Response to the referee comments regarding the manuscript
The solid-state DNP effect in liquids

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I thank the reviewers for the time and effort they put into reviewing this rather long and somewhat technical work, especially since they additionally had to read the companion paper. In the light of their constructive comments, I have included a few new paragraphs in the revised manuscript. These changes, as well as my response to all their questions, are given below in blue color. The comments of the reviewers are reproduced in black.

1 Reviewer 1: Gunnar Jeschke

This manuscript presents a very elegant theory on DNP under slow-tumbling conditions in liquid solution via a mechanism that is historically known as the solid effect. For a paper discussing high-level spin dynamics theory, it is astonishingly clear. The reader is helped gently over the hurdles on the path to understanding (example: pointing out the outer product with identity operators or the identity matrix in Eq. (53)). The theory is sound and it explains observations recently made by Kuzhelev et al. Compared to an earlier approach that the author calls "more ambitious", the new theory leads to much simpler results. Although still elaborate, it is one of these theories that appear straightforward after someone has found how to do it. I do not have many remarks and I did not find any serious problem. In principle, this manuscript could be published as is (just correct the typo). The author might want to consider whether any of the following remarks could still improve it.

At some points of my review I refer to the companion paper "Dynamic view of the solid-state DNP effect" (https://doi.org/10.5194/mr-2023-1).

1. Line 35: You refer to the companion paper and discuss the case where the mw nutation frequency approaches the nuclear Larmor frequency. This case is the basis of NOVEL DNP (https://doi.org/10.1016/0022-2364(88)90190-4). You may want to point this out.

   Thank you for drawing my attention to NOVEL.
   Since NOVEL is a pulsed DNP method involving spin locking, whereas the analysis I present applies only to the steady state of cw irradiation, I do not see under what conditions NOVEL should formally converge to the cw steady state, if at all. Nevertheless, it is interesting that the matching condition of NOVEL, namely $\omega_{\text{eff}} = \omega_I$, emerges naturally from the steady-state analysis. I have added the following sentence to Paper I:

   > It is noteworthy that the equality $\omega_{\text{eff}} = \omega_I$, implied by the approximation (52), also arises as the matching condition of the pulsed DNP method known as NOVEL (nuclear orientation via electron spin locking).

2. Line 50: You describe thermal mixing as a DNP process that involves two electron spins and one nuclear spin. Common usage of this term is that it involves several electron spins, not necessarily only two.

   I agree. The incorrect clarification "in which two electronic spins are involved in the flipping of one nuclear spin" has been removed from the revised version of the manuscript.

3. I understand that the current manuscript needs to repeat some material of the companion paper in order to be self-contained. For my taste, you repeat too much. No derivations are required here. You could simply state the key results of the companion paper before Section 3, where the new derivations and results are described. I would substantially shorten Section 2. Basically, you only need to introduce notation and equations used in later Sections or for generating Figure 3.

   In the revised version of Paper I, I no longer use matrix notation but consecutively eliminate the variables at steady state. However, matrix notation is needed in the current paper for the stochastic Liouville equation. I have, therefore, retained the part that repeats Paper I as is, since it now reviews the previous results but using matrices.

4. Line 338: "partial derivative with respect to the time dependence, at fixed ζ." The reader might be puzzled here, as for any molecule, ζ is generally time dependent, too. Of course, it is mathematically sound to do it this way and average over ζ in the end. However, maybe you want to remind the reader at this point that you are talking about evolution of an ensemble state that contains all orientations. Not all readers might be as familiar with the SLE that they find this obvious.

   I included the following paragraph:

   > Note that in the probabilistic description of the random process by the Fokker-Planck equation (28), the probability density $p(\zeta, t)$ characterizes an ensemble of nuclei, and ζ is treated as an independent variable which is not a function of t. In contrast, when a single nucleus is followed in time (e.g., through molecular dynamics simulations), ζ is a random function of t. Although this second picture of random trajectories was invoked when writing the dipolar correlation function (2), in the following pages we only work with the probabilistic description of an ensemble of identical nuclei.

   Because I have presented the SLE approach procedurally, without really discussing the meaning of its dynamical variables, I have now directed the reader to two new references:

   > For a detailed explanation of SLE the reader is referred to the literature [1, 2]. A more recent discussion can be found in [3].

5. You rightly point out that, with the experimental parameters that you have, you cannot determine the contact distance with sufficient accuracy. However, in principle it may be feasible to determine all parameters that you need (with some effort for B1). Of course, the FFHS model is still a strong simplification. Nevertheless, determining the contact distance within this model may be of interest. Maybe you want to stress this.

   This point relates to question 11 of the second reviewer, which I address below.

Typos:
Line 436: “hallow” should read “hollow”

The typo was corrected.

2 Reviewer 2: Anonymous

The presented manuscript “The solid-state DNP effect in liquids” by Deniz Sezer is devoted to the extremely valued and inappropriately underestimated subject of DNP solid effect (SE) in the presence of dynamics, which is assigned by the author to SE in the liquids. The interpretation of DNP studies in complex systems, especially liquids and soft matter, remains partially phenomenological despite a general understanding of the underlying principles dating back to Abragam’s times. However, only very few researchers have attempted to compute analytically, based on operator formalism, the shape and intensity of DNP spectra and their relation to the easily determined EPR parameters. This contribution is a most welcome addition to the field, and the author provides a systematic and thorough analysis of the effect conventionally labelled “Solid Effect” and its observation in liquids, relating it to the dispersive component of the EPR line which is mostly not considered explicitly in the interpretation of such DNP effects. The current contribution is a logical continuation of the companion paper “Dynamic view of the solid-state DNP effect”, which should be considered while reading through the actual paper. As the main results, the description of SE via the product of the dispersive component of the EPR spectrum and spectrum of electron-nuclear dipolar interaction, as well as the introduction of the force-free-hard-sphere model to all derivations, can be pointed out. In contrast to the static Abragam model, which is widely and perhaps the only used model to describe the solid effect, the newly derived theory allows describing of the solid effect in the system where dynamics plays a substantial role in modulating both an amplitude and DNP profile shape of solid effect. As the authors claimed, the theory presented in the paper is a more simple version of a theory developed by Korringa and colleagues (Papon et al., 1968; Leblond et al., 1971a), the main point of which was describing the transition between SE and Overhauser effect due to the changes of the dynamics in the system. Nevertheless, the way the author presents spin dynamics derivation and implementation of the new concepts is unique, and the paper absolutely deserves to be accepted after minor revision. On the other hand, the paper is remarkably long and dense, perhaps containing a lot of points for further discussion both from fundamental spin dynamics theory points of view as well as perspectives of application for real experimental cases. However, there are some comments and questions below, after answering which the manuscript is suggested to be accepted.

1. Certainly, a detailed derivation of the formalism is beyond the scope, or the abilities, of quite some readers; the author, however, succeeds in making the essential results available in a graphical way by plotting different contributions, and parameter dependences, in figures 3 and 4. Figure 5 is a bit less intuitive. Maybe a short (one-sentence) description of the meaning of “perturbative” within the caption would help.

   I added the following explanation to the figure caption:

   > The eigenvalue problem of the generalized Bloch matrix $\mathscr{B}$ has a simple closed-form solution when $T_{1S} = T_{2S}$. The perturbative approximation uses these analytical eigenvectors and corrects the eigenvalues to first order in the difference $1/T_{1S} - 1/T_{2S}$.

2. Figures 7 and 8 are meaningful and convincing descriptions of a particular experimental case, with an “unusual” DNP enhancement spectrum that is not straightforward to interpret by not using the approach in this work. Are there any arguments that the interpretation given in this paper (despite the good fit) is more realistic than the one in the original JACS paper of Kuzhelev (thermal mixing)? Are these just two alternative interpretations of the spectrum, or are there good reasons why thermal mixing can be ruled out? Can the frequency separation of small offset DNP peaks on J-band DNP spectra of BDPA in lipid bilayers, which seems to be smaller than ν_n 400 MHz, be the reason to exclude thermal mixing or cross-effect from consideration?

   The only argument I make against the interpretation in terms of thermal mixing is in the Introduction:

   > However, thermal mixing is commonly associated with a broad EPR spectrum [4], while the spectrum of BDPA was extremely narrow at the elevated DNP concentration used in the experiment, and the observed spurious enhancement peaks lay outside this narrow spectrum [5, fig. 2].

   This statement is in line with the last sentence of the referee’s question.

   Nevertheless, I would agree with the view that, at the moment, the two interpretations should be considered as two possible alternatives. To convincingly prove that the effect is due to one of them, and not due to the other, it would be necessary to study its dependence on different experimental factors, like mw power, radical concentration, temperature, etc., and to compare the outcomes of the experiments with the predictions of the two alternatives. For the alternative that I propose, it should be possible to generate quantitative predictions using the formalism developed in the paper. Since I am not sufficiently familiar with thermal mixing, I cannot tell whether the theoretical understanding of thermal mixing has the same predictive power.

3. Although the author provides some key quantities (like eq. 87) and follows with a general description, it would be helpful for the reader if it were clearly outlined, possibly in the Conclusion section, which are the conditions when a significant deviation from the classical SE effect is expected; when this might be safely neglected; and possibly when an additional contribution by CE or TM or even OE exists, in other words, how to easily identify or predict the contributions to the DNP spectrum. This could be a separate Section, apart from the existing Discussion (5) that puts this work into context.

   The “classical” solid effect does not account for the modulation of the dipolar interaction by motion. From that perspective, it is fundamentally inapplicable to liquids. Nevertheless, if the time scale of molecular liquid motion is an order of magnitude longer than the electronic T_2, which is very unlikely, then the “classical” solid effect should be fine. Section 4.3 and figure 6 in the paper examine exactly this transition from solid-like to liquid-like behaviour.

   Both the solid effect and the Overhauser effect, which are the only DNP effects that I am familiar with from my own research, are rather sensitive to the magnetic field at which the DNP experiment is performed. At a given magnetic field, these two effects are also sensitive to the mw power, concentration of the radical, relaxation times, and the viscosity of the environment. Given this rich dependence on various factors, I am not aware of general rules that would allow for easy assignment of different features in the DNP spectrum to different effects, and which apply to all magnetic fields, solvent viscosities, etc. In fact, the new feature that I explain in the current manuscript is, indeed, very similar to the thermal mixing observed with BDPA at 0.5 K [6], and will likely be assigned to thermal mixing by any such list of simple rules.

4. Perhaps a short overview of DNP effects, in addition to solid effect and thermal mixing mentioned in the introduction, could help non-expert readers understand the differences between them. Also, the explanation presented in paragraph around line 55 for thermal mixing fits more to the cross effect.

   The confusing explanation around line 55 was removed.

   The aim of this rather technical paper is to show how the modulation of the dipolar interaction by motion can be formally incorporated into the theoretical treatment of the solid effect. I also examine a recently reported DNP spectrum at J-band, mainly to illustrate the application of the developed theory to real data, and to show how DNP spectra in liquids reflect different aspects of the molecular and spin dynamics. Given this extremely narrow focus of the paper, I think that an overview of all DNP effects is neither needed nor justified.

   Regarding the origin of the unusual peaks in the DNP spectrum, the aim of the paper is limited to providing one plausible explanation, which is new in the literature. Even conclusively ruling out the other alternative, i.e., thermal mixing, is beyond the scope of the paper, as any such attempt would require additional experiments under different conditions. Thus, I do not think that a discussion of thermal mixing, let alone of the Overhauser effect or the cross effect, is necessary.

5. Another aspect is related to Figure 2. The design of this diagrammatic representation may be a major simplification of the derivation (in terms of equations), or it may confuse the reader; only time will tell. Since the diagrams are derived and explained in the other paper mr-2023-1, it is suggested to leave fig. 2 out in this paper and rather remove any suggestion for the superficial reader to work through 70 pages instead of only 35. The two papers should remain independent of each other if that is possible.

   There are two different aspects to this comment. One relates to the diagrams in Paper I and the other to the need to read two long papers instead of only one.

   Regarding the second aspect, all I can say is that this second paper will likely be read only by researchers who deal with the solid effect in viscous liquids. Although I cannot be certain, I think that, at the moment, their number is less than 15 on the entire planet. It shouldn't be such a waste of human time if these handful of people had to read two papers instead of one.

   Regarding the first aspect, it is clear from the comments of the reviewers of Paper I that I failed to properly motivate the diagrammatic representation of the spin dynamics. Nevertheless, in my opinion, representing the spin dynamics of several coupled differential equations in a visual form is a significant contribution of Paper I (perhaps more significant than everything else, considering the broader NMR community).

   Such representations of coupled differential equations are routinely used in chemical kinetics and in biochemistry. As an example, no undergraduate Biochemistry textbook ever shows the coupled differential equations of the glycolysis pathway, but all textbooks show the graphical representation of the involved reactions. In fact, I was so used to seeing only the graphical representation of glycolysis, that my first encounter with the differential equations behind these arrows was a little unsettling.

Personally, I am convinced that such graphical tools are similarly needed to think about spin dynamics, as soon as one goes beyond the three dynamical variables of the Bloch equations. Therefore, just like I use the mathematical results of Paper I in this subsequent manuscript, without the need to derive them again, I should be able to use the graphical tools developed in Paper I with only a brief reminder.

6. Line 485: Perhaps, authors could describe for which types of dynamics monoexponential correlation function fits better than for translational diffusion, e.g. rotational dynamics, complex formation etc., with corresponding references.

   The strength of the developed formalism is that it is independent of the mathematical form of the dipolar correlation function, and can be used with different motional models. Developing this formalism is the main aim of the paper. The specific experimental DNP spectrum that is analyzed in the paper is intended as an illustration of how the developed theory could be applied to real data. From this perspective, I think that the discussion of different motional models that lead to analytical dipolar correlation functions is beyond the scope of the current paper. Similarly, the experimental data that I engage with does not justify the discussion of motional models that lead to exponential correlation function.

7. Lines 489, eq. 66: D is a relative diffusion coefficient, which is the sum of diffusion constants of molecules carrying either electron or nuclear spins. Perhaps, it should be mentioned in the text. Table 1 and corresponding fitting in Figures 7-9: T_1s depends on the B_1. Is there any explanation for this phenomenon? Or is it just a fitting procedure drawback? Otherwise, could the author add some more detailed explanation around line 665.

   That D is the sum of two diffusion constants is now stated in the new paragraphs responding to question 11 of the reviewer (see below).

   Regarding the dependence of T_1 on B_1, the explanation for this effect was intended to be provided by the last column of Table 1, and around line 665 that the reviewer mentions.

   In summary, the peaks of the dispersive EPR line are located at the offsets given in eq. (82) of the revised manuscript. Since these offsets depend both on B_1 and on T_1, to keep the offset positions at the "thermal mixing" peaks in the DNP spectrum, T_1 has to change every time a different B_1 is used.

8. Line 670 and perhaps 635: How does the radical concentration affect b (nm), which is sometimes called the minimal distance of approach, which should not depend on the concentration, but the structure of diffusion molecules?

   The dipolar spectral density function $J_{11}(s)$ is proportional to $N/3b^3$, where N is the radical concentration. This proportionality to $N/3b^3$ is then inherited by the DNP enhancement. As a result, the parameter $N/3b^3$ directly scales the overall amplitude of the DNP spectrum, just like T_{1I} in eq. (88). Thus, the fit to the experiment allows me to estimate the factor $N/3b^3$, but not b^3 on its own. It is in this sense that uncertainties in the concentration N affect the *estimate* of b from the overall magnitude of the DNP spectrum.

9. Figure 7. Was the fitting of s_x and T_x done separately, or only their product was scaled with amplitude after adding the broadening?

   The fitting is not performed on the level of s_x and T_x. These are calculated after the fit for the purposes of analysis. To clarify this point I expanded the previous description of fig. 7 as follows:

The top plot in fig. 7 shows the experimental enhancements (red circles) together with the best fit obtained using the FFHS model with $B_1 = 6\,\mathrm{G}$ (solid black line). The solid green line in this plot is the difference between the experimental data and the fit. The corresponding fitting parameters are shown in the first row of Table 1. Note that the fits were performed numerically using the exact expressions of p, $v_\pm$, and the DNP enhancement (eq. (9)), and were not restricted to the dependencies on the fitting parameters r_i ($i = 1, 2, 3$) that are indicated in (88). (For example, the general dependence of the electronic polarization factor p on T_{1S} and T_{2S} is not limited to the ratio T_{1S}/T_{2S}.)

After the fits converged, we used the final values of the fitting parameters to calculate the dispersive component of the EPR line $s_x^{\mathrm{ss}} = p\omega_1 f_x\, s_z^{\mathrm{eq}}$, and the factor T_x, such that $(p\omega_1 f_x)T_x = pv_-$. These are shown in the lower plot of fig. 7, where s_x^{ss} (blue) and T_x (orange) are scaled independently along the vertical axis. Their product (black dotted-dashed line) is also scaled independently along the y axis. Since $p_X \approx 1$ in our case, the product pv_- is itself proportional to the solid-effect enhancement. Hence the black lines in the upper and lower plots of fig. 7 are directly comparable. We can thus visually conclude that the unusual enhancement peaks at small offsets are a direct manifestation of the dispersive component of the power-broadened EPR line.

10. Figure 7, green line: The residual of the fitting exhibits some "peak" around zero offset, which seems to be a result of either an additional DNP effect or a slight misplacing of the offset axis. How was the offset axises correspondence between experimental data and calculated DNP spectra done? Is the Overhauser effect expected at J-band with dynamics corresponding to tau ~ 7 ns?

Generally, there is indeed some freedom in the offset of the experimental DNP spectrum along the horizontal axis, as the g value of the radical in the specific experimental environment may vary slightly from literature values in other environments. However, because the DNP spectrum that is analyzed in the paper shows very clear solid-effect lines, this freedom is not present in our case, as the middle of the spectrum must be exactly between the peaks of the solid effect. As a result, it was not possible to remove the small but systematic discrepancy at zero offset by slightly shifting the experimental spectrum to the left.

Since the remaining discrepancy around zero offset is not substantially larger than the discrepancies at other offsets, it would be unjustified to interpret it as evidence for small Overhauser effect (or any other DNP effect, for that matter). Nevertheless, in order to address the last question of the reviewer, let us assume for the moment that we have a small Overhauser DNP enhancement of about 2 units. Is that possible with a motional time scale of $\tau = 7\,\mathrm{ns}$? The short answer is "No". The long answer is as follows.

If one were to use $\tau = 7\,\mathrm{ns}$ in the FFHS model and calculate the maximum possible Overhauser enhancement at 260 GHz, the result would be orders of magnitude smaller that 2. This is easily understood since the time scale of electronic Larmor precession at this large mw frequency is less than a picosecond, which is four orders of magnitude smaller than the motional time scale of $\tau = 7\,\mathrm{ns}$.

On the other hand, the actual motion of a lipid chain is not expected to be described by the translational diffusion with a single diffusion constant, which is assumed by the FFHS model. Indeed, molecular dynamics simulations of lipid bilayers show that a lot of thermal jiggling takes place on the time scale of half a picosecond, i.e., the electronic Larmor precession at 260 GHz. Of course, the amplitude of this thermal jiggling is small, and thus the amplitude of the spectral density at 260 GHz will also be small. But it will be a lot larger than the prediction of the FFHS model with $\tau = 7\,\text{ps}$. Whether it will be sufficiently large to produce an Overhauser enhancement of 2 units is hard to say.

11. Line 658: Having an average value of tau $\sim$ 7 ns, is it possible to calculate the diffusion coefficient using eq. (66)? How does it agree with the literature?

    This is an excellent point. I have now included the analysis that the reviewer asks for in the revised version of the paper. The added paragraphs are as follows:

    > In spite of the uncertainty in the estimated value of the distance parameter b, let us use τ and b in (67) to calculate the coefficient of relative translational diffusion. With $b = 0.482\,\text{nm}$ (Table 1, first row) and $\tau = 7.1\,\text{ns}$, we get $D = b^2/\tau = 0.033\,\text{nm}^2/\text{ns} = 33 \times 10^{-12}\,\text{m}^2/\text{s}$. Alternatively, with $b = 0.427\,\text{nm}$ (Table 1, second row) and $\tau = 7.1\,\text{ns}$, we find $D = 26 \times 10^{-12}\,\text{m}^2/\text{s}$. The first value corresponds to $B_1 = 6\,\text{G}$ and the second to $B_1 = 5\,\text{G}$.
    >
    > For comparison, the coefficient of lateral diffusion of phospholipids in oriented DMPC bilayers, as determined from pulsed field gradient NMR, is about $11 \times 10^{-12}\,\text{m}^2/\text{s}$ at 308 K, $20 \times 10^{-12}\,\text{m}^2/\text{s}$ at 323 K, and $27 \times 10^{-12}\,\text{m}^2/\text{s}$ at 333 K [7, fig. 5B, 0 mol% cholesterol]. As the temperature of the DNP measurements is closer to the middle value, our two estimates of D are seen to be larger by a factor of 1.65 and 1.3, respectively.
    >
    > However, the D of the FFHS model corresponds to the relative translational diffusion of the electronic and nuclear spins, i.e., $D = D_S + D_I$, where D_S and D_I denote the coefficients of translational diffusion of the two spin types. Disregarding all complicating factors, one could thus take $D_I = 20 \times 10^{-12}\,\text{m}^2/\text{s}$ from the literature value, and rationalize the values that we deduced from the width of the solid-effect DNP lines as implying either $D_S = 13 \times 10^{-12}\,\text{m}^2/\text{s}$ or $D_S = 6 \times 10^{-12}\,\text{m}^2/\text{s}$ for the diffusion coefficients of the free radical BDPA in the lipid bilayer. As the obtained numerical values are rather plausible, we conclude that the quantitative analysis of the J-band DNP spectrum leads to meaningful molecular properties. Without the theoretical framework developed in this paper, neither the molecular distance b nor the diffusion coefficient D would be accessible from a solid-effect DNP spectrum in the liquid state.

12. While the approach presented in the contribution is developed for the ideal case of one homogeneously broadened EPR line, which can be the case for BDPA and trityl-like radicals, how is the situation changed when anisotropy of g-factor and hyperfine interaction are introduced, e.g. for nitroxides or DPPH radicals?

    The additional complicating factors mentioned by the reviewer should certainly be taken into consideration when dealing with nitroxides or DPPH. As far as I am concerned, the effort to extend the presented theoretical framework such that it properly accounts for g-factor anisotropy and hyperfine interaction can only be justified by the need to quantify interesting experimental data. I therefore aim to establish contacts with the research group of Siegfried Stapf, where such experiments are performed. Although, as suggested by the analysis of Paper I and the current manuscript, X band may be a rather unfortunate frequency for extracting molecular information from the DNP spectrum, as the different spectral features exhibited at J band are not resolved.

Additionally, no critical grammar mistakes or typos were found in the text of the manuscript, except the one on line 293, where "states" instead of "sates" was, probably, meant. In some places, missed punctuation can be noticed, but without cutting or changing of any sense, e.g. missed comma before and/or after the adverb "however" or "which", etc.

The typo "sates" was corrected.

References

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