WHAT IS THE SIGNAL-TO-NOISE RATIO OF PHASE CONTRAST IMAGING? CAN IT BE INFINITE?

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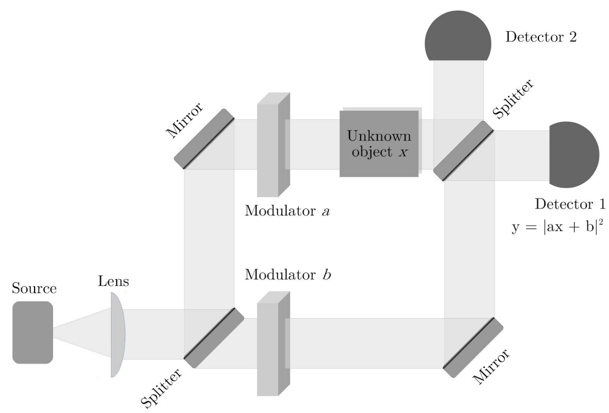
KEY WORDS: Phase contrast

ABSTRACT: In 1902, Siedentopf and Zsigmondy described the "ultramicroscope" [1], leading to a 1925 Chemistry Nobel. Decades later, Frits Zernike demonstrated "phase contrast" microscopy, [2, 3], for which he was awarded the 1953 Physics Nobel. It may not be immediately obvious why adding a bright background to a Nobel-prize-winning background-free measurement merits another Nobel; certainly, adding background light to an optical measurement adds additional noise [4]. The critical detail is that Zernike added a bright *coherent* background, which adds both additional noise and additional signal. How much signal, and how much noise?



A naive derivation leads us to a curious result [5]. If we happen to choose a phase-contrast background field that perfectly cancels our signal field, then our noise goes to zero, but our signal does not! We have no expectation that "infinite" signal-to-noise ratio allows perfect inference of a sample's optical properties, but it's highly suggestive, and interesting to explore what inference it *does* allow. If the "infinite" signal-to-noise ratio case actually yields superior inference, one could imagine imaging methods that tune a spatial light modulator in one arm of an interferometer to cancel the fields transmitted by an unknown object in the other arm (Figure 1).

Does "infinite SNR" actually indicate a high-precision measurement? If so, do we benefit from "hunting" for perfect destructive interference at Detector 1 in Figure 1, or would we be better off searching a diverse set of modulator amplitudes and phases? We explore theses questions and others in the context of a maximum-likelihood inference problem.

[1] Uber Sichtbarmachung und Größenbestimmung ultramikoskopischer Teilchen, mit besonderer Anwendung auf Goldrubingläser; H. Siedentopf and R. Zsigmondy; Ann. Phys., 315: 1-39 (1902) https://doi.org/10.1002/andp.19023150102
[2] Das Phasenkontrastverfahren bei der mikroskopischen Beobachtung; F. Zernike; Z. technische Physik vol 16, p454–457 (1935) https://doi.org/10.1038/ncb1942
[3] Phase contrast, a new method for the microscopic observation of transparent objects; F. Zernike; Physica, Vol 9, p686-698 (1942) https://doi.org/10.1016/S0031-8914(42)80035-X
[4] Handbook of Biological Confocal Microscopy, third edition; J. Pawley; Springer US, ISBN 978-0-387-25921-5, Chapter 2 (2006) https://doi.org/10.1007/978-0-387-45524-2
[5] Andrew G. York, & Sanjay R. Varma. andrewgyork.github.io/adaptive_interference_inference/ (2018) http://doi.org/10.5281/zenodo.1463274