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Electron paramagnetic resonance approaches to study biologically relevant reactions: examples from amyloid aggregation to enzymes

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Propositions

Accompanying the dissertation

Electron Paramagnetic Resonance Approaches to Study Biologically Relevant Reactions: Examples from Amyloid Aggregation to Enzymes

1. Since methanethiosulfonate-based spin labels form dimers during long incubation and tend to detach during experiments and storage, it is better for amyloid-protein scientists to switch to maleimide-based labels as a more stable alternative. (Chapter 2 and 3 of this thesis)
2. The medium-component correlation time of α S in situ aggregation used by Zurlo et al. has the advantage of including aggregation intermediates, but its properties cannot be independently determined, resulting in additional free parameters and overfitting. The method used in thesis, with components experimentally determined from monomer and harvested fibrils, is preferable. (Zurlo et al., *PLOS ONE*, 16(1): e0245548, 2021 and chapter 3 of this thesis).
3. The exchange coupling value used for simulating MTSL-P2 dimer spectra is not accurate. A better understanding of EPR spectra can be achieved by measuring at different temperatures, to distinguish dynamic effects, in combination with multifrequency EPR. (Chapter 2 and 4 of this thesis)
4. Since ambiguities in distance distributions in chapter 5 are partly attributed to orientation selection effects, RIDME should be used as an additional technique to support and validate the structural information obtained by DEER. (Chapter 5 of this thesis and Milikisyants et al., *J Magn Reson.* 2009;201(1):48-56. doi:10.1016/j.jmr.2009.08.008)
5. EFM-EPR demonstrates the potential of EPR spectroscopy to detect spin–electric effects. Applying the method at high field will further enhance its resolution to electric-field-induced effects, thanks to enhanced separation of transitions from the spin Hamiltonian. (Fittipaldi et al., *Nature Materials*, 2019, 18, 329-334)
6. Site-directed-spin-labelling of stable, chemically produced α S oligomers, will allow to obtain structural information on them if combined with different degrees of diamagnetic dilution in cw-EPR and doubly labelled mutants for DEER studies. (Ortigosa-Pasqual et al., *ACS Chem. Neurosci.* 2023, 14, 17, 3192–3205).
7. The patient-specific molecular mechanisms underlying neurodegenerative diseases such as Alzheimer’s and Parkinson’s call for personalized therapeutic strategies, with RNA-based approaches offering greater promise than one-size-fits-all treatments based on antibodies or conventional small-molecule drugs. (Rabbani et al., *Eur. J. Neurosci.* 2025, 61(8):e70110).
8. Panarelli et al. suggest to use T-cycle EPR for the kinetic analysis of biochemical reactions. Given the abundance of other techniques to determine kinetics, the use of T-cycle EPR should be focused on identification to paramagnetic intermediates. (Panarelli et al., *Phys. Chem. Chem. Phys.* 2020, 22, 9487–9493)
9. Outdated but functional scientific equipment and textbooks should routinely be redistributed to underfunded institutions in developing countries, where they can still significantly contribute to research and education.

Leonardo Passerini
Leiden, September 2nd, 2025