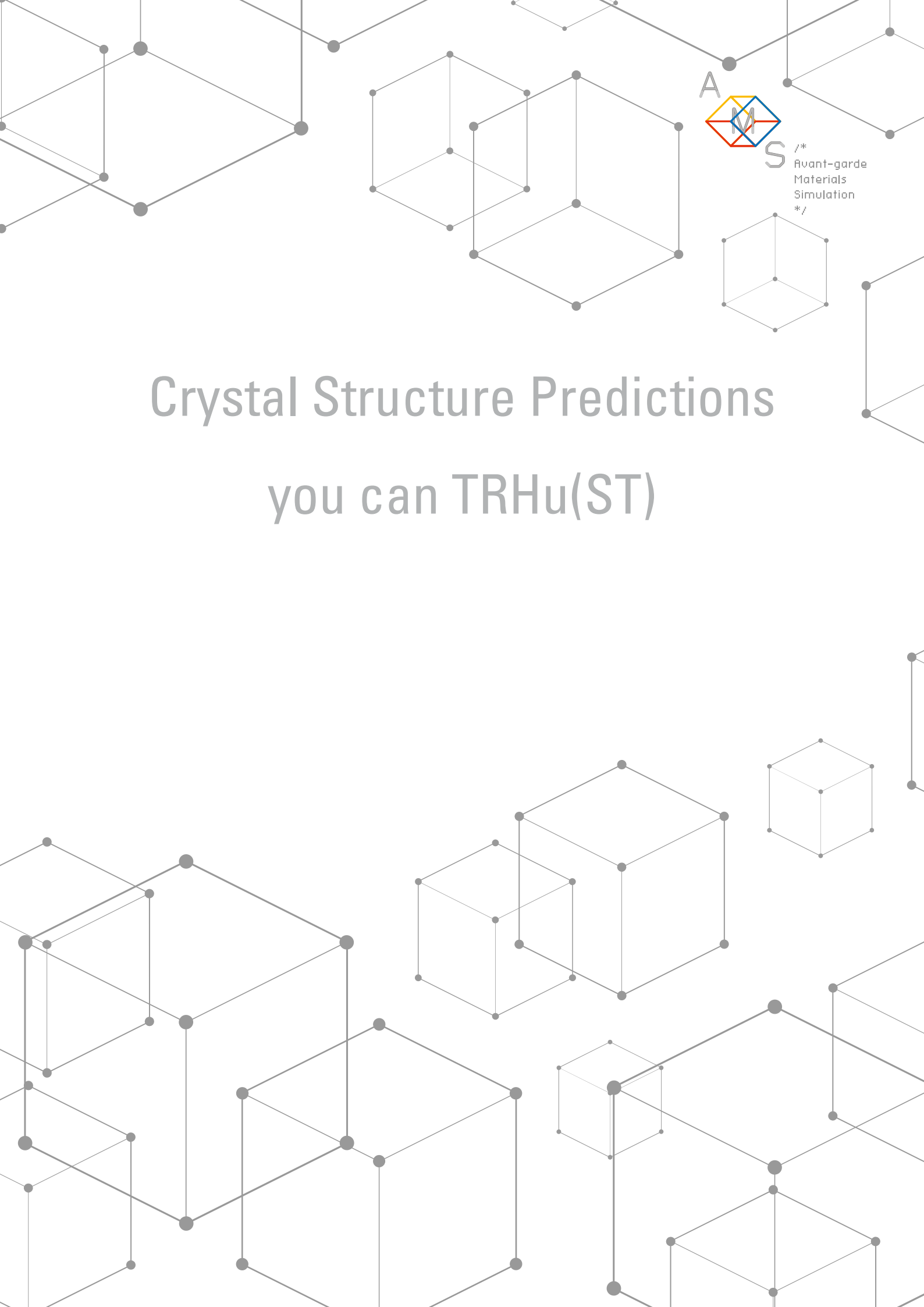

Crystal Structure Predictions you can TRHu(ST)

Dr. Marcus Neumann and his team of researchers at Avant-garde Materials Simulation (AMS), in partnership with leading experts in academia and key collaborators across the pharmaceutical industry, have redefined the state-of-the-art in modeling and predicting the free energy of crystals. Their work on the novel TRHu(ST) method, which has now published in *Nature*, shows that crystal form stability can be reliably and affordably predicted under real-world temperature *and* humidity conditions.[1]

'The pace of scientific advancement for real-world applications through this unique partnership with AMS is truly astounding. This is most evident in the progress reported on the predictions relating the impact of water on crystal forms and their relative thermodynamic stability,' says Ahmad Sheikh, Ph.D., co-author and Global Head of Molecular Profiling and Drug Delivery at AbbVie, a global biopharmaceutical company.

AMS, a pioneer in organic Crystal Structure Prediction (CSP) and developer of the world leading GRACE software for CSP, has spearheaded major developments in the field over the last 15 years. Powered by scientific curiosity and deep technical expertise, AMS is uniquely committed to driving innovation *with* industry that will lead from CSP to in silico materials design *for* industry. Dr. Marcus Neumann points out, 'We owe a fair part of our success to the visionaries among our customers who have enabled us to create an industrial working environment with an academic touch that promotes creativity based on core values such as honesty, integrity, perseverance, team-spirit and genuine care for people and the environment.'

Physical properties (stability, solubility, etc.) critical to the performance of pharmaceutical and functional materials are known to strongly depend on the solid-state form and environmental factors, such as temperature and relative humidity. Recognizing that late appearing, more stable forms can lead to disappearing polymorphs and potentially market withdrawal of a life-saving medicine (*c.f.* ritonavir[2], rotigotine[3]), the pharmaceutical industry has heavily invested in solid form screening platforms. CSP is also now used by most large pharmaceutical companies to complement experimental approaches, helping to ensure that the stable form has been found or to assess the risk posed by an unobserved more stable form. The ensuing selection of the most preferred crystalline form, along with the control strategies to ensure that form is produced exclusively and maintained throughout downstream processing and the product shelf life, hinge on a proper understanding of form stability over a range of processing and storage conditions.

Quantitatively measuring the free energy differences between crystalline forms is no small challenge, however. Metastable crystal forms can be difficult to prepare in pure form and they are frequently susceptible to converting to more stable forms. Thus, having the ability to calculate free energies means that the risks posed by physical instability can be understood and mitigated for all systems, including those that are experimentally intractable. The lack of reliable experimental benchmark data has actually been a major bottleneck in developing computational methods for accurately predicting solid-solid free energy differences. Reports in the literature are sparse and much of the experimental data on free energy determinations for molecules of pharmaceutical interest is simply not in the public domain. To overcome this challenge, AMS has joined with experts in academia and many pharmaceutical companies to compile the first ever reliable experimental benchmark of solid-solid free energy differences for chemically diverse, industrially relevant systems.

Armed with reliable experimental data upon which new computational methods can be tested and validated, AMS has substantially improved both the accuracy and affordability of free-energy calculations with the introduction of a new composite method, TRHu(ST) 23, for the calculation of Temperature- and Relative Humidity-dependent free-energies with STandard deviations.

TRHu(ST) 23 achieves high accuracy by combining dispersion-inclusive density functional theory, many-body dispersion interactions and vibrational contributions to the free energy with an additional single-molecule energy correction. The affordability of the method has been improved by blending force field and ab initio calculations to reduce the CPU time requirements of phonon calculations.

Statistical errors for computed free energies have been addressed, also for the first time, with standard errors of just 1–2 kJ mol^{-1} now possible for complex, industrially relevant compounds.

The development of the TRHu(ST) 23 method would not have been possible without the long-time relationships AMS has forged with trusted customers across the pharmaceutical industry and academia. The interdisciplinary nature of this collaboration has not only accelerated the development of cutting-edge methods and software, but also ensured their rapid uptake by the pharmaceutical industry.

Professor Alexandre Tkatchenko, University of Luxembourg, concurs, 'I am thrilled to see how computational methods developed in my academic group have been quickly adopted to reliably predict the energetics of drug crystal forms in the pharmaceutical industry in a matter of years, breaking the traditional barrier between research and industrial innovation.'

The ability to predict crystal form stability under real-world conditions is expected to transform how solid forms are selected and processes are designed in industry. Priv.-Doz. Dr. Doris Braun, University of Innsbruck, agrees, adding 'By effectively narrowing the gap between the demands of experimentation and computational capabilities, this progress empowers greater control over the selection of industrial crystal forms, ultimately enhancing the safety of (pharmaceutical) products.'

ABOUT AVANT-GARDE MATERIALS SIMULATION

Avant-garde Materials Simulation is a world-leading provider of scientific software (GRACE) and contract research services for crystal structure prediction. To learn more about AMS, please visit www.avmatsim.eu.

Contact details:

Marcus Neumann, CEO
Avant-garde Materials Simulation Deutschland GmbH
Email: pr@avmatsim.eu
Phone: 004915752425521

Additional Material can be requested at pr@avmatsim.eu.

References:

1. Firaha, D., et al. Predicting crystal form stability under real world conditions. Nature. Published November 8, 2023. doi: 10.1038/s41586-023-06587-3.
2. Chemburkar, S. R., et al., Dealing with the Impact of Ritonavir Polymorphs on the Late Stages of Bulk Drug Process Development. Org. Process Res. Dev., 2000, 4, 413–417.
3. Chaudhuri, K. R., Crystallisation within transdermal rotigotine patch: is there cause for concern? Expert Opin. Drug Delivery, 2008, 5, 1169–1171.