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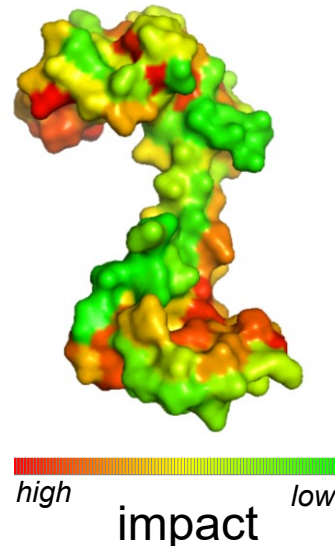
CALM1 Challenge Prediction: Evolutionary Action Approach

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Evolutionary Action
(Katsonis and Lichtarge, 2014)



Protein:	Calmodulin
Gene:	<i>CALM1</i>
Length:	149 aa
Structure:	4DJC
Sequences:	187

Evolutionary Action Model

The diagram shows the equation $\varphi = f(\gamma)$ centered on the slide. A line extends from the word "Phenotype" to the left of the equation, connecting to the symbol φ . Another line extends from the word "Genotype" to the right of the equation, connecting to the symbol γ inside the function $f(\gamma)$.

$$\varphi = f(\gamma)$$

Phenotype

Genotype

Evolutionary Action Model

$$\Delta\varphi \approx \frac{\partial f}{\partial \gamma_i} \cdot \Delta\gamma_i$$

Phenotype change

Evolutionary gradient

Genotype change

The diagram shows the equation $\Delta\varphi \approx \frac{\partial f}{\partial \gamma_i} \cdot \Delta\gamma_i$. Three labels with leader lines point to parts of the equation: 'Phenotype change' points to $\Delta\varphi$, 'Evolutionary gradient' points to $\frac{\partial f}{\partial \gamma_i}$, and 'Genotype change' points to $\Delta\gamma_i$.

Evolutionary Action Model

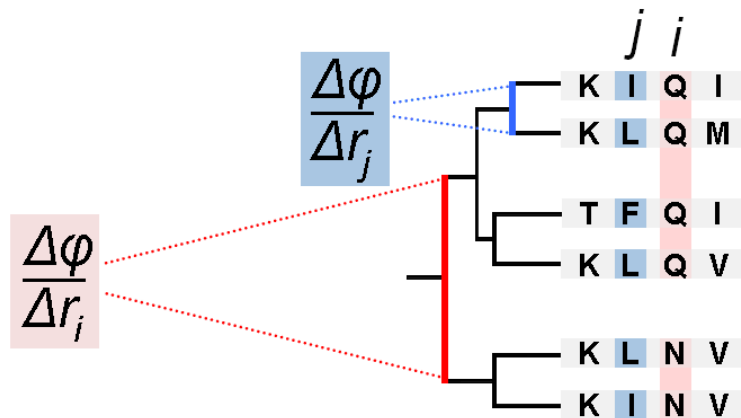
$$\Delta\varphi \approx \frac{\partial f}{\partial \gamma_i} \cdot \Delta\gamma_i$$

Phenotype change

Evolutionary gradient

Genotype change

Evolutionary Trace Ranks



Evolutionary Action Model

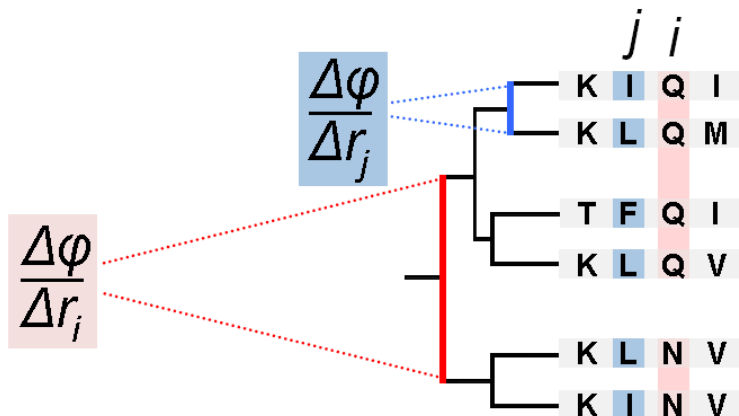
$$\Delta\varphi \approx \frac{\partial f}{\partial \gamma_i} \cdot \Delta\gamma_i$$

Phenotype change

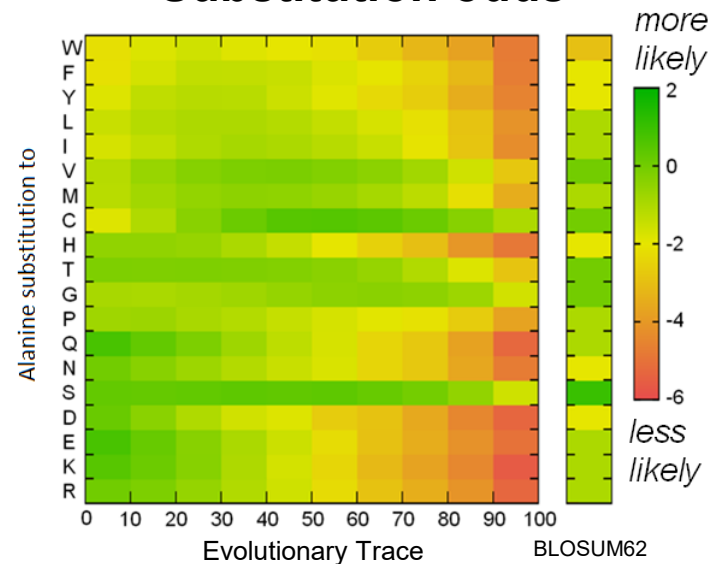
Evolutionary gradient

Genotype change

Evolutionary Trace Ranks

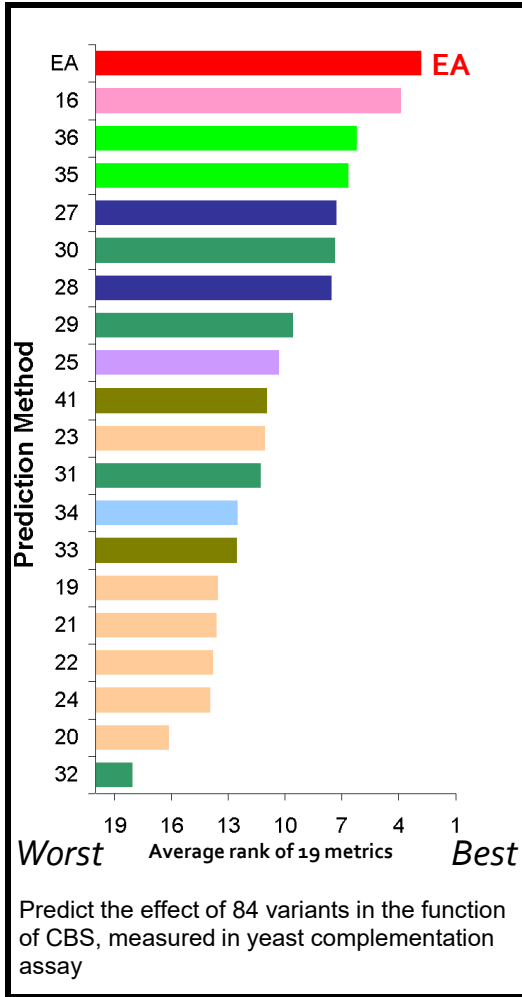


Substitution odds



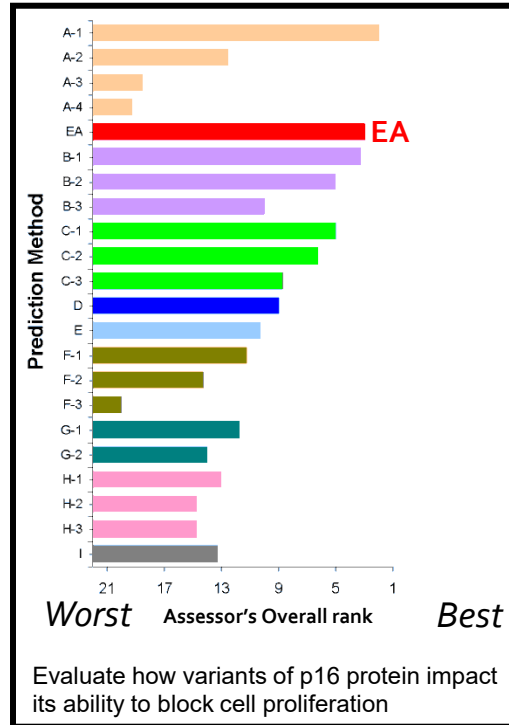
Evolutionary Action at Past CAGI Contests

Cystathionine β -Synthase (2011)

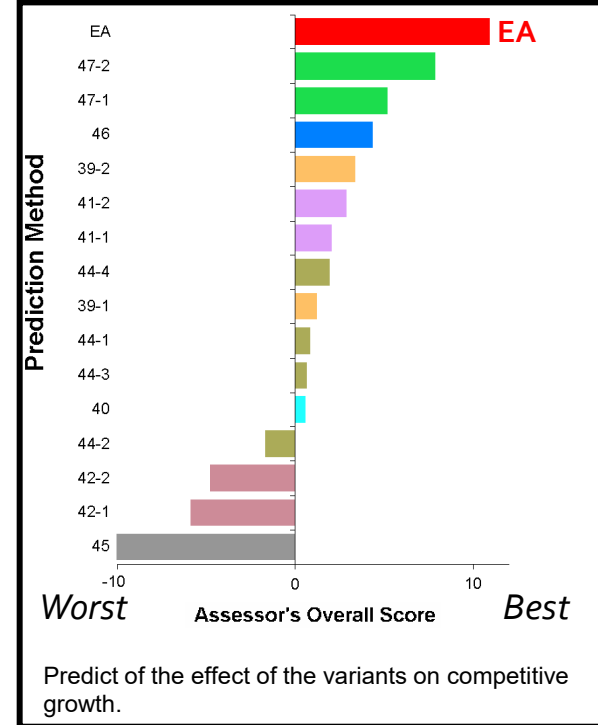


Katsonis P, Lichtarge O, Human Mut, 2017

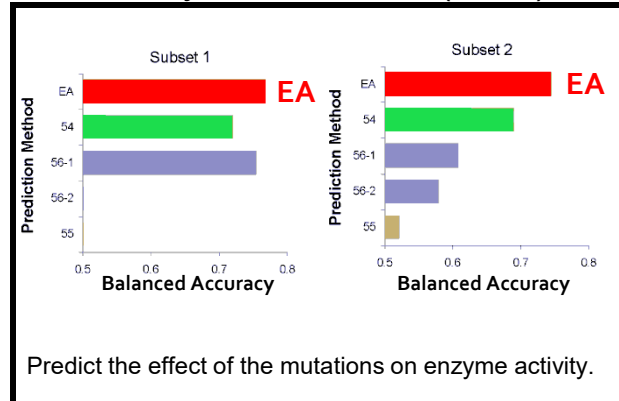
p16 (2013)



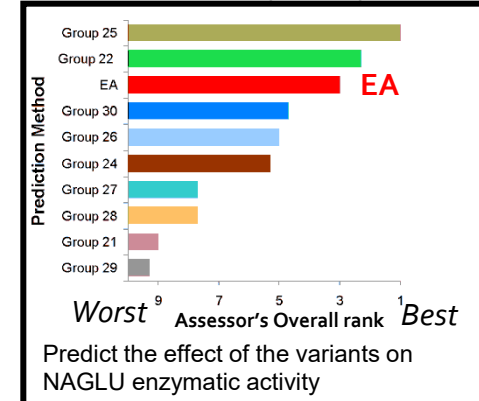
SUMO Ligase (2016)



Pyruvate Kinase (2016)



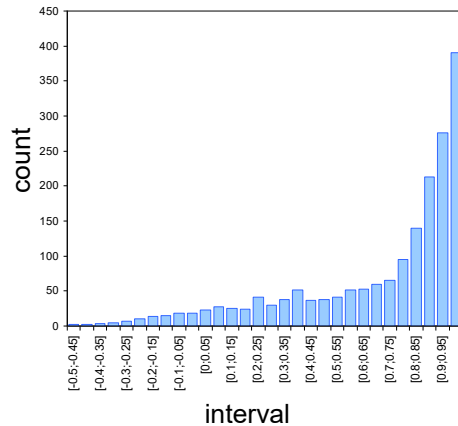
NAGLU (2016)



CALM1 Challenge: Approach

Predict the competitive growth score of 1,813 CALM1 variants

Distribution of
experimental values



Generate numbers that
fit the distribution of
experimental values

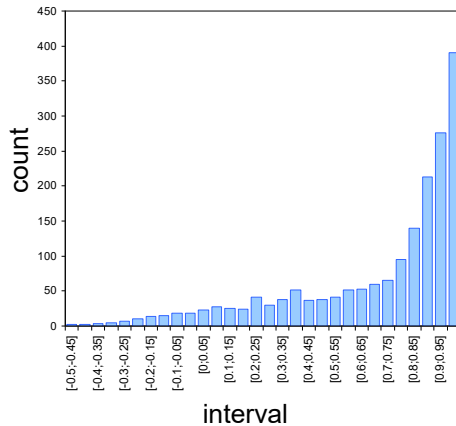


Match inversely these
numbers with EA scores

CALM1 Challenge: Approach

Predict the competitive growth score of 1,813 CALM1 variants

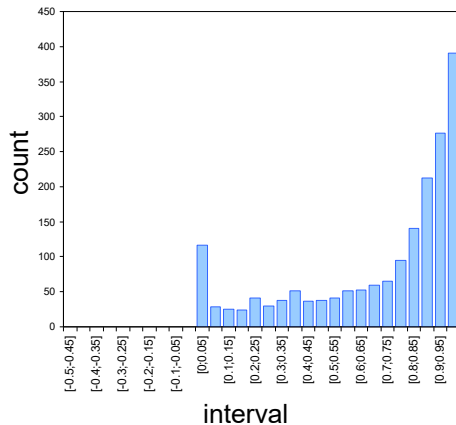
Distribution of experimental values



Generate numbers that fit the distribution of experimental values

Match inversely these numbers with EA scores

Submission 1



Generate numbers that fit the distribution of experimental values

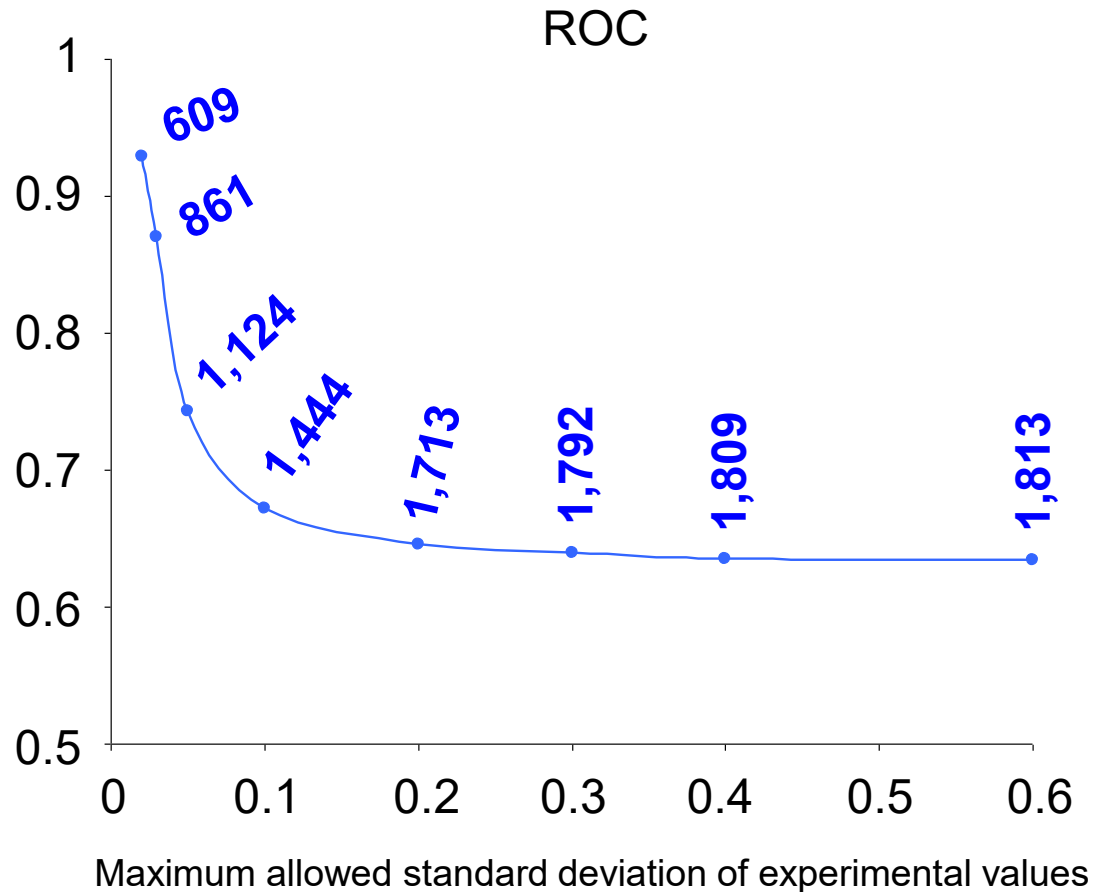
Match inversely these numbers with EA scores

Submission 2

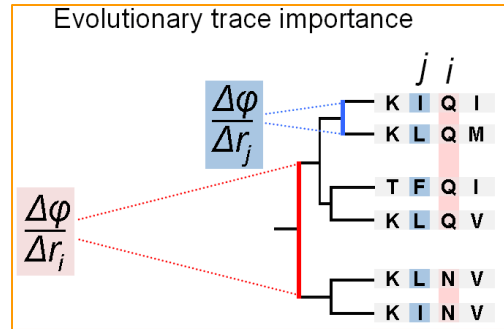
CALM1 Challenge: Results

	Pearson's, r	RMSD	ROC
Submission 1	0.17	0.41	0.63
Submission 2	0.16	0.39	0.63

CALM1 Challenge: Results

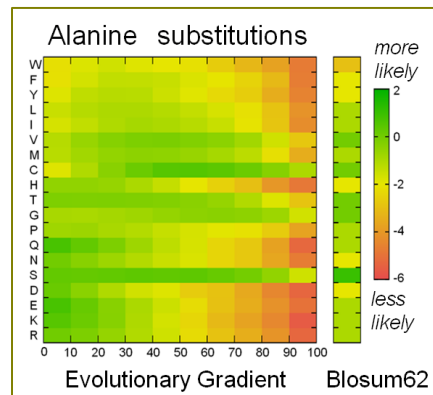


Summary



Phenotype
change

$$\Delta \varphi \approx \frac{\partial f}{\partial \gamma_i} \cdot \Delta \gamma_i$$



EA:

- Uses homology information
 - untrained method
 - no protein function data
 - does not rely on structure data
- Does not account for epistasis