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DUET

DUET: a server for predicting effects of mutations on protein stability via an integrated computational approach

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Abstract

Cancer genome and other sequencing initiatives are generating extensive data on non-synonymous single nucleotide polymorphisms (nsSNPs) in the human and other genomes. In order to understand their impacts on the structure and function of the proteome, as well as to guide protein engineering, robust *in silico* methodologies are required to study and predict the effects of nsSNPs on protein stability. Despite the diversity of available computational methods in the literature, none has proven robust and dependable on its own under all scenarios where mutation analysis is required.

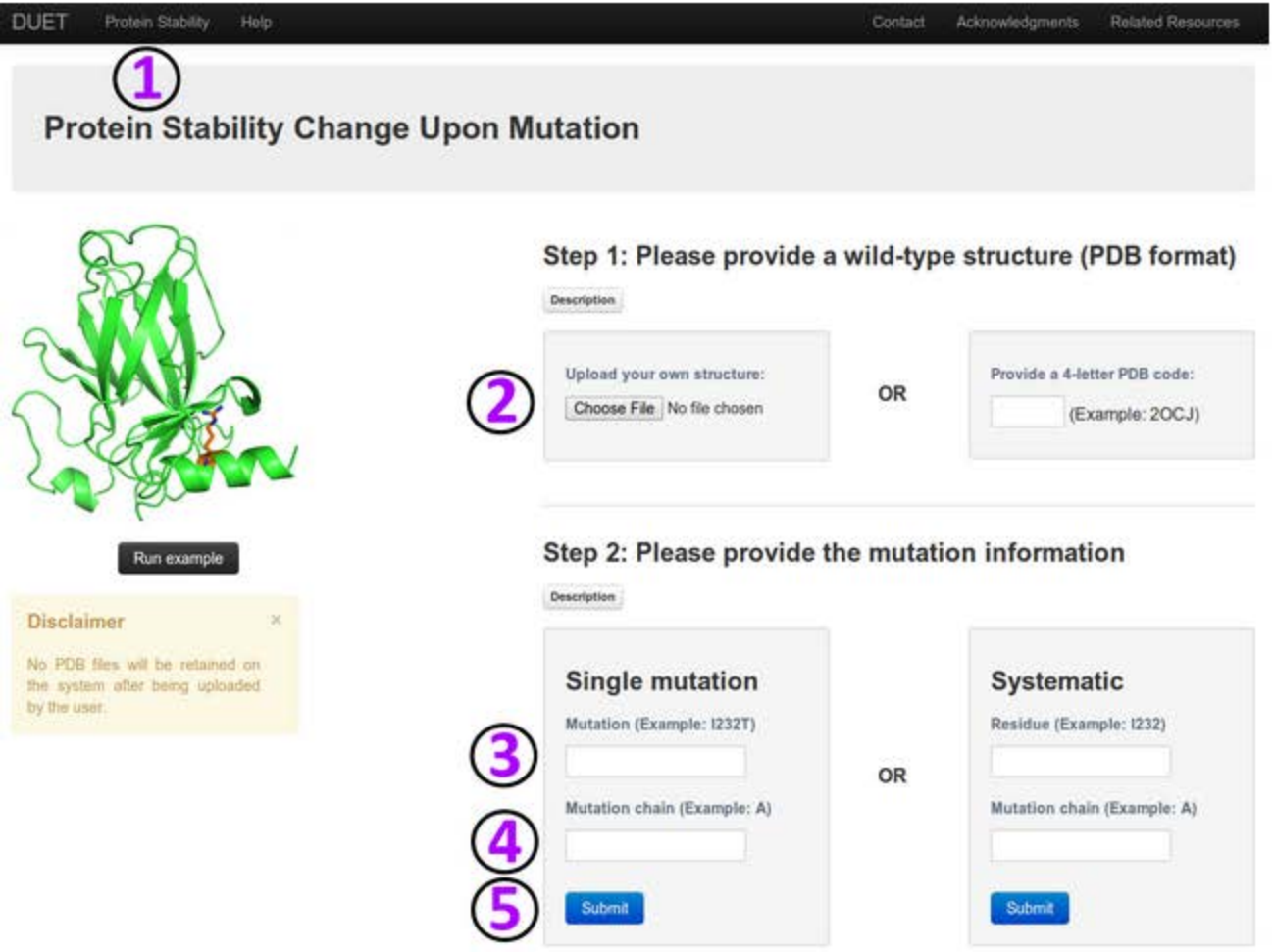
Here we present DUET, a web server for an integrated computational approach for studying missense mutations in proteins. DUET consolidates two complementary approaches (mCSM and SDM) in a consensus prediction, obtained by combining the results of the separate methods in an optimised predictor using Support Vector Machines (SVM). We demonstrate that the proposed method improves overall accuracy of the predictions in comparison with either method individually and performs as well as or better than similar methods.

About DUET

DUET predicts the change in protein stability ($\Delta\Delta G$) upon the introduction of a single mutation by combining two distinct previously published approaches:

- **SDM**: a statistical potential energy function developed by Topham et al. (1997) to predict the effect that single nucleotide polymorphisms will have on the stability of proteins.
- **mCSM**: a predictive model using graph based signatures to represent the three dimensional protein environment developed by Pires et al. (2014) to predict the effects of single mutations on protein stability, and affinity for DNA and protein binding partners

Submission page

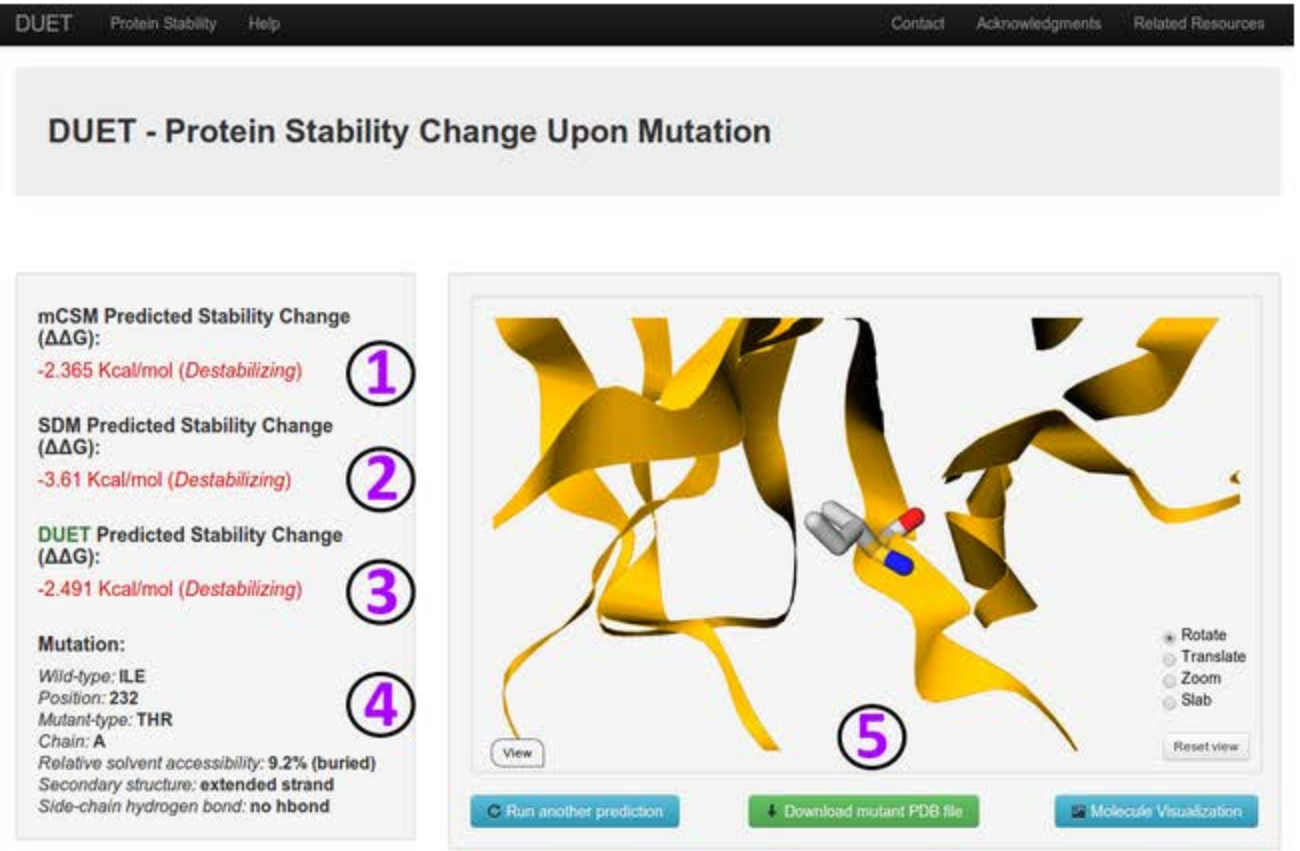


How to run a prediction

To run a prediction:

- Click on "Protein Stability" **(1)** to open the submission page.
- Provide the protein structure either by uploading your own structure file of the wild type protein **(2)**, which must comply with the PDB format, or by providing a 4-letter PDB code.
- The single mutation or the residue for systematic analysis must be identified **(3)**. The position consists of the wild-type residue (using the one letter amino acid code), the sequence number of the residue in the PDB file, and (for single mutation prediction) the amino acid residue you would like it mutated to (also in one letter amino acid code).
- As PDB files may contain multiple chains, the chain which you would like to introduce the mutation into also needs to be identified **(4)**.
- You are then ready to submit your query for analysis **(5)**.

Results page



Results - Single mutation

Your results for a single mutation will be displayed once computations are completed. The results will display the predicted change in folding free energy upon mutation (ΔΔG in Kcal/mol). A positive value (and red writing) corresponds to a mutation predicted as destabilising; while a negative sign (and blue writing) corresponds to a mutation predicted as stabilising. Complementary information also displayed include:

- The mCSM (1) and SDM (2) predicted protein stability changes are displayed individually.
- The DUET prediction, using both SDM and mCSM, is displayed at (3).
- A summary of the mutation is presented (4) highlighting the wild-type residue and position number, the mutation and its three dimensional environment.
- The protein and mutation can also be visualised (5), or a PDB file of the mutant downloaded for viewing in your preferred molecular visualisation software. Please note that neither mCSM nor SDM require or perform minimisation of the mutant structure.

Results page

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Protein Stability Change Upon Mutation

Predicted Stability Change (ΔΔG):

10 records per page (1) (2) (3) (4) (5) (6)

Index	Chain	Wild Residue	Residue Position	Mutant Residue	RSA (%)	mCSM predicted ΔΔG	SDM predicted ΔΔG	DUET predicted ΔΔG
1	A	I	232	A	9.2	-2.372	-1.906	-2.397
2	A	I	232	V	9.2	-1.408	-1.064	-1.179
3	A	I	232	L	9.2	-0.959	-1.068	-0.691
4	A	I	232	G	9.2	-2.871	-2.464	-3.015
5	A	I	232	S	9.2	-2.694	-2.437	-2.83
6	A	I	232	W	9.2	-1.759	-1.008	-1.549
7	A	I	232	T	9.2	-2.365	-2.273	-2.459
8	A	I	232	Q	9.2	-1.943	-2.153	-1.986
9	A	I	232	E	9.2	-2.167	-2.431	-2.277
10	A	I	232	C	9.2	-1.509	-1.052	-1.286

Showing 1 to 10 of 19 entries ← Previous 1 2 Next →

C Run another prediction

Results - Systematic

Your results for a systematic prediction will be displayed in a table format with the following information:

- Option to limit number of records been displayed (1).
- Mutant residue code (2).
- Residue relative solvent accessibility (RSA) (3).
- The mCSM (4), SDM (5) and DUET (6) predictions.

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Contact

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Get in touch

Have you come across a problem on the website or have any requests or suggestions? Please report it here!

Name

Email address

(optional)

Submit

Getting in touch

In case you experience any trouble using DUET or have any suggestions or comments, please do not hesitate in contacting us (1) either via e-mail or through the online form.