

convince most computational biologists, in addition to the competition organizers, that the horizon had been reached: protein structure prediction is now considered “solved” by AlphaFold2 [8].

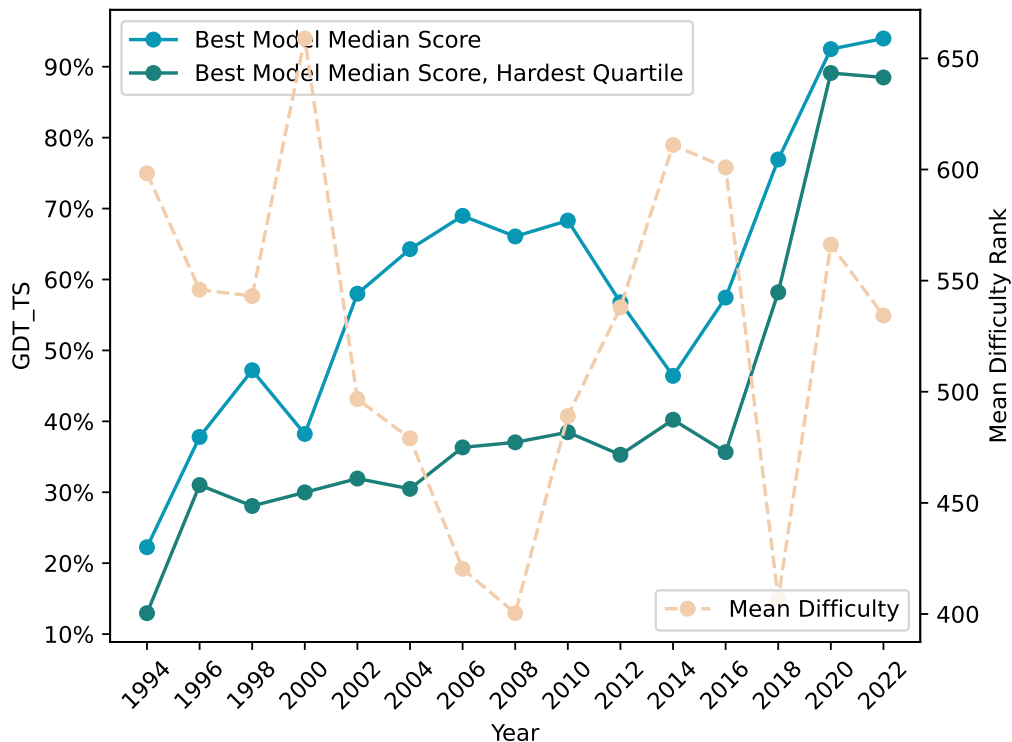


Figure 1.1: Historical median GDT_TS score of the best-performing model in each CASP competition. The blue line depicts median model GDT_TS scores aggregated across all folding targets. The green line depicts median GDT_TS scores for the most difficult quartile of candidate targets. The tan line reports the mean difficulty of candidate proteins within each competition relative to their ranked difficulty across all years.

How did this happen? How was an outside group of machine learning researchers able to surpass, within a four-year span, the collective efforts of hundreds of computational biologists spanning decades, to solve one of the most difficult problems in biology? More importantly, how might we systematize the principles underlying this triumphant application of machine learning to also make progress