Using AlphaFold2 to model TA system protein-protein interactions: A case study with ParDE complexes

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"Type II" Toxin-antitoxin (TA) systems pair a protein toxin with a protein antitoxin through an extensive interface, typically spanning more than 1200 Å2, accounting for more than 20% of the available surface of each protein. These pairings are highly co-evolved, such that cognate interactions are strictly maintained even when multiple types of the same TA family are present in the same cell. Physiological functions of chromosomal TA systems remain unclear, but an "anti-addiction" model posits a chromosomal antitoxin cross-reacting and neutralizing an exogenously-derived toxin, such as encoded by a phage. While plausible, specific examples are scarce. Investigations of the potential for cross-interactions are limited by the relatively small pool of available structures as compared to the varied complexity of the interacting interfaces. We would like to apply advances in prediction models, especially AlphaFold2, to broaden the pool of available highly reliable interfaces. We initiated this using seven available crystal structures of the ParDE type of TA system and comparing these to AlphaFold2 predictions. Remarkable, the predictions match exceptionally well despite the divergent sequence identity between complexes. This highlights how structural conservation can dominate predictions to overcome sequence diversity. This workflow provides a viable means of larger scale Type II TA system protein-protein interface predictions, facilitating studies of cross-reactivity and other sequence co-evolution models.