].

3.3.2
Other Aspects

3.3.2.1 Isotopologues

When magnetic nuclei are present in a spin center, the sH interactions depend on their nuclear spin quantum numbers, their g_n factors (via the nuclear Zeeman and hyperfine terms), and their electric quadrupole moments. Many elements have magnetic isotopes. Several have one single dominant naturally abundant isotope (magnetic: H, F, Na, Al, P, V, Mn, Co, Rh, I, etc.; nonmagnetic: C, O, S, etc.). In these cases, there exists only one dominant isotopologue of the spin center, with other isotopologues mostly negligible. Features from naturally low-abundant ^{13}C

are sometimes visible. On the other hand, many important elements have a mixture of two or more significantly abundant isotopes with different nuclear properties (e.g., B, K, Cl, Ti, Cr, Cu, Pd, etc.). Molecular spin centers with these elements occur as a mixture of isotopologues that differ in their properties, resulting in a series of overlapping spectra. For an accurate EPR simulation, EPR spectra of all significant isotopologues have to be simulated separately and added. For a mononuclear Cu complex with typical organic ligands, there are only two significant isotopologues (^{63}Cu and ^{65}Cu). An extreme case is the cloro-borane radical anion $B_{12}Cl_{12}^{\bullet-}$ with over 16 million isotopologues [127], of which about 2800 have a relative abundance larger than 0.01. Some programs, such as EasySpin and XSophe, automatically generate and loop over all significant isotopologues. Occasionally, the same nominal material from different suppliers might have a different isotope composition. To allow for this and for isotope-enriched samples, programs such as EasySpin and XSophe provide interfaces for specifying custom isotope mixtures.

The sH parameters for different isotopes of the same element in the same molecular environment are different and must be interconverted. Hyperfine matrices A for different isotopes of the same element scale with nuclear g_n factors and can be converted using $A_2 = A_1 \frac{g_{n,2}}{g_{n,1}}$. For hydrogen, this conversion of the hyperfine coupling between protium (^{1}H) and deuterium (^{2}H) is not always fully accurate, as there is the possibility of structural and kinetic isotope effects [128] when substituting ^{1}H for ^{2}H. Nuclear electric quadrupole tensors P can be converted using the nuclear electric quadrupole moments Q_i : $P_2 = P_1 \frac{Q_2}{Q_1}$.

3.3.2.2 Field Modulation for cw EPR

Essentially all cw EPR spectra are currently recorded using field modulation, producing the first harmonic of the absorption spectrum. (For a recently developed alternative, see Chapter 2.) The effect of field modulation can be easily added to a simulated absorption spectrum in a separate step. One approximate method, termed *pseudo-modulation* [129, 130], neglects sidebands and convolves the spectrum with a modulation function. This function is the Fourier transform of a Bessel function and can be represented in terms of a Chebyshev polynomial [12]. In cases where sidebands are resolved experimentally (very high modulation frequencies and/or very narrow lines), field modulation has to be modeled more completely, including the modulation frequency [131]. Various analytical expressions for field modulated lineshapes are available [132–136]. Robinson has published a series of papers on field modulation [137–139].

3.3.2.3 Frames and Orientations

Each second-rank tensorial interaction quantity in the sH represented by a 3×3 symmetric matrix, such as the tensors P and D and the symmetric parts of the matrices g and A, possesses a frame – called the *eigenframe* or *principal-axes frame* (*PAF*) – in which it is diagonal. This frame has a fixed orientation relative to the molecular structure of the spin center. The PAFs of different tensors of the same spin center are generally not collinear. In order to build the matrix representation of the sH, all tensors have to be represented in the same frame. Commonly, an

arbitrary frame fixed relative to the molecule is chosen and called the *molecular frame* (*MF*). It is usually chosen to be collinear with molecular symmetry axes or with the PAF of one of the tensors, for example, the one dominating the energy or the one most anisotropic.

The orientation of a tensor in the molecule can then be described by the orientation of the tensor PAF relative to the MF. The rotational transformation of the PAF to the MF can be represented in several ways: (i) by a set of three Euler angles, (ii) by a full 3×3 rotation matrix (direction cosines matrix, DCM), (iii) by a rotation axis and a rotation angle [140], and (iv) by quaternions. In publications, it is preferable to give the full DCM. Care has to be exercised when using Euler angles, as there are several possible conventions. In EPR and NMR, the prevalent one is zyz [67, 75, 105, 108, 141−144]. The three Euler angles (α, β, γ) apply to the rotation of the tensor PAF first by angle α around the z axis, then by β around the resulting y axis, and finally by γ around the resulting z axis to bring the PAF into coincidence with the MF. This is a passive rotation (transformation of frames, change of representation) that does not rotate the tensor and must be distinguished from an active rotation that rotates the tensor [145]. Tensors of any rank can be rotated and transformed using Wigner rotation matrices [146]. In EPR, quaternions have been useful in modeling restricted anisotropic rotation diffusion [147] and in generating Brownian trajectories for nitroxide EPR simulations [148].

In a powder sample, spin centers are randomly and uniformly oriented in space relative to the spectrometer reference frame. This reference frame is called the *lab frame* (*LF*). Conventionally, the LF z axis is defined parallel to the static field B_0, and the LF x axis is along the linearly oscillating microwave B_1 field.

If the spin center is static, simulations are commonly carried out in the MF. In that frame, the only sH parameter that changes from spin center to spin center in a powder or frozen solution sample is the orientation n of the static magnetic field $B_0^T = B_0(n_x, n_y, n_z)^T$. The sH and its matrix representation can be written as a linear combination

$$H = F + B_0^T G = F + B_0(n_x G_x + n_y G_y + n_z G_z)$$

where x, y, and z are the MF axes. In this form, the matrices F, G_x, G_y, and G_z do not depend on the magnetic field orientation and can be precomputed and then reused during a powder simulation, resulting in substantial time savings. Many programs take advantage of this approach.

In some non-static cases, most importantly in the presence of rotational dynamics, it is more convenient to carry out the simulation in the LF. There, the orientation of the external fields is fixed, but all tensors reorient and are rotated from spin center to spin center. To handle tensors in the LF most efficiently, they are best represented via their ISTO components and rotated via Wigner rotation matrices. Methods for simulating EPR spectra with rotational dynamics are discussed later in the chapter.

3.4
Static cw EPR Spectra

In this section, we summarize methods for the simulation of cw EPR spectra of ordered and disordered systems such as crystals, powders, glasses, and frozen solutions in the low-microwave power limit. In these types of samples, the spin centers are immobile. Therefore, the regime is called the *rigid limit*. Since dynamic processes are absent, the equations of motion are not necessary. Although they can be used [149], they are not required. Only the energy eigenstates of the sH need to be computed. We first discuss orientational properties of the sample, then discuss the various methods for computing field-swept spectra, and lastly cover frequency sweeps, inhomogeneous broadenings, and simulation artifacts.

3.4.1
Crystals and Powders

Crystals and powders differ in the nature of the orientational distribution of the spin centers in the sample. While the former have an orientational distribution that consists only of a small finite set of discrete orientations, the latter have almost continuous distribution of orientations. This difference means that EPR spectra of powders are much more demanding to simulate.

3.4.1.1 **Crystals**

Dedicated methods of analysis for single-crystal EPR data date back to the early days of EPR [150–153]. The relation between crystal symmetry and EPR spectra has been reviewed in great theoretical detail [154]. Two levels of symmetry have to be distinguished: (i) the space group of the crystal and (ii) the molecular symmetry group within the asymmetric unit (molecule, protein) of the crystal. In full powder averages, both the crystal symmetry and the molecular symmetry can be neglected.

On the basis of their point group and their translational symmetry, crystals belong to one of 219 different space groups. In spatially homogeneous static and microwave magnetic fields, EPR spectra are invariant under translation of the spin center; therefore, only the 32 crystallographic point groups underlying the space groups are relevant [154]. In addition, the EPR spectrum of a crystal is invariant under spatial inversion (substituting B with $-B$ in the sH does not affect the set of its eigenvalues), so that the spectra of a crystal of a centrosymmetric point group (e.g., D_{2h}) and any of its non-centrosymmetric subgroups (e.g., C_s or D_2) are identical. This is analogous to X-ray crystallography, where the diffraction pattern is inversion symmetric. Owing to this inversion symmetry, the 32 point groups fall into 11 Laue classes, each containing a centrosymmetric point group (C_i, C_{2h}, D_{2h}, C_{3i}, D_{3d}, C_{4h}, D_{4h}, C_{6h}, D_{6h}, T_h, and O_h) and its non-centrosymmetric subgroups. EPR can only distinguish between the 11 Laue classes. The number of asymmetric units in these classes range from 1 to 16. Only the smallest Laue class (space groups P1 and P$\bar{1}$, point groups C_1 and C_i) has a single asymmetric unit per unit cell. A

crystal of any other Laue class in a general orientation (magnetic field not along any symmetry axis or in any symmetry plane) gives an EPR spectrum that is an overlap of multiple spectra from identical, but differently oriented spin centers. The terms *single-orientation* and *single-crystal* should therefore be carefully distinguished.

While the crystallographic point group determines the number and orientations of the asymmetric units in the unit cell of the crystal, each asymmetric unit (molecule, protein) might house one or more equivalent or nonequivalent spin centers. The asymmetric unit itself can have non-crystallographic symmetry such as fivefold rotational symmetry. This molecular symmetry can increase the line multiplicity and complexity of the crystal EPR spectrum.

3.4.1.2 Partially Ordered Samples

Between the two limiting cases of single crystals with discrete orientational order and powders or frozen solutions with complete uniform orientational disorder, there exist systems with partial orientational order. These comprise liquid crystals and solid stretched films. In these, molecules and spin centers can have an orientational distribution that is continuous but not uniform, certain orientations being more probable than others. The spin center orientation $\Omega = (\phi, \theta, \chi)$ is described relative to a frame fixed with the liquid crystal or film geometry (the director frame), and the anisotropic orientational distribution is commonly described by a function of the form $P(\Omega) = \exp\left(\frac{-U(\Omega)}{k_B T}\right)$ where $U(\Omega)$ is an ordering (pseudo)potential, k_B is the Boltzmann constant, and T is the temperature. $U(\Omega)$ can be an arbitrary function of orientation [155]. A very simple and common form is the axial Maier–Saupe potential based on the second-order Legendre polynomial $U(\Omega) = -k_B T \frac{\lambda(3\cos^2\theta - 1)}{2}$ with the potential coefficient λ. The axial order can be quantified by the order parameter $S_{2,0} = \left\langle \frac{(3\cos^2\theta - 1)}{2} \right\rangle$, which ranges between $-1/2$ and $+1$.

3.4.1.3 Disordered Systems and Spherical Grids

The orientation of a spin center in space relative to the spectrometer can be described by a set of three tilt angles ϕ, θ, and χ (Euler angles). In disordered systems such as powders, glasses, and frozen solutions, these orientations are randomly and uniformly distributed. Only ϕ and θ are necessary to specify the orientation of $\boldsymbol{B}_0$ in the MF. Therefore, the transition fields are independent of the third angle, χ. However, χ is required to determine the orientation of $\boldsymbol{B}_1$ in the MF and thereby the transition probability.

To simulate a powder spectrum, a three-angle integration must be performed. For cw EPR spectra, the integral over the third angle χ can be performed analytically [1, 12, 156, 157]. For pulse EPR spectra, any third-angle anisotropy of the transition matrix elements that affect the pulse propagation operators has to be integrated numerically. Often, it is neglected.

The integral over the first two tilt angles ϕ and θ is usually approximated by a summation over a finite set of orientations (ϕ_k, θ_k). These orientations can be represented as a spherical grid of points (knots) on the unit sphere. The spectrum of the sH is invariant under inversion of the magnetic field in the sense that $H(\boldsymbol{B})$ and $H(-\boldsymbol{B})$ have identical sets of eigenvalues. Therefore, the (ϕ, θ) integration can

be limited to four octants of the unit sphere (e.g., the upper hemisphere with $\theta \leq \frac{\pi}{2}$). Additional symmetries in the sH allow restriction of the integration range to two or one octants, or even to a quarter of a meridian, resulting in additional savings in computation time [12].

In simple cases, it is possible to derive closed-form analytical expressions for the overall powder spectrum. Several authors published and applied such expressions for axial and orthorhombic systems [158–164]. Much of this work is based on earlier results by Kneubühl [158]. More recently, analytical solutions for triplet spectra based on path integrals along field isolines in a ternary orientational diagram have been derived [165].

Since the computation of the EPR spectrum for a given orientation is time consuming, powder simulation methods try to minimize the number of orientations needed to compute the powder spectrum. Many different schemes for spherical grids have been proposed and studied over the years, with the hope of finding one that is optimal in terms of giving the fastest convergence to the correct powder spectrum as a function of the number of orientations. The performance of various integration grids [166] have been extensively compared [12, 167, 168]. Despite this effort, no grid has proven to be consistently superior. It appears that any grid that has a reasonably uniform point density over the unit sphere is about equally efficient, as long as proper weighing factors based on approximate or exact Delaunay triangles or Voronoi cells are included [1]. The differential efficiency of similar grids often depends on the particulars of the sH.

Spherical grids can be either analytical (orthogonal or non-orthogonal), randomly generated, or numerically optimized. The simplest possible grid is rectangular, where ϕ and θ are varied independently in fixed increments. This grid has very nonuniform density with crowding at the poles. It was very common in the early days of EPR simulation. Grids based on randomly generated points [169] are very inefficient.

One of the first analytically constructed latitude–longitude grids published steps θ in constant intervals and adjusts the number of points on the latitude circle (constant θ) [37]. With increasing distance from the north pole ($\theta = 0$), an increasing number of points were placed on the latitude circles. This grid is commonly referred to as *igloo grid* [37, 170, 171], although igloos, the snow houses built by the Inuit, are usually constructed in a spiral form.

Sophe [17] and EasySpin [1] use a simple triangular latitude–longitude grid. Its grid points (over one octant) are obtained from $\theta_{k,l} = \left(\frac{k}{M} \right) \left(\frac{\pi}{2} \right)$ and $\phi_{k,l} = \left(\frac{l}{k} \right) \left(\frac{\pi}{2} \right)$ with $0 \leq k \leq M$ and $0 \leq l \leq k$. Essentially, as θ is increased in equal steps from the pole to the equator, one ϕ grid point is added for each θ step. This grid was originally introduced in meteorology in the 1960s [172]. It is well suited for global and local angular interpolation [17].

Several grids consisting of one or more spirals over the unit sphere have been used in EPR and other areas. One such grid employed in EPR uses numerical optimization to determine the position of the grid points on the spiral [35, 173], but it has been shown that these can be found from explicit expressions [168]. This spiral grid has also been used for DEER simulations [174]. Another spiral grid

with very uniform density is the spherical Fibonacci grid [175–177], whose planar version describes the arrangement of the seeds in a sunflower head.

Other spherical grids include icosahedral [178, 179] and octahedral [180] grids, the Zaremba–Conroy–Wolfsberg scheme [60, 181], numerically optimized grids based on electrostatic repulsion between grid points [167] and similar metrics, and an iteratively generated grid [182]. In NMR powder simulations, Gaussian spherical quadrature methods have been applied [183].

Quantum chemical (QC) calculations based on density functional theory (DFT) also employ angular grids as part of a numerical integration over three-dimensional (3D) space [184]. Gaussian and ORCA, two QC software packages that are widely used in EPR, implement Lebedev grids. Lebedev grids are also extensively used in NMR simulations [185].

An iterative method was proposed that starts with a low number of orientations N to approximate the powder spectrum and then doubles N in each iteration [186]. With this method, convergence can be easily assessed automatically.

The problem of powder integration is still an area of active research, with new grids and integration methods continuing to appear [187–192].

One method to avoid calculating transition fields explicitly for many orientations is to leverage already computed orientations by angular interpolation. Interpolation schemes can be local [157, 193], global, or a combination thereof [12, 17]. Interpolation functions can be linear or cubic (Hermite splines, monotonic Fritsch splines). The spiral grid can be combined with one-dimensional (1D) interpolation along the spiral [35]. Two-dimensional (2D) interpolation over small triangular or rectangular patches of solid angle has been used as well [180, 193]. EasySpin uses bivariate cubic tensor product splines [1]. The SOPHE interpolation scheme combines a global cubic interpolation with an efficient local linear interpolation [17].

A method that utilizes already computed orientations maximally is the triangle projection method due to Ebert and Alderman [180, 194]. In this approach, the transition fields and intensities calculated for three close orientations are used to construct an analytical surface for the transition fields within the solid-angle triangle determined by the three orientations. This surface is then analytically projected into the field domain, yielding a triangle-shaped subspectrum. Combined with a Delaunay triangulation of the original grid, this greatly increases the convergence rate of powder simulations. For axial spectra, the projection method operates with spherical zones and is very efficient. EasySpin implements the projection method [1].

Yet another trick to speed up convergence rate as a function of the number of orientations utilizes the gradient of the transition fields with respect to orientation (θ and ϕ) to compute an additional artificial line broadening that is applied to the lines of each orientation. For orientations where the transition fields are strongly orientation dependent (e.g., between principal axes), the resulting smoothing is strong. For orientations with vanishing gradients, that is, along principal axes of tensors, or at extra absorption directions [195], the smoothing is minimal. This gradient smoothing is implemented in EasySpin [1], sim [39, 40], and XSophe, where it is termed the *mosaic misorientation linewidth model* [22].

3.4.2
Field-Swept Spectra

In field-swept cw EPR, the Zeeman terms of the sH change during the experiment. This means that spectral simulation requires more than just a single diagonalization of the sH. The main computationally intense task of any rigid-limit simulation is the determination of the transition fields and transitions intensities for each orientation. A transition field is the external magnetic field value at which two levels $|u\rangle$ and $|v\rangle$ are in resonance such that the applied microwave can induce a transition: $|E_v - E_u| = \hbar\omega_{mw}$. In the following, we summarize the main classes of methods available, starting with the most accurate and involved (eigenfields) to the least accurate and fastest (perturbation theory).

3.4.2.1 **Eigenfield Method**

The problem of finding transition fields can be very elegantly and compactly formulated as an eigenproblem in Liouville space [196–199]. The super-Hamiltonian $\widehat{\widehat{H}}$ is separated into field-independent and field-dependent contributions, $\widehat{\widehat{H}} = \widehat{\widehat{F}} + B\widehat{\widehat{G}}$ with the zero-field superoperator $\widehat{\widehat{F}} = F \otimes 1 - 1 \otimes F^T$ and the Zeeman superoperator $\widehat{\widehat{G}} = G \otimes 1 - 1 \otimes G^T$. The Liouville-space eigenfield equation is $\widehat{\widehat{F'}}Z = B\widehat{\widehat{G}}Z$, with $\widehat{\widehat{F'}} = \omega_{mw}\widehat{\widehat{I}} - \widehat{\widehat{F}}$. The eigenvalues B represent the transition fields, and the associated eigenvectors Z contain $|u\rangle$ and $|v\rangle$, the two states involved in the transition. The associated matrix equation is a general eigenvalue problem, where the representations of $\widehat{\widehat{F'}}$ and $\widehat{\widehat{G}}$ are $N^2 \times N^2$ matrices for an N-level spin system.

If the microwave quantum is larger than the maximum zero-field splitting $E_N(0) - E_1(0)$, then $\widehat{\widehat{F'}}$ is positive-definite and can be inverted and the eigenfield equation reduces to an ordinary eigenproblem $\widehat{\widehat{F'}}^{-1}\widehat{\widehat{G}}Z = \left(\frac{1}{B}\right)Z$, whose eigenvalues are the inverse transition fields [196]. To reduce the computational effort for large systems, a perturbational treatment of the eigenfield equations was introduced [84, 198]. A method for obtaining the eigenfields via the characteristic equation [200] has been proposed as well. It has been shown that the eigenfields ansatz can be used to formulate a Hilbert-space differential equation that can be solved using the filter diagonalization method [201]. The method is, however, limited to situations with $E_N(0) - E_1(0) < \hbar\omega_{mw}$, which are easier to solve by other methods.

Transition probabilities can be calculated from the eigenvectors Z in a very simple manner [196]. However, due to the large dimensionality of the superoperator space, it is often worthwhile to forgo computation of Z. Instead, the transition probabilities can be calculated for each transition field obtained from the eigenfield equation by solving the Hilbert-space energy eigenproblem. Another advantage of this hybrid method [200, 202] is that the frequency-to-field conversion factor [157, 203] (see below) can be obtained more easily.

Although the matrices involved in the eigenfield equation are very large, they are generally sparse. It is feasible to employ this method for systems with high spins or many coupled electron spins in case the energy level diagram gets so complicated

that the Hilbert-space matrix diagonalization-based energy level diagram modeling as discussed below requires an excessive number of diagonalizations. In general, because of its mathematical and implementational simplicity, the eigenfield method can serve as a reference method for other approaches.

3.4.2.2 Matrix Diagonalization

All methods except the eigenfield method compute transition fields in two steps. They first determine energy levels and possibly states at one or several pre-chosen magnetic field values using a range of possible methods (matrix diagonalization, perturbation theory, or a combination thereof), and then use these energies to obtain the transition fields by interpolation or extrapolation along the field axis. Some methods combine these two steps, and others iterate between them.

To obtain the energy eigenstates and their energies for a given external field, the sH matrix can be numerically diagonalized, and transitions can be determined by comparing all energy level pair differences to the microwave quantum [86, 157, 186, 204–206]. In principle, for a field sweep, this diagonalization has to be repeated for each point along the swept field range. In this wasteful but sure-fire brute-force method, typically on the order of 1000 diagonalizations per spectrum per orientation are required. This is prohibitive for powder spectra.

The number of diagonalizations can be reduced by combining matrix diagonalization for a limited subset of field values (knots) with interpolation, extrapolation, or root-finding along the field axis. Methods based on root-finding algorithms [2, 81, 157, 186, 207–209] can locate one transition field per state pair within a narrow field range. Another method minimizes via least-squares fitting the square of the deviation between the energy difference of two levels and the microwave quantum [206, 210–214]. The simplest methods for the computation of transition fields use energies at one field only, combined with linear or quadratic extrapolation based on a Taylor-series expansion or perturbation theory [49, 193]. When the sH is diagonalized at multiple fields, instead of diagonalizing at each field value independently, eigenvalues and eigenvectors of the sH for one field can also be obtained by homotopy [19, 212, 214] or extrapolation [215] starting from the results from a nearby field.

The method implemented in EasySpin models the energy level diagram over a desired field range using an adaptive iterative bisection and interpolation algorithm [216]. Initially, H is numerically diagonalized at the minimum and the maximum of the requested field range, and an approximation of the energy level diagram is constructed by Hermite cubic spline interpolation. Next, H is diagonalized at the center field and the resulting eigenvalues are compared to the interpolated ones. If the difference is above a given threshold (typically a few parts per million of the microwave energy), the left and right field segments are interpolated and diagonalizations done at their centers. This procedure is repeated recursively until all segments are accurately modeled by splines. Transition fields are then determined from the spline model of the energy level diagram. The method is robust and adapts the number of diagonalizations to the complexity of the energy level diagram. EasySpin's methods were inspired by a bisective root-finding

algorithm [186, 209]. Other nonadaptive interpolation methods use cubic splines [39, 217] or Chebyshev polynomials [10]. Sophe subdivides the field search range into segments, diagonalizes the Hamiltonian once per segment, and then uses second-order perturbation theory to locate transition fields [24].

Once the energy level diagram is modeled by splines, it has to be searched for transition fields. In principle, this involves searching all $\frac{N(N-1)}{2}$ unique pairs of levels for an N-level system. Most of these searches are in vain, as most level pairs do not give significant EPR lines because they are either off resonant over the entire field range or have negligible transition matrix elements. A simple heuristic procedure, termed *transition preselection*, can be used to narrow down the search range of level pairs [1]. It is based on the observation that the same subset of level pairs usually gives nonzero transitions for all or most orientations. It involves precomputing energies and transition intensities at the center field for one or a few orientations. From this set, the subset of level pairs with nonzero transitions is selected, and the subsequent field searches for the full powder simulation can be limited to this subset. The method, however, runs into problems for large field sweeps with significant zero-field or hyperfine interactions, where the center-field states are not representative of the entire field range. It should be avoided in systems with multiple nuclei with similar hyperfine coupling, as strongly field-dependent state mixing might occur.

No matter how they determine transition fields, all the above methods use matrix diagonalization. There are numerous diagonalization libraries available that implement very efficient algorithms for computing all eigenvalues and eigenvectors of a Hermitian matrix [218, 219]. However, algorithms differ in efficiency depending on whether the matrix is dense or sparse, on whether eigenvalues only or eigenvalues and eigenvectors are required, and on whether all or only a few of the lowest eigenvalues are requested. Efficient large-scale algorithms (Arnoldi, Lanczos, Jacobi, Davidson) are available [220].

There has been much concern about energy level crossings as a function of field magnitude and orientation and the associated ambiguity in labeling the states involved. Several methods of assigning states left and right of the crossing by tracking or Jacobi diagonalization have been proposed [35, 157, 193, 209, 214]. However, since crossings occur only at isolated points within the symmetry-unique subset of field orientations [221], these procedures are not necessary. Levels can be uniquely sorted and labeled in order of increasing or decreasing energy.

If the microwave quantum is smaller than the largest zero-field gap, $|E_N(0) - E_1(0)|$, then there can be multiple transition fields between pairs of levels that feature anticrossings [196]. For such level pairs, the number of transitions as a function of magnetic field orientation is not a constant. In a powder spectrum, the resulting looping transitions are often present only over a subset of field orientations, coalesce at orientations where the anticrossing gap matches the microwave quantum, and vanish for the rest. This makes interpolation more involved and leads to complications in the modeling of line broadenings. Accurate treatment of such looping transitions is more difficult [212, 217].

In some systems, for example, Ni(II) with $S = 1$, two-photon ("double-quantum") transitions are visible. The theoretical basis of these transitions has been discussed in several publications [10, 205, 222], but they are not routinely incorporated in simulations.

3.4.2.3 Perturbation Theory

When one interaction in the spin Hamiltonian dominates, perturbation theory can be used to compute the resonance field positions. Methods that treat the electron Zeeman interaction as the main interaction, the hyperfine interaction as perturbation, and neglect the nuclear Zeeman and the nuclear quadrupole interaction have been used since the early days of EPR both for solids and liquids simulations [223]. The nuclear Zeeman and quadrupole interactions can be included in a second step using sequential perturbation theory.

When the three nuclear interactions (hyperfine, Zeeman, quadrupole) are of similar strength, the treatment is more complicated. Expressions that treat hyperfine and nuclear Zeeman interaction on an equal footing have been given by Lefebvre and Maruani [224], Iwasaki [225], and others [226, 227]. When equivalent nuclei are present, transformation of the spin Hamiltonian into a coupled representation is required [112, 228]. In the presence of multiple nuclei, the inclusion of internuclear cross terms might be necessary [226]. Byfleet has developed a method based on seventh-order perturbation theory [229] applicable to a fairly general spin Hamiltonian. Generalized operator transforms based on methods developed by Bleaney and Bir can be used to derive perturbational expressions for anisotropic systems [230−232].

A specific application case for perturbation theory that has received significant attention is mononuclear Mn^{2+} ($S = \frac{5}{2}$). Its sH has isotropic g and A, but a significant anisotropic zero-field splitting. Expressions for eigenenergies and transition fields at second- and third-order levels of perturbation theory have been published many times [231, 233−237]. Perturbation theory for coupled spins using a full anisotropic spin Hamiltonian has been developed for transition metal dimers [238, 239], for transition metal−nitroxide complexes [240], and for dipolar-coupled pairs of radicals [241, 242].

From a software perspective, there are several problems with perturbation theory: (i) Most expressions are scalar and long. The resulting code is usually error prone and very difficult to debug. (ii) Scalar perturbational expressions are not general, as they almost always are limited to specific systems such as one electron spin and a certain number of nuclei, and to specific symmetries. In fact, many early programs differed mainly in the number of spins and symmetry of interaction matrices that were supported. (iii) Perturbation theory has inherently limited scope with respect to the relative strengths of the various interaction parameters. The accuracy of the simulated spectrum is a function of this, which is not a desirable software behavior from a user perspective. (iv) Lastly, very few programs check the validity of the perturbation theory approximations for the given set of input sH parameters and leave the user in the dark about the accuracy of the computed spectrum. However,

with proper checks, the main advantage of perturbation methods – speed – can be harnessed for specific systems.

3.4.2.4 **Hybrid Models**

If the interaction strengths in a spin system are such that the spins fall into two distinct groups, one with strong interactions and one with weak interactions, hybrid methods can be used. These proceed in two steps. First, they utilize matrix diagonalization for the subset of strongly coupled spins to obtain energy levels and states for the corresponding subspace. Then, they apply a perturbational theory approach to calculate the splittings resulting from the subset of weakly interacting spins. Ligand nuclei in transition metal complexes can be treated in this manner [186]. Hybrid methods have been applied to di-manganese systems [243], where the electron spins are treated exactly and the ^{55}Mn nuclei perturbationally. Compared to full matrix diagonalization methods, hybrid methods provide a considerable saving of computer time.

3.4.3
Transition Intensities

Generally, cw EPR spectra are acquired with non-saturating levels of microwave power. Then, first-order time-dependent perturbation theory and Fermi's Golden Rule are applicable. The intensity I_{vu} of a transition between initial state $|u\rangle$ and final state $|v\rangle$ in a field-swept EPR spectrum is determined by three factors.

$$I_{uv} \propto |\langle v|H_1|u\rangle|^2 \cdot \left(\frac{\mathrm{d}\Delta E}{\mathrm{d}B}\right)^{-1} \cdot (p_u - p_v)$$

The first factor is the transition probability, the square of the transition matrix element of the microwave sH, $H_1 = \mu_\mathrm{B} \boldsymbol{B}_1^\mathrm{T} g \boldsymbol{S}$. If the state vectors of the two states $|u\rangle$ and $|v\rangle$ are known (e.g., from matrix diagonalization or perturbation theory), then this matrix element can be evaluated numerically. Within the assumptions of first-order perturbation theory with dominant H_{ez}, states can be written as products of electron and nuclear substates, and the matrix element can be evaluated analytically. The expression is [225]

$$|\langle v|H_1|u\rangle|^2 = (\mu_\mathrm{B} B_1|G|)^2 \cdot |\langle m_{S,v}|\boldsymbol{S}^\mathrm{T}\boldsymbol{n}|m_{S,u}\rangle|^2 \cdot |\langle m_{I,v}|M_{vu}|m_{I,u}\rangle|^2$$

where G is the effective g-factor along the direction of $\boldsymbol{B}_1$. The second factor is the spin transition moment squared. To first order, its value is $S(S + 1) - m_S(m_S + 1)$ for the allowed transition $m_S \leftrightarrow m_S + 1$. The last factor is a nuclear overlap matrix element and is analogous to a Frank–Condon factor [244]. It is central to ESEEM spectroscopy (see below).

The second factor in the expression for I_{vu} is the frequency-to-field conversion factor. It accounts for the fact that the spectrum is field-swept and not frequency-swept. It was originally discovered by Aasa and Vänngård [203] in 1975 for spin-$\frac{1}{2}$ systems with anisotropic g, where it is proportional to $\frac{1}{g}$. van Veen [157] gives the general expression. The presence of this factor implicitly assumes that unit-area absorption lines are employed for modeling line broadenings [157]. It was

extensively discussed by Pilbrow [170, 245, 246]. Neglecting this factor can lead to errors for half-field transition intensities (used for distance measurements [247]), relative linewidths in systems with large g anisotropy, and in spin quantitation. The only systems where the factor does not affect the spectral shape are spin-$\frac{1}{2}$ systems with essentially isotropic g-matrix and only fully allowed transitions, for example, organic radicals. When this factor is used, it is crucial to use a frequency-domain (FD) line broadening model, and not a simple field-domain convolutional linewidth. If not, wrong intensities will result, for example, for half-field transitions in triplets.

The third factor in I_{vu} represents the polarization of the transition. p_u and p_v are the populations of the initial and final state, respectively. This difference is positive and leads to absorptive lines if $p_u > p_v$, which is the case under thermal equilibrium for $E_u < E_v$. The thermal-equilibrium Boltzmann population is given by $p_u = \frac{\exp(\frac{-E_u}{k_B T})}{\sum_q \exp(\frac{-E_q}{k_B T})}$. For a spin-$\frac{1}{2}$ system with isotropic g value, the thermal polarization is $\Delta p = p_{+\frac{1}{2}} - p_{-\frac{1}{2}} = \tanh\left(\frac{\mu_B B g}{2 k_B T}\right)$. In the high-temperature limit $k_B T \gg \frac{\mu_B B g}{2}$, this simplifies to $\Delta p = \frac{\mu_B B g}{2 k_B T}$. Nonthermal equilibrium situations, for example, spin-correlated radical pairs or photoexcited high-spin states of organic molecules, can be easily accommodated.

Closed-form analytical solutions for anisotropic transition probabilities have been given for many cases: axial g tensor [248], forbidden hyperfine transitions [249], and rhombic g tensor [203, 225, 250–254]. For powder spectra, the transition intensity can be integrated analytically over the third Euler angle even for the case of a rhombic g-matrix, yielding compact expressions [225, 248, 251, 254]. A different derivation has been used by Kneubühl and Natterer [255]. With numerically obtained transition intensities, integration over the third angle can also be carried out effortlessly [156].

Most solid-state simulations assume non-saturating levels of microwave irradiation. In the case of saturation, a more complete theory based on the SLE has to be used [126]. Saturation is important in the context of saturation-transfer EPR, where a detailed theory has been developed by Dalton and Robinson [256–259].

3.4.4
Isotropic Systems

For systems that are isotropic (either intrinsically, or by virtue of sufficiently fast rotational averaging), the spin Hamiltonian simplifies considerably. In each sH term, only the isotropic average survives, leaving isotropic g and A matrices, isotropic g_n factors, and isotropic exchange. Zero-field splitting terms and the nuclear quadrupole term average to zero. In general, resonance fields for the isotropic spin Hamiltonian can be solved using matrix diagonalization, as discussed in Section 3.4.2. However, in the case of one electron spin $S = \frac{1}{2}$ and one nucleus with $I \geq \frac{1}{2}$, two more efficient approaches are possible: (i) Breit–Rabi solution and (ii) perturbation theory.

The Breit–Rabi formula [260–262] is an exact explicit expression for the energy levels $E(m_S, m_I)$ of a $(S, I) = \left(\frac{1}{2}, \frac{1}{2}\right)$ system. Using this, the resonance condition $E\left(+\frac{1}{2}, m_I\right) - E\left(-\frac{1}{2}, m_I\right) = \Delta E(m_I) = \hbar \omega_{\mathrm{mw}}$ can be written in the implicit form $B = f(B)$ and solved for the transition field B using a fixed-point iteration ($B_{k+1} = f(B_k)$) with the starting resonance field B_0 obtained from first-order perturbation theory. The solutions converge to numerical accuracy within a few iterations, even for very large hyperfine couplings. This is computationally superior to perturbation expressions and is the default method in EasySpin [1]. Fixed-point iterations can be applied to any situation where the resonance field is only known as an *implicit function of the microwave frequency* and the *spin Hamiltonian parameters* and can be formulated as $B = f(B)$. This applies to many perturbation expressions and has been applied, for example, to bisnitroxide spectra [242].

For isotropic systems, many programs implement standard perturbation theory. EasySpin provides such methods up to fifth order. The expressions are based on solving the equation $\Delta E - \hbar \omega_{\mathrm{mw}} = 0$ with a Taylor expansion in a_{iso} of the Breit–Rabi expression for ΔE. For a desired perturbation order n, the resulting equation is multiplied by B^{n-1} and truncated after the a_{iso}^n term [263]. This yields a polynomial in B, whose roots are the resonance fields and can be determined using any root-finding algorithm, for example, the Newton–Raphson method with $B = \frac{\hbar(\omega_{\mathrm{mw}} - m_I a_{\mathrm{iso}})}{\mu_{\mathrm{B}} g}$ as the starting value. These methods can be applied to systems with multiple nuclei as well, as long as cross terms are properly taken into account [226]. Since it is so easy to solve the Breit–Rabi equation, perturbation expressions have mostly only didactic value.

3.4.5
Line Broadenings

There are two types of broadening: homogeneous and inhomogeneous. Homogeneous broadening is due to the limited lifetime of the excited states populated by microwave absorption. In solid-state EPR, this broadening is mostly negligible compared to the second type, inhomogeneous broadening.

Inhomogeneous broadening is due to site-to-site heterogeneity in the sH, which can have several different origins. The first, with the largest effect, is orientational disorder (different spin centers have different orientations) and leads to powder spectra. It needs to be treated explicitly and was discussed in Section 3.4.1.3.

The second type of inhomogeneous broadening is due to small and unresolved couplings between the electron spin(s) described in the sH and spins that are not explicitly incorporated in the sH. This includes superhyperfine (shf) interactions to nearby nuclear spins, and dipolar couplings to other electron spins. Different spin centers experience different magnetic states of spins in the nanoenvironment, which leads to a multitude of small splittings. Generally, the large number of couplings results in an overall line broadening.

The third type of inhomogeneous broadening is structural. Parameters in the sH are (sometimes) sensitive functions of the geometry of the spin center and its immediate environment. Any static structural disorder, either geometric or

electronic, will lead to a distribution of magnetic parameters with a finite width. As a consequence, transition fields are shifted, and the overall spectrum broadens. Variations in geometric degrees of freedom can include variations in ligand distances and coordination geometry in a transition metal complex, variations in the length and orientation of hydrogen bonds in organic radicals, and slight misorientations in crystals.

3.4.5.1 Dipolar Broadening

When a large number of unresolved couplings due to roughly homogeneously distributed magnetic moments (solvent nuclei, other spin centers) contributes to the line broadening, it can be modeled using an FD linewidth tensor that provides an orientation-dependent linewidth $\Gamma(\Omega)$ for a Gaussian lineshape. The FD linewidth can then be converted to the field domain using the frequency-to-field conversion factor discussed in Section 3.4.3. Various expressions for this linewidth tensor have been proposed and are being used [1, 23, 170], and none of the forms appears to be better or worse than the other.

If the dipolar broadening is solely due to weak dipolar coupling to a spin center at a specific distance from the spin center of interest, the cw EPR spectra can be convoluted with the dipolar Pake powder pattern. A computational analysis of this Pake broadening can be used to extract distances in dipolar coupled bisnitroxides [47, 264].

Occasionally, for accurate analysis of lineshapes in solution, it is important to explicitly compute the shf splitting pattern and use it as a convolutional line broadening function instead of a Gaussian function [265].

3.4.5.2 Strains

To model geometric heterogeneity, strain models are used. Site-to-site structural variations cause corresponding variations of the sH parameters, so that each combination of sH parameter values will have a certain probability density $P(g, a, \ldots)$. Generally, Gaussian distributions of parameters are assumed. The variations of different parameters can in principle be correlated.

To include strain broadenings in the simulation, spectra have to be simulated for many points within the distribution P in parameter space and then integrated. This is the only viable approach if the parameter distributions are wide. If the distributions are narrow, the energy levels and the transition fields vary mostly linearly over the narrow parameter range [170]. For a transition between two levels $|u\rangle$ and $|v\rangle$, the width of the (Gaussian) FD distribution of an sH parameter p can then be directly converted to a field-domain linewidth using the derivative of the energy gap with respect to p and the $\frac{1}{g}$ factor [1, 12]. The former can be obtained from the sH and the eigenstates using the Hellmann–Feynman theorem [266].

Structural heterogeneity of spin centers can lead to a distribution in g values, for example, in transition metal complexes and clusters as well as in organic radicals in frozen solution. The resulting distribution of g tensors, g strain, is often simply modeled by three uncorrelated Gaussian distribution functions of the

three principal *g* values. This model works well in many cases, even though it can miss visible details. A more sophisticated correlated statistical model of *g* strain has been developed for metalloproteins by Hagen [267, 268]. Physical models for *g* strain based on crystal field theory have been derived and utilized as well [269, 270].

In transition metal complexes, such as in Cu^{2+}, variations in the principal values of *g* and *A* matrices are interrelated [271]. In frozen solution with structural heterogeneity at the spin center, this leads to correlated *g* and *A* strains [272] that have been included in simulations using a bivariate normal density distribution function [273, 274].

There has been substantial work on modeling the heterogeneity of the *D* tensor in solid-state samples, as the *D* tensor can be very sensitive to structural features. The *D* tensor components were related to the components of the external stresses via a spin–strain tensor [275, 276]. For general application and without extensive computational chemistry predictions, this is an overparameterized model. Simple uncorrelated distributions in the zero-field splitting parameters $D\left(=\frac{3}{2}D_z\right)$ and $E\left(=\frac{D_x - D_y}{2}\right)$ are used extensively [277–280]. In cases where the ratio $\frac{E}{D}$ (rhombicity) determines resonance line positions, such as high-spin ferric ions, the strain can be modeled with a single distribution of that ratio [281, 282]. Joint probability distributions $P(D, E)$ or $P\left(D, \frac{E}{D}\right)$ using 2D Gaussians (correlated *D* strain) have been used as well [38, 283, 284], for example, using complete anticorrelation between *D* and *E* [285]. Closely related to *D* strain is *r*-strain, a distribution of the inter-metal ion distance in dimers that affects the magnetic dipole coupling and consequently the linewidth [243].

Line broadening in the EPR spectra of solid crystals has been found sometimes to be due to variations in unit-cell orientations (misalignment, mosaicity, misorientation) [277, 286–288].

3.4.5.3 Lineshapes

For homogeneous broadenings, the Lorentzian function is used. For inhomogeneous broadenings, the Gaussian function is most common [6]. They are applied to the simulated spectrum using convolution [289]. If the broadening is anisotropic, each single-orientation spectrum is convolved separately. If it is isotropic, a single convolution of the final powder spectrum is sufficient. The convolution of a Lorentzian and a Gaussian function is called a *Voigt function*. Convolutions can be performed numerically [290], but other methods are available as well [291–293] and need to be deployed if many Voigt shapes are required. A popular approximation to the Voigt lineshape is a linear combination of Lorentzian and Gaussian functions [294], also called the *pseudo-Voigt profile*. Other shape functions for inhomogeneously broadened lines include the Holtzmark and Stoneham lineshapes [6]. Small deviations from the Lorentzian shape due to incomplete rotational averaging of anisotropies can be modeled by a two-parameter extension of the Lorentzian function [295]. The Tsallis distribution generalizes Gaussian and Lorentzian lineshapes [296].

3.4.6
Frequency-Sweep Spectra

The increased use of wideband frequency-sweep EPR spectrometers up to the terahertz range has prompted the development of corresponding simulation methods [297]. Unlike in field-sweep EPR, the Zeeman terms in the sH are constant during the experiment. Therefore, the computations are more straightforward. As in the field-sweep case, matrix diagonalization, perturbation theory, or hybrid methods are applicable. For the transition intensities and linewidths, the same expressions as for the field-swept case apply, except for one important difference: The frequency-to-field conversion factor, discussed in Section 3.4.3, is not required.

3.4.7
Simulation Artifacts

There are a number of common artifacts of solid-state simulations that need to be identified and remedied if present.

1) If the number of orientations in a powder simulation is small, ripples ("simulation noise" or "grass") appear in the simulated spectrum. For a given number of orientations, the severity of these ripples increases with increasing overall width of the field-swept spectrum. They can be removed by increasing the number of orientations. Simulation ripples can also be removed via low-pass filtering using Fourier transformation [267]. Another remedy is to use an iterative orientational averaging with increasing grid density until convergence is achieved [186]. Similar ripples can appear experimentally if the powder does not contain a sufficient number of microcrystallites for complete orientational averaging. Gradient smoothing [1, 22, 39] and analytical projection techniques [1, 180, 194] reduce the occurrence of ripples significantly.

2) Simulation programs differ in the implementation of the evaluation of Lorentzian and Gaussian lineshapes. Since repeated explicit evaluation of the corresponding expressions are numerically intense, look-up tables are often used. This can lead to truncation and interpolation errors. If convolutional line broadenings are applied via Fourier transformation, artifacts at the lower and upper field range limits may occur.

3) Near coalescence points, looping transitions can yield artifacts in powder spectra in the form of missing spectral intensity that leads to pairs of spurious peaks. These problems can be alleviated by substantially increasing the spherical grid density near coalescence points, or by using dedicated methods [217].

4) Some programs (such as EasySpin) apply transition preselection or screening procedures before starting a simulation. These procedures attempt to determine level pairs that will yield transition fields before starting the full powder simulation, with the goal of discarding level pairs that are never resonant. In complicated spin systems with high electron spins, high-order operators, or

large hyperfine couplings, such procedures can miss transitions, and should be used carefully.

3.5
Dynamic cw EPR Spectra

Many dynamic processes can affect the shape of an EPR spectrum ([65]; see [298] for an early review). In addition to a variety of spin-relaxation processes, two types of molecular processes that are of great importance are rotational motion and chemical exchange. Both require dedicated simulation techniques and can be modeled at various levels of theory, with different scope and accuracy.

3.5.1
Rotational Diffusion

The random rotational or reorientational motion (tumbling) of spin centers such as nitroxides in solution can be modeled using the SLE [27, 28, 299, 300] with a rotational diffusion superoperator. The time scale of the rotational dynamics is characterized by the rotational correlation time τ_c. Based on the relation between τ_c and the rigid-limit powder spectral width $\Delta\omega$, several dynamic regimes are distinguished: (i) the fast-motion limit (τ_c essentially 0), (ii) the fast-motion regime ($\tau_c^{-1} \gg \Delta\omega$), (iii) the slow and intermediate motion regime (τ_c^{-1} similar to $\Delta\omega$ within about 2 orders of magnitude), and (iv) the rigid limit (absence of rotation, $\tau_c^{-1} = 0$).

3.5.1.1   Fast-Motion Limit

Fast-motion limit spectra are isotropic [301]. All anisotropies in the spin Hamiltonian are averaged out on the time scale of the EPR experiment. Spectra can be easily simulated by the isotropic solid-state methods described in Section 3.4.4 by using a spin Hamiltonian with isotropic interaction matrices and tensors. In the isotropic limit, many of the perturbational expressions simplify considerably. Residual broadenings are due to inhomogeneous (isotropic) hyperfine couplings, Heisenberg exchange with other spin center such as dioxygen, or lifetime broadening.

The exponential growth of the number of EPR lines with the number of nuclei coupled to an electron spin makes simulations in the field or FD by summation over all possible lines very slow for large spin systems. An alternative is to perform the simulation in the inverse-field or time domain (TD), where each line can be represented by a decaying exponential, and the convolutions reduce to simple multiplications. This Fourier transform method [25, 302–305] assumes a first-order perturbational regime, that is, that the nuclear spin states do not affect the state of the electron spin. In this method, the effect of the modulation amplitude can be incorporated in the inverse domain [25, 305]. An analysis method based on Fourier transform is the cepstral analysis [306].

3.5.1.2 Fast-Tumbling Regime

In the fast-tumbling regime, the rotational motion can be treated using perturbational Redfield–Wangsness–Bloch relaxation theory. A detailed derivation with many references is given in Atherton's book [143]. On the basis of this theory, the linewidths can be expressed as polynomials in the nuclear projection quantum numbers, m_I. Kivelson has developed expressions for several cases [307, 308]. Freed has presented very general expressions [112]. A diagonalization-free implementation of Redfield relaxation theory for large spin systems has recently been developed [309].

3.5.1.3 Slow-Tumbling Regime

In the slow and intermediate motional regimes, the reorientational motion of the spin label is on a time scale similar to the EPR time scale, and the EPR spectrum is broadened. In these regimes, perturbation treatments have to be abandoned, and a more complete theory has to be employed.

Simulation methods for this regime differ in how the different levels of orientational dynamics are treated and can use either deterministic or stochastic models [310]. Deterministic models are based on atomistic molecular dynamics (MD) simulations and are able to treat complex local and internal dynamics. Stochastic dynamics (SD) models describe the reorientational motion as rotational diffusion of a rigid rotor and can account for simple local or global rotational dynamics.

One stochastic model, jump diffusion, assumes rotational diffusion via random jumps between multiple equivalent sites differing in the orientation of the spin center [27, 311]. This has been observed in a few cases [312]. A stochastic memory function approach that assumes random instantaneous rotational jumps by a small angle has been used to model reorientation of spin labels in supercooled water [313].

The most common stochastic model for rotational motion in solution is Brownian rotational diffusion, a random walk in 3D orientational space [314]. The anisotropy of the reorientational rate constant τ_c^{-1} due to the nonspherical shape of the spin center is described by an anisotropic diffusion tensor fixed in the MF. For a spin center freely diffusing in solution, the local environment is isotropic. On the other hand, the environment is generally anisotropic for a spin label bound to a protein or other biomolecule, resulting in preferential alignments and excluded orientations [28]. In these partially ordered samples, the free energy of the label is a function of its orientation Ω and is described by an orientational potential $U(\Omega)$. Expressions for ordering potential have been discussed above.

Simple SD models such as Brownian diffusion in a restricting potential are accommodated in the SLE by including a rotational diffusion operator [155, 314]. The SLE then describes the joint time evolution of both the quantum spin degrees of freedom and the classically treated spin center orientation $\Omega = (\alpha, \beta, \gamma)$. EPR spectra are simulated by calculating the low-power steady-state solution of the SLE, with an equilibrium orientational probability distribution of an ensemble of spin centers determined by the orientational potential. Very efficient SLE solvers were developed by Freed and coworkers [27, 299, 311, 315, 316]. A didactic review [28] summarizes the main features of the approach.

The orientational distribution of the spin center is represented in a basis of Wigner functions $\mathscr{D}_{KM}^{L}(\Omega)$ with $L = 0, 1, \ldots$ and $-L \leq K, M \leq +L$, which is, in principle, of infinite size. For a given spin system, the matrix size and the computational effort scale with the number of orientational basis functions. The orientational basis is usually truncated to a subset of functions with $L < L_{\max}$. (The orientational potential is also expressed as a linear combination of a few low-L Wigner functions.) This basis yields manageable expressions for the matrix elements of the Liouville superoperator. For accurate simulations, the basis size needs to be increased with decreasing rotational diffusion rate and increasing complexity of the potential. In principle, the SLE approach can be used to simulate a rigid-limit spectrum. However, the basis size required for achieving converged spectra is large, so that dedicated rigid-limit methods are preferred.

In a basis truncated at $L_{\max}$, some of the basis states with $L < L_{\max}$ are negligibly populated and can be removed using heuristic pruning techniques, as introduced by Freed [27, 299]. Similar and more general state space restriction methods have recently been developed for general spin dynamics simulations [64], as discussed later.

If the rotationally diffusing spin center is attached to another entity that provides an orienting potential, not only the local dynamics of the spin center but also the global dynamics of the latter need to be included in the SLE simulation. Most commonly, this is observed for nitroxides attached to proteins. With a protein that provides an ordering potential, the slow-motion spectrum depends on the orientation of the ordering potential with respect to the external magnetic field.

Two theoretical models are available, MOMD [317] and SRLS (slowly relaxing local structure) [318]. If the protein is randomly orientationally distributed in the sample but static on the time scale of the EPR experiment, a powder average has to be computed. This is called the *MOMD model* [317]. It can be generalized to partial static order. If the protein is not static, its rotational dynamics couples to the rotational dynamics of the spin center and must be included in the simulation. In the SLE approach, the protein dynamics is also treated stochastically. A second diffusion operator is added in the SLE, and the orientational distribution of the protein is described by a second set of Wigner basis functions $\mathscr{D}_{KM}^{L}(\Omega_2)$. This SRLS model introduced by Freed [318–320] is a two-body coupled rotor model. It is implemented in the software available from the Freed group that includes multifrequency fitting [320, 321]. SRLS is also implemented in the software E-SpiReS [33]. The model is not only used for spin labels, but also for methyl dynamics and ^{15}N relaxation in protein NMR [322]. A dedicated program, C++ OPPS, is available [323]. Currently, EasySpin implements the MOMD model for spin systems with one electron spin and several nuclear spins.

Mostly, SLE simulations have been limited to nitroxides with $(S, I) = \left(\frac{1}{2}, 1\right)$. However, in some cases, the SLE method has been applied to larger spin systems such as diphosphanyl radicals [324], doubly nitroxide-labeled peptide [325], nitronyl nitroxides [326], and fullerene-bisnitroxide adducts [327]. Misra [324] has derived explicit scalar matrix element expressions for the two-nuclei case. The theory of slow-motional EPR spectra of triplets is theoretically well described [328–330].

In general, the matrix elements for any spin system can be constructed in a straightforward manner from the single-spin spherical tensor operators. If the sH interactions are restricted to zero- and second-order tensors, the sH Liouville operator can be decomposed into 26 static rotational operator components [309].

As a more general alternative to solving the SLE for a stochastic model, EPR spectra can be directly computed from sets of explicit trajectories that describe the change in time of the orientation of the spin center in space. A trajectory determines the time dependence of the magnetic parameters and therefore the EPR spectrum of a moving spin center. This method is applicable to trajectories obtained from both stochastic and deterministic models.

From a trajectory, the time evolution of the magnetization following a 90° pulse is computed using density matrix or Bloch magnetization vector propagation [147, 331, 332]. From the resulting FID, the EPR spectrum is obtained by Fourier transformation. To generate a converged spectrum, FIDs of a set of trajectories generated from a range of possible initial orientations of the spin label have to be combined. The appropriate time resolution of the trajectories is determined by the spectral width via the Nyquist criterion. The length of the trajectory is determined by the required spectral resolution and has to be of the order of the transverse relaxation time T_2 to yield accurate EPR spectra.

The computation of SD trajectories is fast, and the number and length of trajectories required for accurate spectral simulations are easily obtained. Stochastic Brownian dynamics trajectories were introduced by Robinson *et al*. [331] and widely applied [242, 333]. On the other hand, MD trajectories [334, 335] are computationally significantly more demanding. The expense of computing long MD trajectories can be avoided. Accurate simulations can be achieved from short MD trajectories generated over the decay time of the auto-correlation function of the motion [336, 337], or by deriving an effective orientational potential from short MD trajectories and then using it to generate SD trajectories [333] or to solve the SLE [338]. A single MD trajectory can be reused several times by rotation or resampling. In general, despite being much slower than the SLE approach, trajectory methods are superior in the complexity of dynamics that can be modeled [339]. Global dynamics cannot rely on MD simulations, so stochastic models are used [148]. The methodology for simulating slow-motional EPR spectra of two coupled spin labels attached to the same macromolecule is not as established as for single labels. There exist methods based on the SLE [325] and on trajectories [242] for the simple case of a tumbling protein with two rigidly attached labels. MD trajectories have been used to simulate spectra from proteins labeled with two nitroxides [340] and to compare spin relaxation times from explicit dynamics to those obtained from Redfield–Wangsness–Bloch relaxation theory [341]. Implicit solution methods for the SLE have been investigated [342].

For multinuclear spin systems, perturbation treatments can be applied if one hyperfine coupling anisotropy dominates and the hyperfine anisotropies of the others are so small that they are in the fast-motion range. In this case, a post-convolution technique can be used [343, 344]. It has been implemented in a program for copper spectra [345] and is also available in EasySpin.

Computationally, the main challenge with SLE methods is the matrix size. It is the product of the sizes of the spin basis (N^2 for a full basis) and the orientational basis. The spin space dimension increases exponentially with the number of spins. In addition to pruning the orientational basis, as mentioned above, the spin space can be restricted in the high-field limit [27]. More general spin space truncation methods are applicable as well [64], but are not implemented in dedicated slow-motion EPR simulation programs.

3.5.2
Chemical Exchange

Chemical exchange summarizes situations where dynamic transformations between different chemical or conformational states (called *sites*) of a spin center change the sH parameters. These changes can affect EPR spectra if the timescale of the process is not much slower than the timescale of the EPR experiment, which is equal to the inverse of the spectral shift caused by the exchange processes. Depending on this relative timescale, slow, intermediate, and fast exchange regimes are distinguished. Generally, it is assumed that the transitions between sites are ''sudden,'' that is, negligibly short compared to the periods of the spin coherences. One prominent example of spectral effects of chemical exchange in EPR is alternating linewidths [346, 347]. They have been reviewed in great detail [298].

Two structurally distinct situations can occur [143]: intramolecular exchange, where a dynamic process transfers spin polarizations and coherences within a molecule from each transition to a unique target transition (e.g., conformational equilibria); and intermolecular exchange, where a process transfers coherences from one molecule to another and therefore from one transition to a set of transitions with different probabilities, determined by the spin state of the other molecule (e.g., intermolecular electron transfer). Mutual exchange denotes a special case of intramolecular exchange, where the molecular structures before and after the exchange are indistinguishable [348]. The spin Hamiltonians for all sites are identical except for the labeling of the nuclear spins. The fractional population of each of N sites is therefore $\frac{1}{N}$, and the dynamic behavior is characterized by a single rate constant.

For a two-state kinetic system, chemical exchange effects can be modeled using modified Bloch equations [349, 350]. A more general approach is formulated in Liouville space using the SLE including an exchange superoperator or kinetic matrix that describes the transfer of coherences from one transition to another as a result of the dynamic process. This Liouville method was first developed [351–353] and then generalized and extended [125, 354] in NMR, including a simple index-permutation method [355]. It is valid for all three exchange regimes. In general, chemical exchange is modeled in the composite direct-sum space of the Liouville spaces of the various sites. In the case of mutual exchange, the Liouville matrix can be block-diagonalized, and the composite Liouville space can be reduced to the Liouville space of a single site [348]. Any kinetic network between a number of sites can be implemented, for example, for independent exchange processes

occurring simultaneously such as electron transfer and internal conformational changes. Multiple superimposed intermolecular exchange processes can be modeled as well [356]. There exist efficient NMR simulation programs [357], even for nonequilibrium chemical exchange [358]. More recently, Monte Carlo approaches to the simulation of dynamic NMR spectra have been developed [359].

Freed and Fraenkel [112], in their ground-breaking work, have developed the general exchange theory for alternating linewidth effects in EPR. Intermolecular triplet transfer has been described by Hudson and McLachlan [360]. Norris has derived a simple equation for intramolecular multisite exchange under the conditions of a single average lifetime for all the sites and exchange pathways between each pair of sites [361]. The Norris equation and the Liouville method (see above paragraph) have been implemented by Grampp and Stiegler [362]. Heinzer [44] has implemented the NMR Liouville method for EPR and adapted it for least-squares fitting using analytical derivatives of the spectral and shape vectors [45]. His programs have been popular for a long time, and a more recent program has extended the functionality to biradicals [363]. Rockenbauer has combined least-squares fitting with chemical exchange simulations based on the modified Bloch equations for a two-site model that can also include fast-tumbling effects [43, 364]. EasySpin follows Heinzer's Liouville method [44, 45] and extends it to larger spin systems. Most current chemical exchange EPR simulation programs are limited to isotropic first-order spectra of $S = \frac{1}{2}$ coupled to a few nuclei. Spinach [64] supports arbitrary exchange matrices. Efficient and general programs for situations where more than a few nuclei are involved, or where the sH is anisotropic and contains nonsecular contributions, are not currently available.

As shown for the case of intramolecular multisite exchange with some equivalent sites in NMR, permutational and other symmetries in the Liouville operator can be exploited to reduce the size of the Liouville space that needs to be included in a spectral simulation [122, 365, 366]. Taking advantage of these symmetries is crucial for improving the performance of simulations for large spin systems. They have yet to be leveraged substantially in general EPR simulation programs.

Although it might appear that chemical exchange processes are not relevant in solid-state systems at low temperatures, methyl reorientations by hindered rotation (hopping) or tunneling can dynamically affect EPR and ENDOR spectra [143]. In addition, experimentally observed Jahn–Teller pseudorotation of fullerene in its photoexcited triplet state was successfully simulated using a multisite chemical exchange model [367].

3.6
Pulse EPR Spectra

To compute pulse EPR spectra, a differential equation describing the time evolution of the spins in the spin system must be solved. Depending on the particular experiment and on the algorithm, this can be done in the time or in the frequency domain. Three different levels of theory are generally employed: (i) the Bloch

equations, (ii) the LvN equation in Hilbert space, and (iii) the LvN or SLE in Liouville space. All spin dynamics simulations are normally carried out in the rotating frame or a similar interaction picture [67, 75, 368].

3.6.1
Bloch Equations

The classical torque equation for the magnetization vector, that is, the Bloch equation without the relaxation terms, has been used to describe spin echo phenomena since their discovery [369]. The Larmor or Bloch equations are adequate for simulating pulse EPR and NMR experiments on spin centers with a single spin with isotropic gyromagnetic ratio. They can accommodate arbitrary excitation fields. Many closed-form solutions have been derived, but it is also straightforward to solve them numerically using standard ordinary differential equation solvers. The Bloch equations form an important classical description of magnetic resonance experiments [370].

As shown by Feynman *et al.* [371], the state of any two-level quantum system can be described by a magnetization-like vector, and its coherent dynamics can be modeled using a Larmor- or Bloch-like equation as mentioned above. This leads to the concept of the Bloch sphere, as utilized, for example, for optical transitions.

3.6.2
Hilbert space

The Hilbert-space LvN equation describing the spin dynamics in terms of the density matrix has been used for spin dynamics since the early days, for example, by Bloom [372]. Solutions of the Hilbert-space LvN equation can be derived and implemented at several levels. For simple systems and pulse sequences, scalar expressions can be obtained. For more complicated spin systems, the coherent dynamics can be modeled using numerical density matrix propagation. Longitudinal and transverse relaxation can be taken into account phenomenologically in a manner similar to the Bloch equations. In the presence of stochastic processes such as chemical exchange and rotational diffusion, the density matrix equation has to be solved in Liouville space.

3.6.2.1 Scalar Equations

Scalar expressions for the simulation of two- and three-pulse ESEEM [75] traces go back to the theory developed by Mims [373–375] and others [376, 377], excellently summarized in the first chapter of a monograph by Dikanov and Tsvetkov [378]. These scalar expressions are valid only for $S = \frac{1}{2}$, isotropic g values, and $I = \frac{1}{2}$, but have been extended to $S > \frac{1}{2}$ [368, 379, 380] and anisotropic g-matrices [381]. Scalar expressions are very valuable for physical insight [382].

For $I > \frac{1}{2}$, perturbational expressions have been derived that assume that the quadrupole interaction is smaller than the hyperfine and the nuclear Zeeman interactions. For $I = 1$ and $I = \frac{3}{2}$, it is possible to incorporate the quadrupole

interaction exactly, since general scalar-level expressions for the eigenfrequencies and eigenvectors of the corresponding nuclear spin Hamiltonians are known [383, 384]. A graphical method for their solution was devised [385–387].

For HYSCORE and other more advanced ESEEM experiments, explicit analytical scalar expressions are available [75, 388–392]. These types of expressions can be readily derived using algebraic methods [393–396] using programs such as Mathematica or Maple. However, for anything but the simplest pulse sequences, they are too complicated to offer much physical insight.

For the out-of-phase ESEEM observed in spin-correlated radical pairs, an analytical scalar expression based on a density matrix dynamics description has been derived and can be easily implemented [397, 398].

3.6.2.2 **Matrix Equations**

More general methods for pulse EPR are based on the solution of the LvN equation using matrix representations of density matrix, propagator exponentials, and detection operators in Hilbert space. Mims originally introduced this description for $S = \frac{1}{2}$ in the high-field approximation [374, 375]. In that limit, hyperfine terms containing S_x and S_y are neglected, so that the spin Hamiltonian is block-diagonal, with two nuclear sub-Hamiltonians on the diagonal [14]. The equation can then cleanly be transformed into the rotating frame [368]. The final expressions for the TD signals contain products of elements from the unitary overlap matrix between the nuclear eigenstates in the $+\frac{1}{2}$ and $-\frac{1}{2}$ electron spin manifolds [374, 375, 378, 399, 400]. This matrix is denoted M and sometimes called the *Mims matrix*. Its matrix elements are the branching factors that determine the nuclear echo envelope modulations and are analogous to the Frank–Condon factors for vibronic transitions.

In all their incarnations, Hilbert-space methods in essence generate a list of frequencies ω_ξ and complex amplitudes Z_ξ that together determine the complex exponentials that constitute the final TD signal [14]. For example, for 2D data

$$V(t_1, t_2) = \sum_\xi Z_\xi \cdot e^{-i\omega_{1\xi} t_1} \cdot e^{-i\omega_{2\xi} t_2}$$

where Z_ξ is a product of matrix elements from M, and ω_ξ are differences of eigenvalues of the nuclear sub-Hamiltonians. For a general summary of the Hilbert-space method, see [14].

Frequencies and amplitudes are used to construct either the TD directly or via the frequency domain [58, 61]. Three approaches are possible. (i) The most straightforward and most widely employed method is direct brute-force evolution in TD [55, 376, 377, 401, 402]. This is simple, but can be computationally overly expensive for situations with many peaks or large TDs. (ii) The second method utilizes the frequencies and amplitudes obtained from the density matrix calculation to construct an FD histogram, which is then converted to TD using Fourier transform. This FD "binning" method [49, 50, 54, 374, 380, 399] is very fast and advantageous for situations with many peaks, as it involves essentially no computational cost per peak. The costliest operation is the Fourier transform.

It is particularly efficient for powder simulations. However, FD binning is only approximate, as it involves rounding the frequency of each peak to the nearest discretized frequency in the FD histogram. It can lead to systematic errors, for example, incomplete phase interference in powder simulations. (iii) The third method is a variation of FD binning that addresses these shortcomings [403]. It is based on the convolution and deconvolution of a short finite impulse response filter kernel. It is much faster than the TD method and orders of magnitude more accurate than FD binning.

A bottleneck in the simulation of pulse EPR spectra is the computation of the propagator matrices U via matrix exponentiation. In Hilbert space, the matrix exponential is required to compute the propagation sandwich product. Many numerical methods for computing matrix exponentials are known [404, 405], for example, Taylor-series expansion, Padé approximation, Chebyshev approximation, differential equation solvers, and matrix diagonalization.

Several ESEEM simulation programs have been developed, described, and applied in the past few decades: MAGRES, from Nijmegen, was probably the first general ESEEM simulation program based on density matrix theory [49, 50, 406]. HYSCORE simulation programs were developed and described by Goldfarb [54], Schweiger [55], and others [407]. OPTESIM, a recently described 1D ESEEM simulation program, includes a least-squares fitting algorithm [57]. SimBud [56] has a UI. Molecular Sophe [24] supports pulse EPR simulations. EasySpin supports arbitrary user-defined pulse EPR sequences [14].

ESEEM theory for high-spin systems is well developed and can be implemented in a straightforward manner. Compared to a spin-$\frac{1}{2}$ system, where only one allowed EPR transition is present, many more are present in high-spin systems. All methods compute the expectation value of the electron spin angular momentum vector $\langle \boldsymbol{S} \rangle_i^{\mathrm{T}} = (\langle S_x \rangle_i, \langle S_y \rangle_i, \langle S_z \rangle_i)^{\mathrm{T}}$ for each energy eigenstate ($i = 1, \ldots, 2S + 1$) of the electron spin and then use this to construct spin Hamiltonians for the nuclear sub-manifolds:

$$H_{\mathrm{nuc}}(i) = \sum_k \langle \boldsymbol{S} \rangle_i^{\mathrm{T}} A_k \boldsymbol{I}_k - g_{\mathrm{n},k} \mu_{\mathrm{N}} \boldsymbol{B}_0^{\mathrm{T}} \boldsymbol{I}_k + \boldsymbol{I}_k^{\mathrm{T}} P_k \boldsymbol{I}_k$$

Among the first high-spin ESEEM simulation examples were Cr^{3+} (spin $\frac{3}{2}$) and its Al^{3+} neighbors [408] in ruby, and protons in photoexcited triplet states of various organic molecules [379, 409, 410]. The theory for high-spin transition metal ions with small zero-field splittings has been detailed by Peisach [411], and graphically represented by Singel [380]. Peisach neglected nonsecular terms in the zero-field splitting, leading to $\langle S_x \rangle_i = \langle S_y \rangle_i = 0$. These terms have been shown to be important by Astashkin and Raitsimring [368]. For small zero-field splittings, $\langle S \rangle_i$ can be obtained via perturbation theory [368, 412], whereas more generally, matrix diagonalization must be used [14]. Oliete has used ESEEM simulations for fluorine ligands in an $S = 2$ Cr^{2+} system [413].

When multiple nuclei are present in a spin system, the combined nuclear sub-Hamiltonians can be factored into direct products of single-spin nuclear sub-Hamiltonians. As a consequence, the overall echo modulation amplitude can be

factored into a sum of products of modulations as long as pulses are nonselective. These ''product rules'' have been derived and published for two-pulse ESEEM [373, 374, 408], three-pulse ESEEM [378, 414, 415], and HYSCORE [416], as well as for two-pulse ESEEM on triplets [379]. A general form of the product rule was derived for and implemented in EasySpin [14].

Hilbert-space density matrix propagation methods can also be applied to multifrequency experiments. Such simulations have been performed for DEER [417] and double-quantum coherence (DQC) [300, 418] experiments.

Many software packages have been developed that provide efficient Hilbert-space and Liouville-space spin dynamics simulations for both EPR and NMR. Highly optimized packages include SMART [419], Gamma [55, 402, 420], BlochLib [421], and the more recent high-performance packages Simpson [62], SPINEVOLUTION [63], and Spinach [422]. All can be applied advantageously to EPR in some situations. There are several opportunities for parallelization in Hilbert-space methods. Once frequencies and amplitudes are calculated, they can be combined into TD traces or binned into an FD histogram in parallel. Recent work has identified ways to parallelize density matrix propagation directly using appropriate decomposition of the density matrix [423, 424].

Despite a well-developed theoretical basis, the current accuracy of pulse EPR simulation methods is not entirely satisfactory. Simulations of ESEEM and HYSCORE spectra often do not match very well with experimental data. Peak positions can often be reproduced, but peak intensities tend to be off. This discrepancy indicates that the theoretical models are too simple and should be improved. Reasons for the discrepancy are as follows: (i) Most simulations assume ideal rectangular pulses, whereas in practice pulses are neither infinitely short nor perfectly rectangular. (ii) Because of the product rules, simulations of ESEEM spectra of one nucleus can only be accurate if all other nuclei are included. This is currently not done. (iii) The position and width of the detection integration window relative to the echo transient affect the modulation intensities (observer blind spots [389]). For example, an integration window with nonzero width acts as a low-pass filter. Most simulations assume a single-point detection at the simple τ point, which need not even be the echo maximum. (iv) Site-to-site heterogeneity and correlated hyperfine strains between different nuclei on the same spin center can affect line positions and intensities, but are never taken into account.

In NMR, simulation methods for time-dependent problems such as magic angle spinning (MAS) have been developed [61, 425, 426]. Two recent reviews summarize the application of Floquet theory to such problems in solid-state NMR simulations [427, 428]. For EPR, these techniques can be used to describe experiments with simultaneous irradiation at multiple frequencies such as rf-driven (radiofrequency) ESEEM [429], cw multi-quantum EPR [430], double-modulation EPR [431], and standard cw EPR [131].

3.6.3
Liouville Space

The most general equation for the simulation of spin dynamics in pulse magnetic resonance experiments is the SLE. In NMR, it is widely applied [64, 432]. In EPR, apart from its central importance in the simulation of slow-motion, saturation, and chemical exchange cw EPR spectra, the SLE has been used only in a few pulse EPR experiments: 1D and 2D Fourier transform EPR experiments in ordered and viscous fluids [316, 433–435], 2D DQC experiments [436], EXSCY [437], and a few others [75]. In general, the SLE has not seen widespread use in pulse EPR, since most current pulse applications are on solids and do not require the incorporation of stochastic processes.

Since the matrices associated with the SLE are very large, simulations tend to be slow. Two approaches are possible to improve performance: (i) more efficient algorithms and (ii) reduction of space dimensionality.

Much effort has been spent in finding more efficient algorithms. Sparse matrix methods can be advantageous, and methods based on Lanczos methods [27] are routinely utilized. An improved Lanczos-based method for matrix reduction to tridiagonal form has recently been presented [438]. Finite-element methods have also been proposed [439]. In Liouville space, in contrast to Hilbert space, the costly computation of the matrix exponential can be avoided and replaced by faster methods that directly apply the propagator to a density matrix (in vector form) as a matrix–vector multiplication. Methods that reduce the dimensionality of Liouville space by pruning the basis set to exclude insignificant dimensions were originally introduced in slow-motion EPR simulations that employed the Lanczos algorithm [440, 441], as discussed in Section 3.5.1.3. More recently, Kuprov has developed state space restriction methods for NMR that reduce the size of the Liouville space and the size of the associated density vector and Liouville matrix, leading to large gains in performance compared to a brute-force approach [64, 422, 442–444]. NMR simulation methods for large spin systems is an active area of research [445, 446].

3.7
Pulse and cw ENDOR Spectra

ENDOR spectra are acquired in the presence of a constant external magnetic field, so that the sH does not change during an experiment. Therefore, ENDOR spectra in the rigid and fast-motion limits can be simulated much more easily than cw EPR spectra in the same regimes. No field-dependent Zeeman energy level diagram needs to be constructed. As will be described below, the main difficulty is the efficient and accurate computation of line intensities.

3.7.1
Transition Frequencies

The computation of the transition frequencies for ENDOR is identical in complexity to that for frequency-swept EPR spectra. For this step, two levels of theory, matrix diagonalization and perturbation theory, are used. Using matrix diagonalization, the full sH matrix with the chosen external static field is diagonalized once to determine all energy eigenvalues and eigenstates. The differences of the eigenvalues give the transition frequencies. This approach has been implemented in several programs [49, 208] including EasySpin and works well for small spin systems. However, the size of the Hamiltonian matrix scales exponentially with the number of ENDOR nuclei.

Therefore, in the case of a large number of nuclei (e.g., when modeling matrix lines), analytical first- and second-order perturbation theory expressions [225, 227, 447–449] are used to obtain approximations to the eigenvalues. For multiple nuclei, cross terms between hyperfine couplings within pairs of nuclei are present [226]. They cannot be neglected if one of the hyperfine couplings is substantial. A relevant example is ^{1}H ENDOR in Cu complexes with large Cu hyperfine couplings. Perturbative treatments can become unacceptably inaccurate for systems with multiple large hyperfine couplings such as [55]Mn ENDOR on oligonuclear Mn clusters. As in the case of cw EPR spectra, the validity of perturbational approximations should be checked carefully. Unfortunately, few programs do this consistently, leaving the user uninformed on whether the chosen level of theory is accurate enough. Hybrid methods, as used for cw EPR and ESEEM, are applicable to ENDOR as well.

3.7.2
Intensities

While the computation of ENDOR line positions is straightforward, the accurate and general calculation of line intensities is more challenging. To the best of our knowledge, no generally available program is currently able to do this. Unlike cw EPR, where Fermi's Golden Rule gives accurate approximations to the line intensities in the experimentally relevant non-saturating limit, ENDOR involves either saturating irradiation (cw ENDOR) or bandwidth-limited and spectrally selective excitation (pulse ENDOR). For cw EPR, the full steady-state LvN equation needs to be solved, including relaxation rate constants. This often leads to over-parameterization. For pulse ENDOR, at least the Hilbert-space LvN equation for the density matrix is required.

In a simplified picture, the intensity of an ENDOR transition between two levels $|u\rangle$ and $|v\rangle$ can be written as a product of several factors

$$I_{uv}^{\mathrm{ENDOR}} \propto t_{uv}(\boldsymbol{B}_2) \cdot \alpha_{uv}(\omega_{\mathrm{mw}}, \tau, t_{\mathrm{p}}) \cdot \Delta p_{uv}(T) \cdot f(\omega_{\mathrm{rf}} - \omega_{uv})$$

where t_{uv} is the transition moment, α_{uv} is a selectivity factor that depends on experimental settings, Δp_{uv} is the Boltzmann polarization of the transition, and f is the excitation profile of the rf excitation [450].

One aspect of the transition moment that affects both cw and pulse ENDOR spectral intensities, and distinguishes ENDOR from NMR, is hyperfine enhancement [451–453], the fact that the presence of the hyperfine-coupled electron spin amplifies the driving rf field strength at the nucleus. Theoretically, this is accounted for by including the electron Zeeman Hamiltonian in addition to the nuclear Zeeman operator in the transition operator [1]. In cw ENDOR, this results in increasing intensity with increasing ENDOR frequency. In pulse ENDOR, this results in increased nutation frequencies and effective flip angles during rf pulses with increasing ENDOR frequency, affecting spectral intensities in a nonlinear way. In principle, these distortions can be modeled using a complete Hilbert-space density matrix treatment. One approximation uses a product of NMR and EPR transition moments, where the latter are summed over all EPR transitions that share one level with the given ENDOR transition [49]. In general, ENDOR simulations tend to be most quantitative for single-isotope pulse ENDOR spectra over a relatively narrow frequency range, for example, ENDOR of weakly coupled ^{1}H at Q-band, where transition moments do not vary much across the spectrum.

The second aspect that distinguishes ENDOR from NMR is the selectivity α imposed by the narrow-bandwidth microwave excitation. The intensity of an ENDOR transition not only depends on matrix elements of the Zeeman operator, but also on the microwave frequency. Only a nuclear transition for which one of the nuclear levels is part of an EPR transition that is resonant with the microwave frequency will yield significant ENDOR intensity. This leads to strong orientation selectivity in anisotropic systems and transition selectivity in systems with hyperfine couplings that are larger than the microwave excitation bandwidth. For powder simulations, this selectivity is a significant computational burden, since often only a small fraction of computed orientations of the spherical grid exhibit nonvanishing ENDOR intensity. The majority of evaluated orientations are not significant to the final spectrum. There seems to be no general remedy against these superfluous computations. In some cases, a viable work-around is an orientation preselection procedure: the selectivity is computed for all orientations for a reduced spin system consisting only of spins with anisotropic interactions larger than the electron excitation bandwidth. In a second step, the ENDOR spectrum of the full system is computed only for those orientations where the selectivity factor is above a chosen threshold [1, 14]. Alternatively, the simulation in this second step can be restricted to a spin system containing only the nuclei of interest, using an effective hyperfine field [14, 55, 454]. All pulse EPR experiments are orientation selective if the spectral width exceeds the excitation bandwidth of the pulses, as is most commonly the case.

In pulse ENDOR, there exist additional selectivity effects. Intensities in Mims ENDOR spectra are affected by τ-dependent blind spots. In Davies ENDOR spectra, intensities are attenuated by the nonselectivity of the first inversion pulse (self-suppression) of length t_p. Again, these effects arise automatically if full density matrix simulations are performed. However, an intermediate approach that

circumvents density matrix dynamics solvers, but still reproduces the selectivity amplitude features of specific pulse ENDOR experiments, uses analytical approximate excitation and detection envelopes [450] that can model effects from limited excitation bandwidth and τ-dependent blind spots. The simulation of blind spots and matrix suppression in Mims and Davies ENDOR have been investigated in great detail [455−457].

High-spin pulse ENDOR simulation methods were developed for Mn systems [368, 458, 459], and iron(III) [460] and diiron(II) centers [461]. They follow along the lines of high-spin ESEEM simulations, as discussed in Section 3.6.2.2.

Full-density matrix methods have been used to simulate pulse ENDOR spectra [462] and can include both coherence and relaxation [463]. These models tend to suffer from over-parameterization, but can be trimmed down. For instance, most pulse ENDOR experiments are based on polarization transfers [75]. For such experiments, a simplified density matrix dynamics approach is often used [464]. Coherences are neglected, and the vector of populations, containing only the diagonal elements from the density matrix arranged in a column, is propagated in time. This is equivalent to restricting the Liouville-space spin basis for the density operator to longitudinal terms (S_z, I_z, $S_z I_z$, and identity operator). T_1 relaxation and saturation effects are easily included. Multi-sequence pulse ENDOR experiments [465, 466] have been modeled and analyzed using this approach.

Some of the difficulty of quantitatively simulating ENDOR intensities is due to instrumental imperfections. In contrast to EPR and NMR, ENDOR involves a broadband rf transmitter. Over the broad rf ranges that are swept in ENDOR, the frequency characteristics of the transmitter (source power, amplifier gain, coil impedance) are rarely completely flat. Any non-flatness directly affects the power delivered to the sample and therefore the ENDOR intensities. This could in principle be taken into account by convolving the spectrum with the transmitter characteristics, but would require extensive rf characterization of the instrumentation. Spurious resonances in the rf transmitter can lead to spurious features in the ENDOR spectrum.

3.7.3
Broadenings

Line broadenings in ENDOR spectra are usually modeled by simple convolution with a combination of Gaussian and/or Lorentzian lineshapes. Anisotropies in these broadenings are rarely modeled. No physical models are used. Often, *A* strain is thought to contribute to the broadening. Broadening effects due to the pulse length of the ENDOR pulse can be included using convolution with a sinc function.

3.8
Pulse DEER Spectra

Although pulse DEER methods can be simulated using the density matrix methods outlined in Section 3.6 [300, 417, 418], the main need for computational methods for DEER data is in data analysis. Fitting of experimental DEER data requires intricate data analysis methods. Therefore, we mention some of these recent methods. Methods for the extraction of distance distributions from dipolar time traces based on Tikhonov regularization [467, 468] and maximum entropy [469] have been developed. DeerAnalysis [470] is a widely used program that provides a large number of analysis and fitting methods for DEER data. DEFit [471, 472] provides multi-Gaussian distance distribution models. MMM [473] can use protein structures to derive a distributional model for nitroxide pair distances and orientations, and compute the DEER trace from that.

For molecules with two flexible spin labels, the computation of the solid-state DEER spectrum involves summation over all possible relative orientations and distances between the two spin labels [174, 474]. For a powder simulation, this requires integration over a total of six degrees of freedom: two Euler angles that describe the orientation of the molecule with respect to the external magnetic field, three additional Euler angles that describe the relative orientation between the two spin labels, and the interlabel distance. The combined conformer/distance distribution is generally described by a multidimensional probability distribution function. As a consequence, the corresponding simulations doing this brute-force integration are painfully slow. However, parallelization is trivial and can result in tremendous speed-ups. Computational aspects of the dynamics and conformational distributions of spin labels have been reviewed very recently [475]. PRONOX is an algorithm for rapid computation of distance distributions based on conformer distributions [474]. MtsslWizard is a plugin to PyMOL that allows *in silico* spin labeling and generation of distance distributions [476].

3.9
Least-Squares Fitting

Methods for ''automatic'' least-squares fitting of simulated spectra based on an sH model to experimental spectra have been developed from the very early days of EPR [477, 478]. In these methods, a set of sH parameters is varied in consecutive simulations until an optimal match between the simulated spectrum and the experimental spectrum is achieved. The match is generally quantified by an objective function (goodness-of-fit function, error function, target function) that depends on some measure of the difference between the simulated and experimental spectra.

Least-squares fitting methods have also been used in other aspects of EPR data analysis, for example, to computationally determine the center of symmetry of a

spectrum [479]. These applications lie beyond the scope of this overview. Least-squares fitting methods are used in conjunction with locating transition fields [211] and have been mentioned in the corresponding section above.

In this section, we review the various choices available for the objective function and for the fitting algorithm, as well as their application to multicomponent and multispectral problems. Unless otherwise stated, cw EPR is assumed. In addition, we discuss error analysis. The early literature on fitting methods in EPR have been reviewed in the book by Mabbs and Collison [10]. For a review of direct search methods that do not rely on derivatives, see [480].

3.9.1
Objective Function

To assess the quality of the fit between a simulated and an experimental spectrum, the sum of squared deviations is most commonly used:

$$\chi^2 \propto \sum_i \left(\frac{y_{\exp,i} - a y_{\text{sim},i} - b_i}{w_i} \right)^2$$

where $y_{\exp,i}$ are the data points of the experimental spectrum, $y_{\text{sim},i}$ are the corresponding ones from the simulated spectrum, a is a scaling factor, and b_i are the data points from a baseline correction function. Each difference in χ^2 is additionally weighted by w_i, for example, the error in the measurement. Most often, $w_i = 1$.

Conventionally, for cw EPR, the y values in the above expression are taken directly from the first-harmonic spectrum. However, this is not the only choice. The spectral derivative, the integral [47], or even the double integral [481, 482] can be used as basis for χ^2. Both the integral and double integral as target functions have the advantage that search algorithms are less likely to get trapped in local minima in the case of EPR spectra with many resolved lines. Integration also reduces the effect of noise. A multistep procedure has been proposed where the fit is initially based on the double-integrated spectrum, in a middle stage on the integrated spectrum, and finally on the spectrum as recorded [481, 482].

For spectra of organic radicals with many hyperfine lines, it might be beneficial to fit the Fourier transform of the spectrum [304], since this dramatically smooths the error function by removing many local minima. Another objective function that can be used for spectra with distinct maxima and minima is the aggregate mismatch in line positions between experiment and simulation. This has recently been used in linear combination with the conventional χ^2 function [483]. An objective function that subdivides the spectral deviation into segments has been proposed [484].

Despite the added flexibility with a choice of objective function, there are still situations where almost all fitting algorithms can get stuck. A prototypical example is a two-component mixture of two spin-$\frac{1}{2}$ systems with orthorhombic g-matrices, with two maximum g values separated from the others and resolved among themselves. This leads to two minima of almost identical depth in any objective function. If the two g values are assigned to the wrong components in the fitting, it is

almost impossible to get out of this minimum by change of objective function alone. Only permutation of the values, followed by further optimization, will improve the fit. To prevent these types of failures, additional physical constraints on the ranges and correlations of the fitting parameters need to be taken into account. Ideally, additional experimental data are included to resolve this ambiguity.

3.9.2
Search Range and Starting Point

In addition to a smooth error function, two other keys to success in least-squares fitting with iterative methods are (i) a choice of the starting parameter values close to their values at the expected global minimum and (ii) the choice of an adequate search range. The choice of the fitting algorithm is secondary to these aspects.

A poor choice of starting point will often lead to non-convergence or to the convergence to a physically nonsensical solution. The search range should be restricted to a parameter subspace large enough to contain the expected solution, but small enough to be searchable in a reasonable amount of time. The set of parameters can also be transformed from one basis to another to deal with correlations between parameters. For example, instead of searching the space of two g-factors $(g_\perp, g_{||})$, the search can be done with the transformed coordinates $(\Delta g, \overline{g})$ with $\Delta g = g_{||} - g_\perp$ and $\overline{g} = \frac{(g_{||} + 2g_\perp)}{3}$.

3.9.3
Fitting Algorithms

The choice of the algorithm for least-squares fitting has profound influence on the convergence rate and on the robustness of the search, that is, on the ability to find the global minimum despite local minima and noise. The dependence of EPR spectra on magnetic parameters is nonlinear, so that nonlinear least-squares methods are used [485]. Broadly, they fall into two groups: local and global. Local methods are generally fast, but are only able to locate a minimum in the objective function close to a starting parameter set. Global methods search the parameter space more widely and are able to locate a global minimum in the objective function, although mostly at the cost of a significantly slower convergence rate. EasySpin provides the user with a selection of algorithms as do XSophe [23] and other programs [486].

3.9.3.1 Local Methods
Local methods involving derivatives based on analytical expressions [215] and Feynman's theorem [487] have been employed. The first instances of local least-squares fitting of EPR spectra used the Gauss–Newton or gradient descent methods with analytical derivatives [45, 477, 478, 488, 489]. These algorithms are still used occasionally. Another simple algorithm, the Newton method, is based on a local quadratic approximation of the error function. Misra [211, 213, 214, 490, 491]

has used it together with explicit first and second derivatives of χ^2 in a general least-squares fitting program.

The *de facto* standard method of local nonlinear least-squares search is the Levenberg-Marquardt (LM) algorithm. The LM method adaptively varies the step size and direction. Far from a minimum of χ^2, it acts similarly to a gradient descent method, stepping in the direction of steepest descent of χ^2. Close to a minimum, it acts similarly to the Gauss–Newton method that assumes that χ^2 is locally quadratic and steps accordingly. Typically, this method converges rapidly toward a minimum. The LM algorithm has been deployed many times in EPR, both with analytical [290, 492, 493] and numerical gradients. For the fitting of slow-motional nitroxide spectra, the LM algorithm [494] as well as a trust-region modification [433] were implemented. These two approaches and the simplex methods were recently compared [46].

The popular Nelder–Mead simplex method is simple and relatively robust. For the search of an N-dimensional parameter space, it sets up a set of $N + 1$ parameter values that geometrically constitute the vertices of a simplex in parameter space (e.g., a triangle for $N = 2$, a tetrahedron for $N = 3$). On the basis of the χ^2 values at each of the vertices of the simplex, new vertices are chosen and evaluated. The simplex ''walks'' through parameter space to a nearby local minimum. The method is robust, but not very fast. It is used extensively in EPR [295, 484, 495–500].

Other local-search methods used in EPR simulations include the Hooke and Jeeves pattern search [20, 22] and Powell's conjugate gradient method [42, 501]. Multidimensional fits can be performed by consecutive 1D minimizations [43].

3.9.3.2 Global Methods

Global methods are able to search the parameter space more completely, increasing the likelihood of locating the global minimum. Most of them rely on an element of randomness and often involve large sets of parameter sets.

Many forms of random Monte Carlo search methods have been proposed and implemented. They range from simple random-step downhill walk [350, 502] to simulated annealing [20, 22, 23, 242, 484, 503–506], an adaptation of the Metropolis algorithm.

In recent years, several variations of the genetic (evolutionary) algorithm have been applied to EPR [498]. In these methods, the goodness-of-fit (''fitness'') for a group of M candidate parameter sets are computed. Each parameter set is treated as an individual, and a process akin to natural selection based on the fitness values is applied to the M sets by crossover and mutation to form the next generation of M parameter sets. This process is repeated until the population converges to a minimum. The main appeal of these methods lies in the fact that they are random, but directed. Genetic methods have been combined with local-search algorithms such as Powell or simplex [42, 501, 507] to accelerate convergence once close to a minimum.

Artificial neural network models have been used to extract rotational correlation times from motional spectra [508]. Other nature-inspired algorithms such as particle-swarm optimization and bacterial foraging have not seen visible usage in EPR.

Systematic grid searches [86, 509] form another set of methods that can locate the global minimum. In contrast to the methods above, they are nonrandom and systematically scan the entire parameter space. For large parameter spaces, they are very slow. For example, for searching a six-dimensional parameter space with 10 points along each dimension for each parameter, 10^6 simulations are necessary. However, they can be expanded into weighted tree searches and combined with local-search methods to improve efficiency. Their main appeal lies in the fact that they return the global minimum. They are well suited for massively parallel computer architectures, as all the simulations are independent of each other.

3.9.4
Multicomponent and Multispectral Fits

In spectra consisting of multiple components, the fitting parameter space includes not only a set of magnetic parameters for each component but also the relative weights of each component. In this case, the spectrum is a linear combination of nonlinear functions of the spin Hamiltonian parameters. These types of problems can be efficiently solved using separable nonlinear least-squares methods [510]. A special case of multicomponent spectra is a spectrum that contains baseline distortions. These can be treated as an additional component and included in the fit, usually as a linear or quadratic function (see χ^2 definition above).

Multicomponent spectra are in general very challenging to analyze. If no good starting guess for the component parameters of a multicomponent spectrum is available, an attempt at decomposition into single components can be made using principal component analysis (PCA) [511] or maximum-likelihood common-factor analysis [512]. A fitting program for multicomponent nitroxide spectra has been implemented [31]. EasySpin supports general multicomponent fits.

The simultaneous fit of multiple cw EPR spectra acquired at different microwave frequencies (e.g., S, X, Q, and W band) can help constrain the parameter space and reduce the number of local minima for a multidimensional search space. One simple way to implement such multispectral fits is to concatenate all experimental spectra into a 1D array with appropriate weights and then use standard methods on this concatenated spectrum. A set of ENDOR or ESEEM spectra acquired at different magnetic fields is another common multispectral fitting problem. Simultaneous fits of spectra acquired at different temperatures can constrain static and dynamic parameters together, for example, in chemical exchange problems [43, 513].

3.9.5
Limits of Automatic Fitting

Most fitting algorithms depend on a series of parameters, such as default step sizes and damping factors. The values of these parameters can affect the convergence rate and determine whether fitting will be successful or not. Therefore, there are several levels of user choice in least-squares fitting: (i) the dimensionality and representation of the parameter space, (ii) the starting point(s), (iii) the search

range, (iv) the objective function, (v) the fitting algorithm, and (vi) the configuration of the fitting algorithm. These choices depend strongly on the problem at hand and on the expertise of the user. This renders a general "automatic" least-squares fitting procedure applicable to all types of EPR spectra essentially impossible. Despite tremendous effort, the goal of fully automated fitting of EPR spectra is as distant as ever. However, the host of developed algorithms provides a rich toolbox that can greatly assist the search for a good fit. EasySpin provides an interface that lets users make and change settings at all levels of choice.

3.9.6
Error Analysis

Once converged, least-squares fitting algorithms return a set of supposedly optimal parameters. Several questions need to be answered before these values should be taken as a final result: (i) Is the fit close enough? Even if the fit returns the global minimum, the χ^2 error might be too large. In this case, the physical model needs to be modified. (ii) Are the optimal parameters physically meaningful? If not, other minima with similar χ^2 values need to be examined, or the model needs to be modified. (iii) How accurate are the obtained parameters? To answer this question, a statistical error analysis that establishes estimates for the parameter variances needs to be performed, for example, based on the covariance matrix or on Monte Carlo simulations of synthetic parameter sets [514]. Misra was the first to present a method based on the curvature matrix (matrix of second derivatives of χ^2) [515]. Others have provided similar approaches [57, 214, 433, 486, 516]. However, in the experimental literature, this crucial aspect of least-squares fitting is very often neglected.

3.10
Various Topics

3.10.1
Spin Quantitation

Accurate quantitation of spin centers in an EPR sample is very desirable in many applications [517]. Two different principles of quantitation can be used: comparison of double integrals and quantitation by simulation. Among software programs, SpinCount has special provisions for spin quantitation [26]. EasySpin returns simulated cw EPR spectra with calibrated intensities for all systems and regimes, so that quantitation by simulation is possible.

The experimental method of double integration and comparison to a separate concentration or quantitation standard is feasible for certain classes of spin centers, for example, organic radicals and other species with narrow spectra. This method usually relies on a set of assumptions that can all introduce systematic errors if not valid: (i) sample geometry, placement, fill factors, and Q factors of the analyte and standard sample are identical; (ii) the transition moments of all lines in the

spectra of both samples are identical; (iii) the full EPR spectra of both samples are acquired; and (iv) neither spectrum is saturated. Progress has been made recently in addressing some of these potential biases. The effect of sample geometry and spatial B_1 distribution within EPR resonators has been incorporated in commercial software [517].

The second method uses computer simulation to quantitatively simulate the EPR spectra of both the analyte and the standard sample [282]. From the scaling factors, relative concentrations can be derived. Compared to the first approach, this method does not make assumptions about intensities and spectral extent. It correctly includes differences and anisotropies in transition moments, and it can easily deal with spectra that are partially out of range. However, it still has to be ascertained that sample geometry and placement are controlled, and that neither sample is saturated.

3.10.2
Smoothing and Filtering

Many filtering and resolution-enhancement techniques have been proposed, but very few are regularly utilized, probably because of the reluctance of spectroscopists to tinker with experimental raw data. Among digital techniques, moving-average and Savitzky–Golay filtering [478] and smoothing as well as lineshape deconvolutions are the most common. Analog filtering is based on a resistor–capacitor filter as implemented in hardware in most EPR spectrometers, but is clearly limited compared to the myriad digital filtering tools available for spectral post-processing, and is now generally discouraged. An adaptive digital filtering technique can be used to increase the signal-to-noise ratio of cw EPR spectra [518].

3.10.3
Data Formats

The two most common data formats are Bruker's old ESP format (file extensions par and spc) and Bruker's current BES^{3}T format (file extensions DTA and DSC). Both store the data in binary form in one file, and experimental parameters, plus other metainformation such as details on the data storage format, in a separate second file. Both formats are open source and documented, although the older ESP format exists in a somewhat confusing variety of versions. JEOL spectrometers store data in a proprietary single-file binary format. Custom-built spectrometers generally employ simple text files to store data. Reading and storing these formats is straightforward. There exists an EPR version of the JCAMP-DX data format standard developed by the International Union of Pure and Applied Chemistry (IUPAC) [519]. This format has yet to gain traction, although the universal adoption of a standard format would have clear benefits [520].

3.11
Outlook

Currently, EPR spectra can be modeled reasonably well on the basis of currently available methods described in this chapter. A large range of systems and experiment types are supported, and simulations are fast enough in many cases to allow interactive fitting for smaller spin systems. However, both the scope and the speed of current methods can be significantly increased. Extending and automating approximation methods should enable a more flexible choice of theory level free of user interference. This will benefit the simulation of larger spin systems. Parallel computing, either multi-CPU or GPU-based, will significantly enhance the performance of simulation methods, as many algorithms, from matrix diagonalization to powder averaging and least-squares fitting, can be trivially parallelized.

A major challenge for simulation methods is the increasing size of spin systems that are of current interest, such as oligometallic clusters and molecular magnets in EPR and entire proteins in NMR. Efficient simulation of these systems requires the development of dedicated and highly optimized large-scale methods.

Additional work is necessary to develop more general and usable methods and software for multispectral fits, which would allow the simultaneous analysis of multifrequency data (X-band and high-field) or multi-method data (EPR, ENDOR, ESEEM). It remains to be seen whether multiple types of spectra can be fitted with a single underlying model without an inordinate increase in the dimensionality of the parameter space.

Except for very simple spin systems and pulse sequences, pulse EPR simulation methods are still slow and quantitatively not entirely reliable. As a consequence, they lag far behind cw EPR simulation methodology and hinder the development of the field. More work is needed to implement faster and more accurate pulse EPR simulation methods and to calibrate these against experimental data, for example, for HYSCORE. This is especially important given the recent emergence of optimal control pulses [521, 522] that will open up a wide array of new possibilities in pulse EPR.

A general trend is observed where EPR simulation methods are increasingly combined with other computational methods, to provide complete end-to-end solutions for certain areas of research. This includes integration with computational chemistry methods such as DFT [33] and direct fitting of molecular structures to EPR spectra [523]. MD methods are of increasing importance in spin-label studies, as discussed in the section on slow-motion simulations. Advances in these areas will be significant [475].

As an ultimate goal, all types of EPR spectra, no matter whether from solids or liquids, or including any number of relaxation or other dynamic effects, should be in principle analyzable on a time scale that is short relative to the effort of sample preparation and spectral acquisition. This would eliminate the current bottleneck of spectral simulation and analysis. I hope that this goal is reached in the near future.

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