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Winning the battle of Signal vs Noise

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The success or failure of any structure determination effort is dictated by the signal-to-noise ratio, so a quantitative understanding of both signal and noise is needed to have the best chance of success and to avoid wasted effort on samples that simply aren't good enough. There are three main hurdles to every structure determination effort: the Phase Problem, the Amplitude Problem, and the R-factor Gap. The Phase Problem is hampered mainly by sources of relative error, such as shutter jitter, incident beam flicker, sample vibration, detector calibration, and non-isomorphism, including that induced by radiation damage. High multiplicity is the best way to combat relative error, but it must be "true" multiplicity, where no spot is ever measured the same way twice. Conversely, the Amplitude Problem, also known as "poor diffraction" is dominated by the background under weak spots, and the finite number of photons appearing in a weak spot before the crystal dies. This radiation damage limit can be outrun with femtosecond pulses, but even X-ray Free Electron Lasers (XFELs) cannot make a disordered crystal diffract. Screening for order is best performed at synchrotrons. The R-factor Gap is the large discrepancy between ($R_{\text{cryst}}/R_{\text{free}}$) and the error in the data itself ($R_{\text{merge}}/R_{\text{meas}}$). Closing this Gap requires a better understanding of dynamics, which itself is relevant to function. Overall, the Three Hurdles can be overcome by improved methodology, better sample preparation, and improved macromolecular models that will open new doors in structural biology.

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