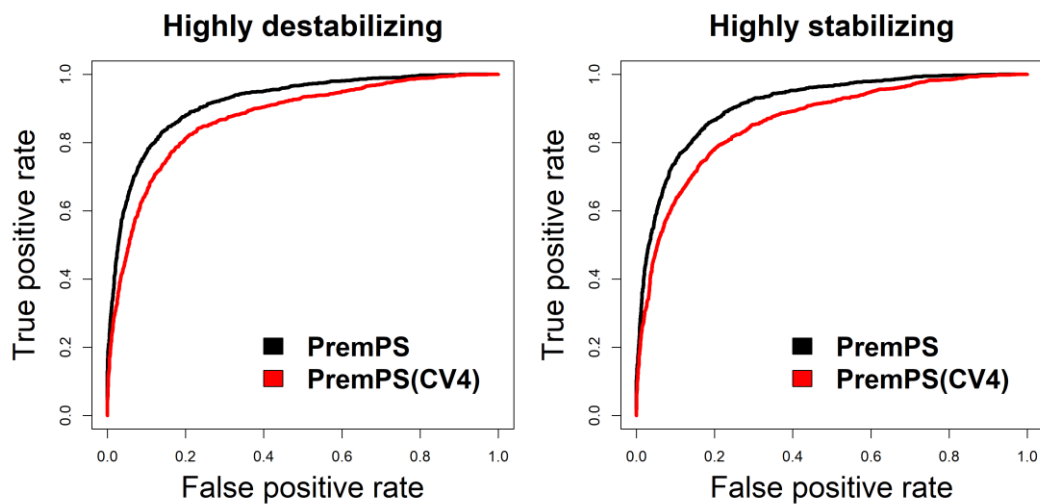


### A. Test on S5296



### B. Test on S921

Method	Highly destabilizing		Highly stabilizing	
	AUC	MCC	AUC	MCC
PremPS	0.88	0.61	0.87	0.58
INPS3D	0.83	0.54	0.79	0.43
PoPMuSiC	0.81	0.49	0.67	0.21
FoldX	0.80	0.49	0.72	0.35
mCSM	0.75	0.44	0.61	0.14

### C.

Category		Definition	# of mutations	
			S5296	S921
Highly destabilizing	Positive	$\Delta\Delta G_{exp}$ (kcal mol <sup>-1</sup> ) $\geq 1$	1364	360
	Negative	$\Delta\Delta G_{exp}$ (kcal mol <sup>-1</sup> ) $< 1$	3932	561
Highly stabilizing	Positive	$\Delta\Delta G_{exp}$ (kcal mol <sup>-1</sup> ) $\leq -1$	1364	109
	Negative	$\Delta\Delta G_{exp}$ (kcal mol <sup>-1</sup> ) $> -1$	3932	812