



IMMUNE EPITOPE DATABASE
AND ANALYSIS RESOURCE

TCRmatch

Predicting T-cell receptor specificity based on sequence similarity to previously characterized receptors

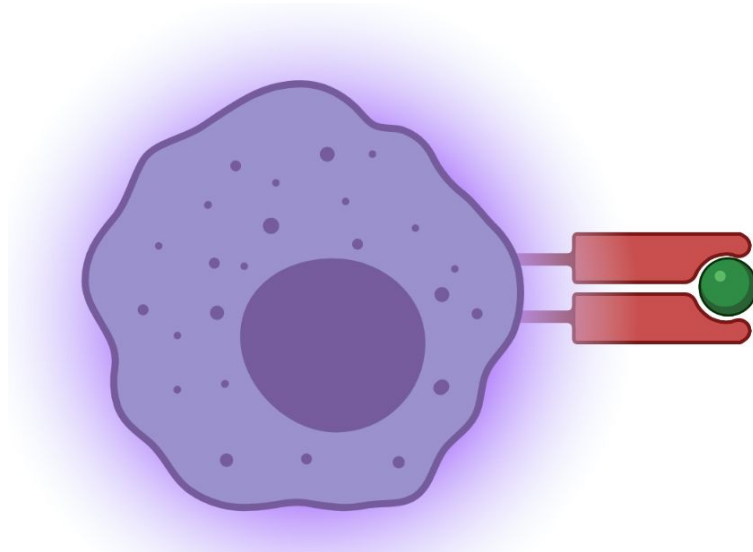
Presented by
Raphael Trevizani

TCRmatch

- MHC presenting an antigen to a T-Cell
- T-cell receptor: α/β units
- Somatic recombination
- Each chain: 3 CDRs
- CDR3 β
 - Most variable
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- Repertoire sequencing
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- How to find the most similar sequences?

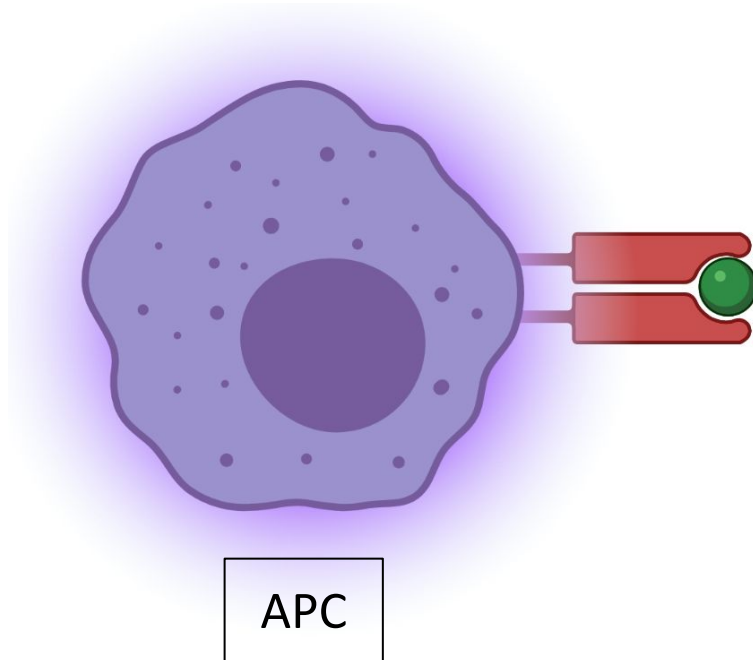
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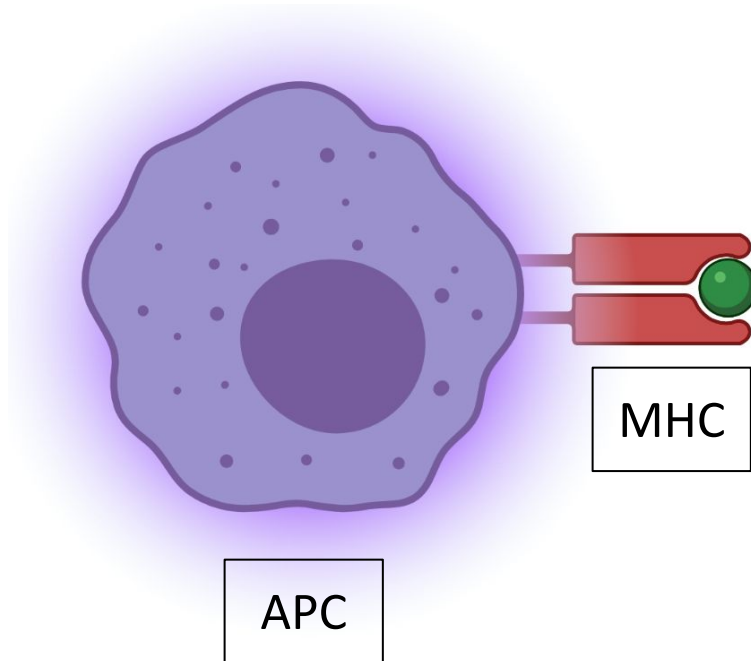
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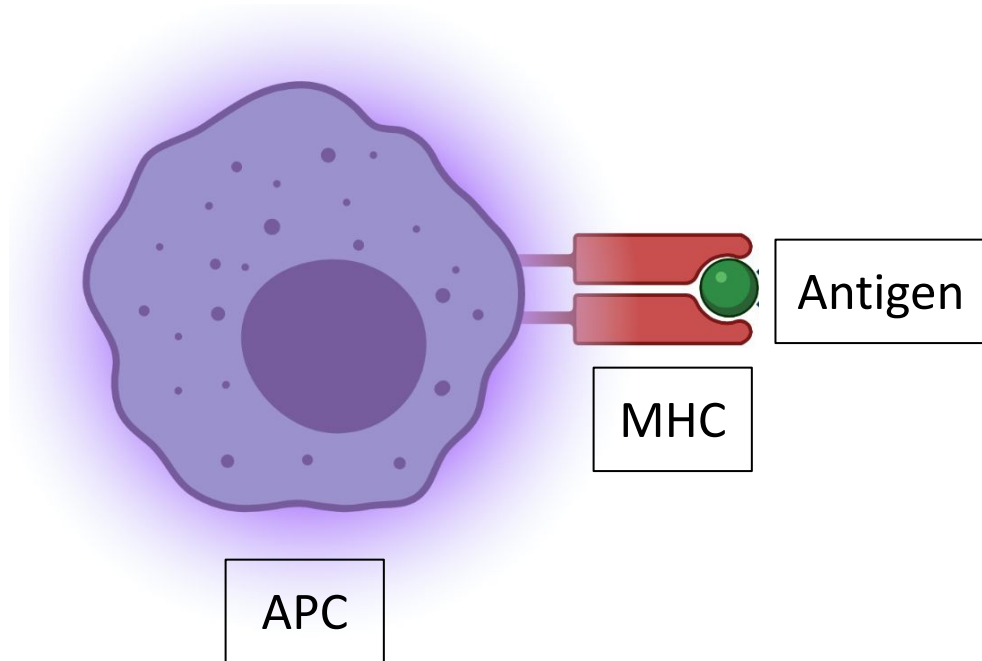
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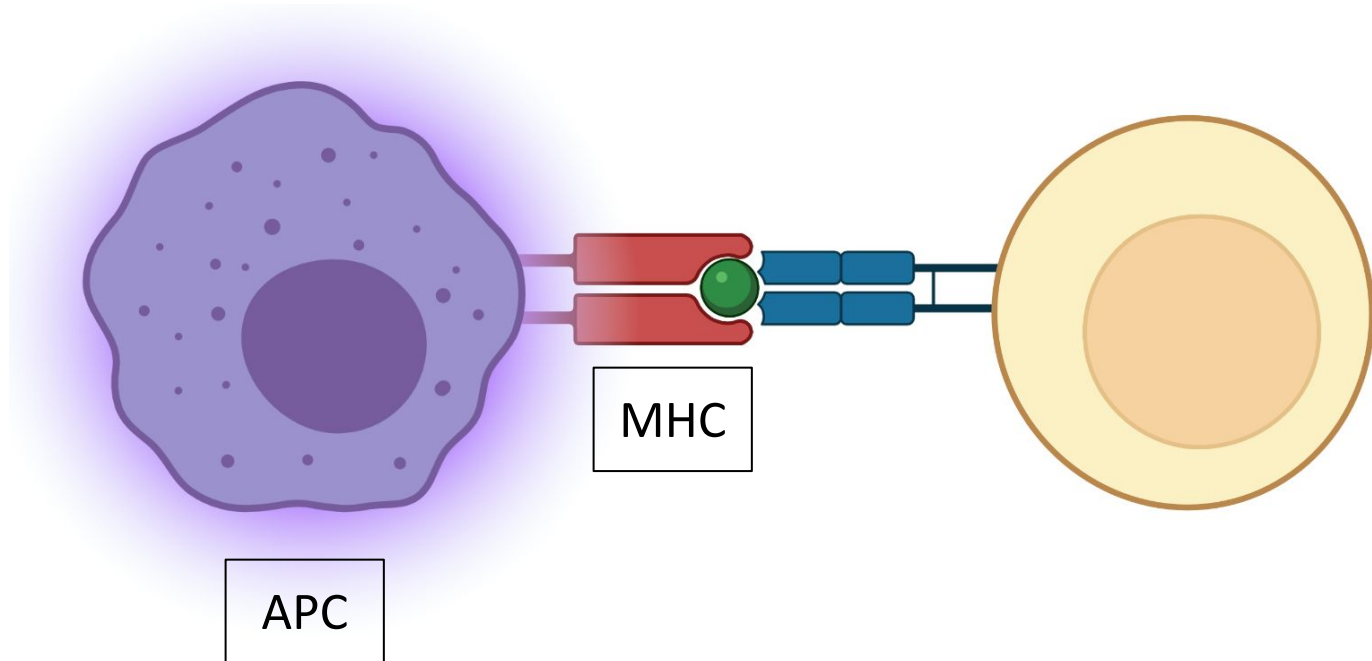
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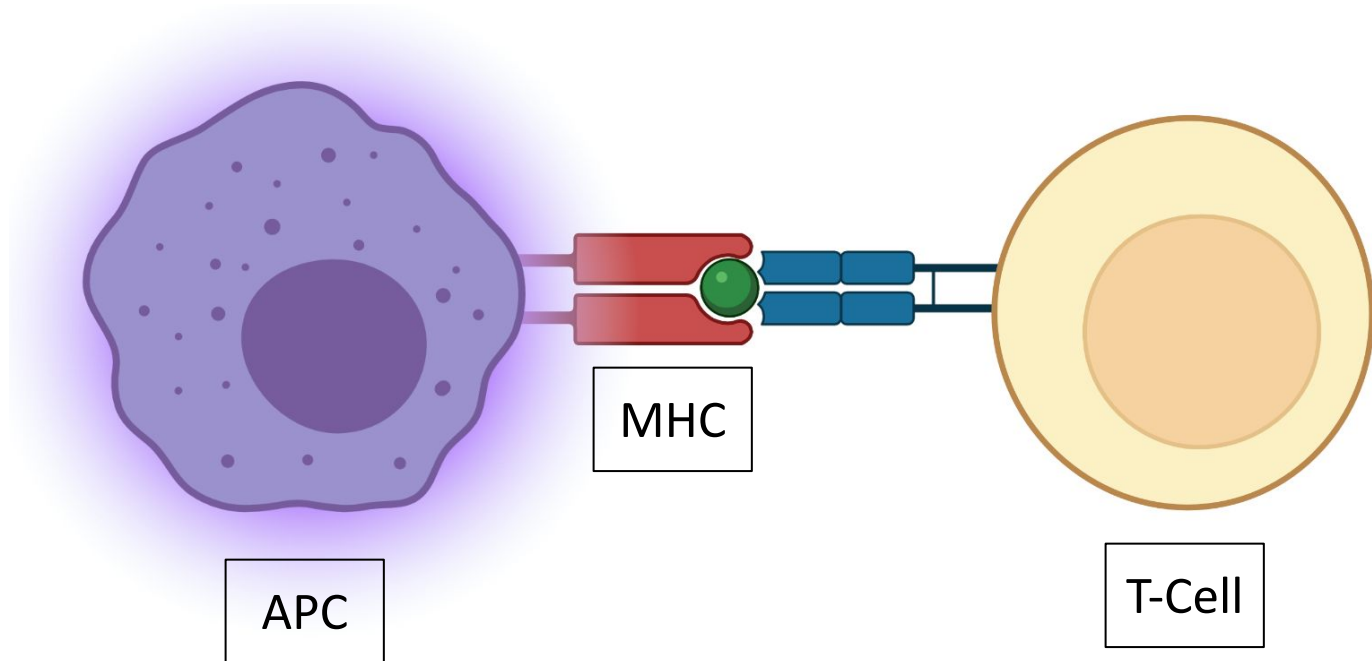
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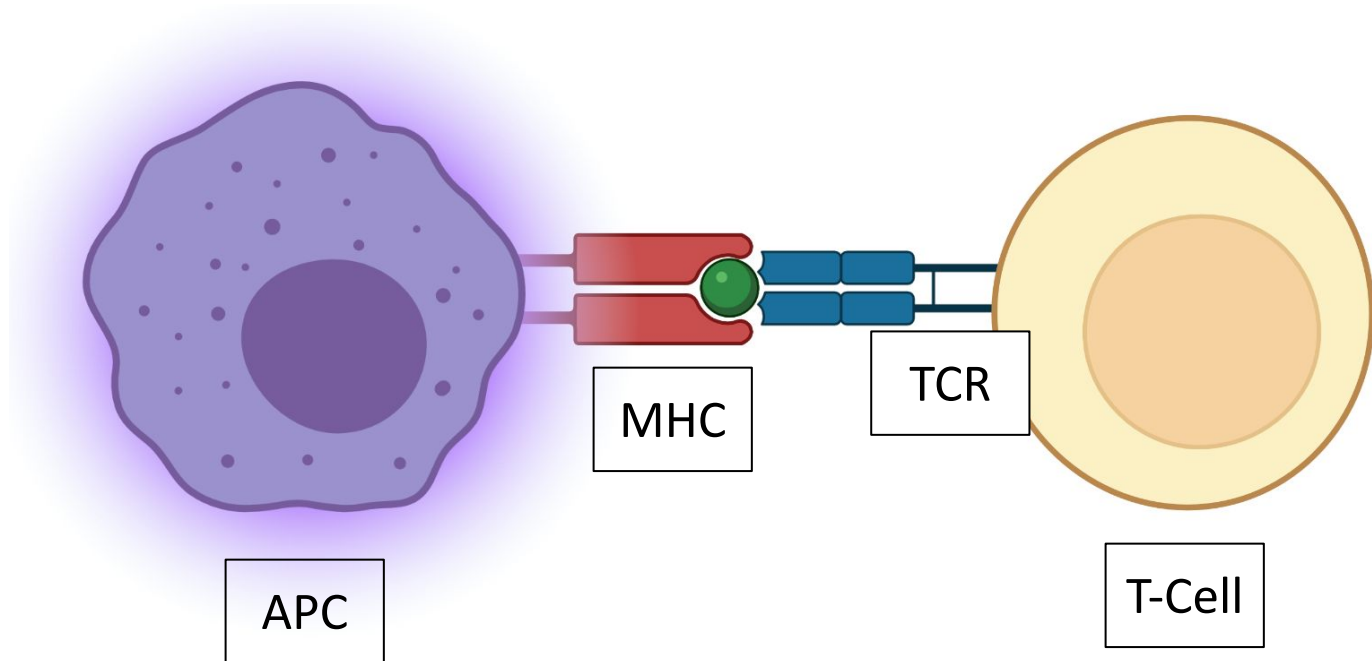
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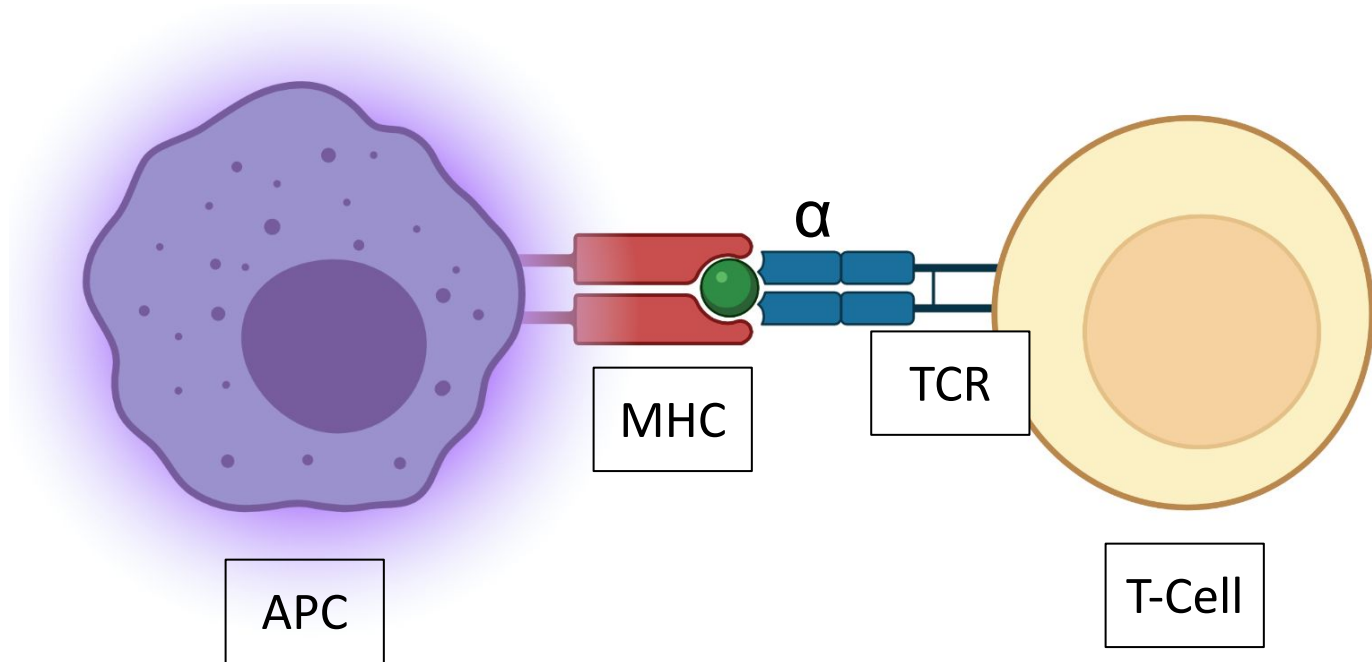
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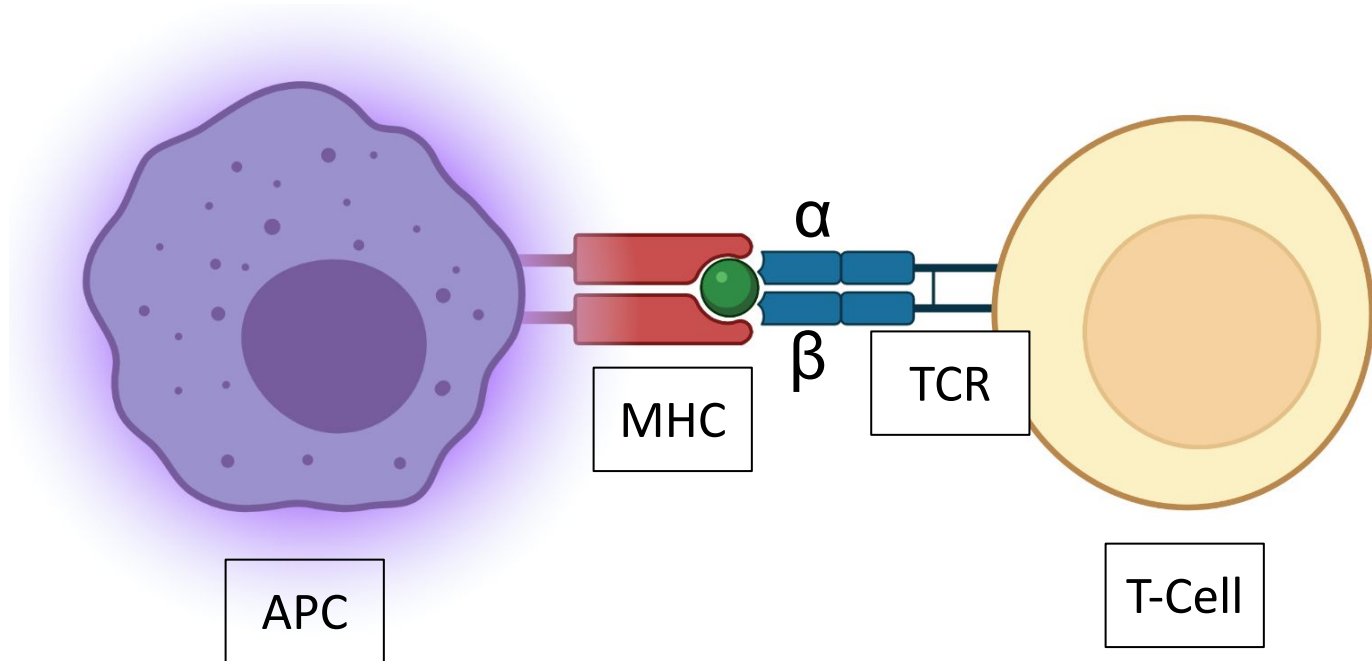
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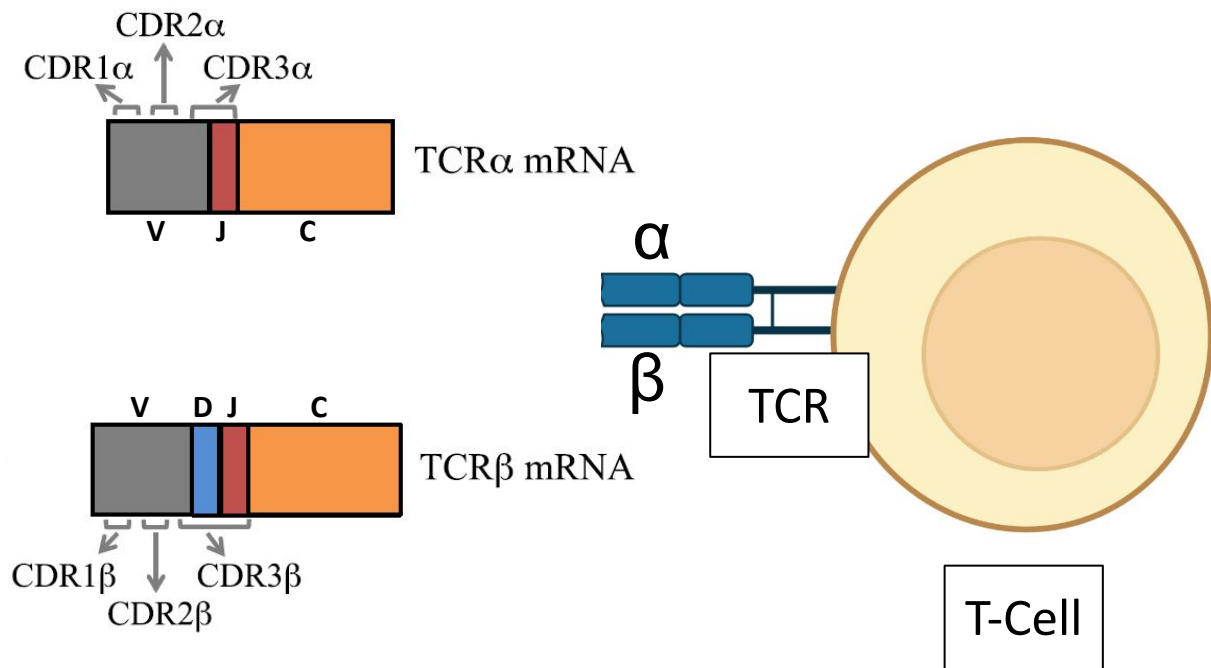
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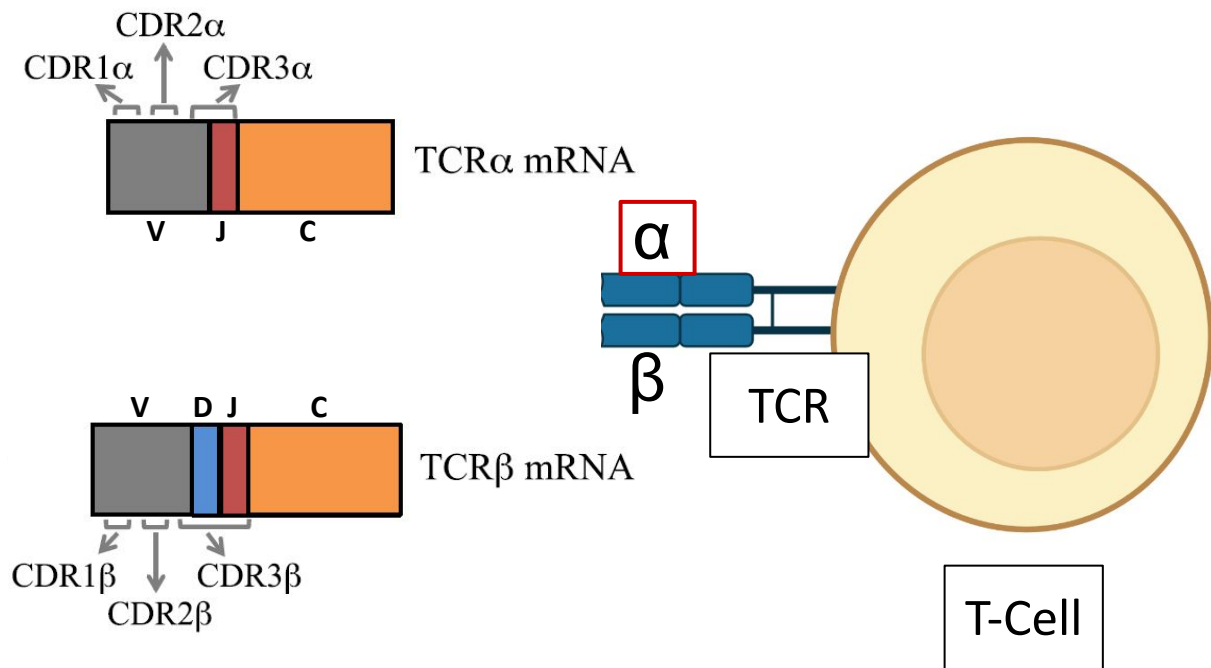
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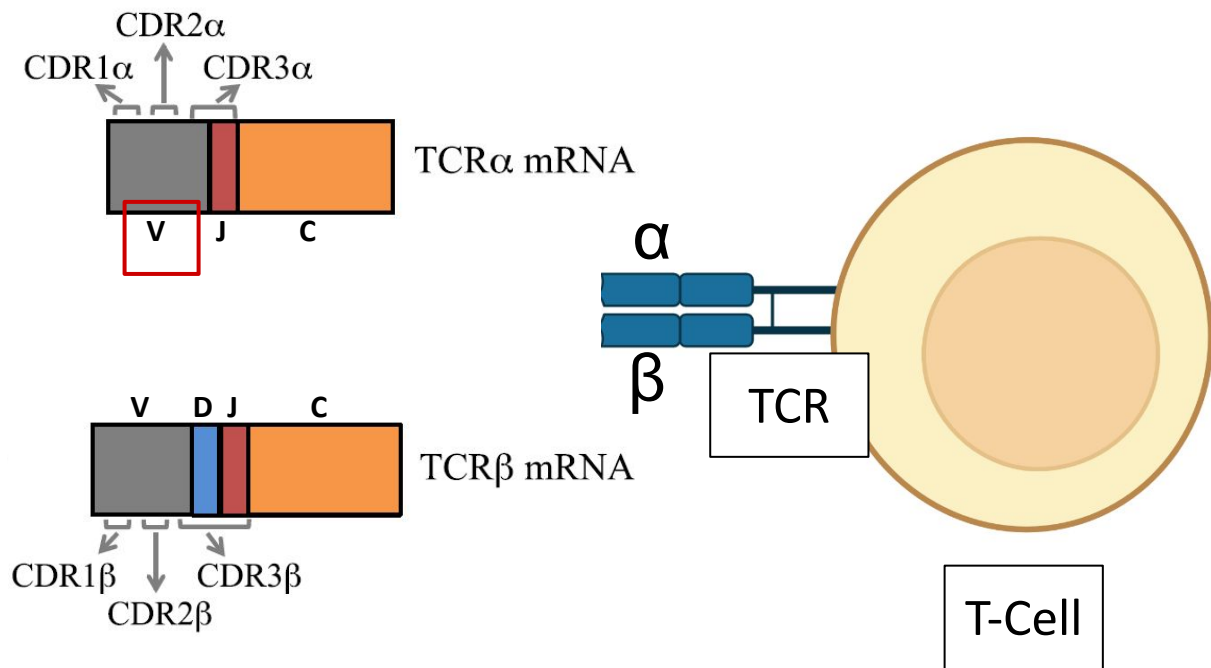
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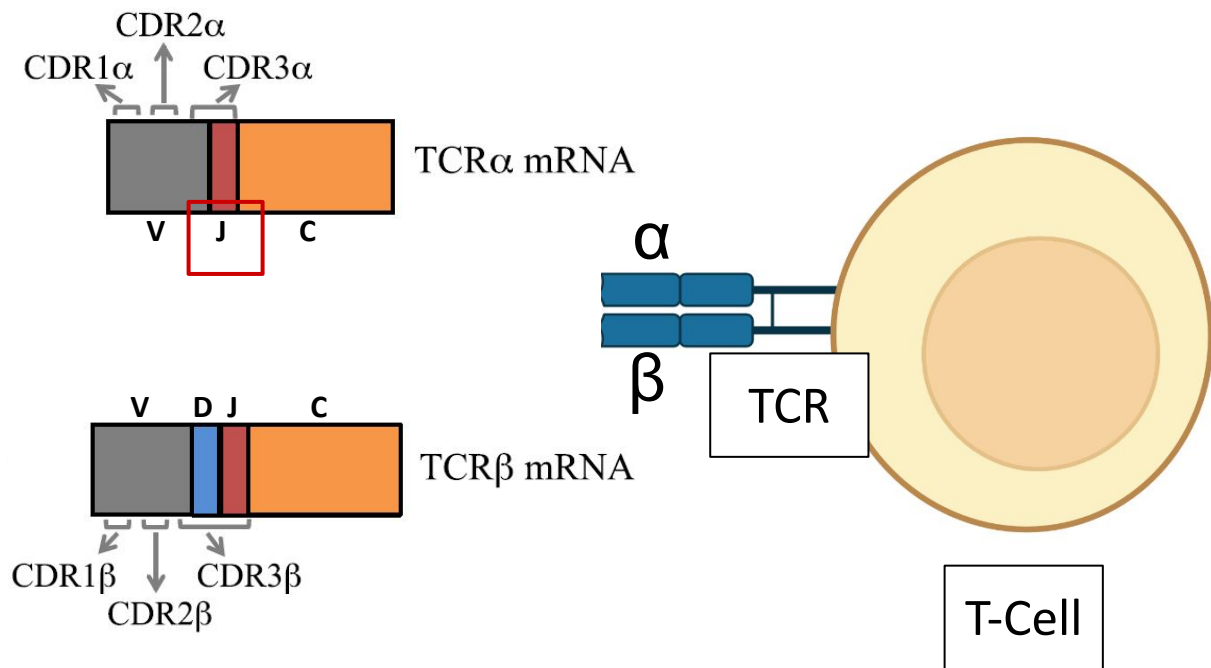
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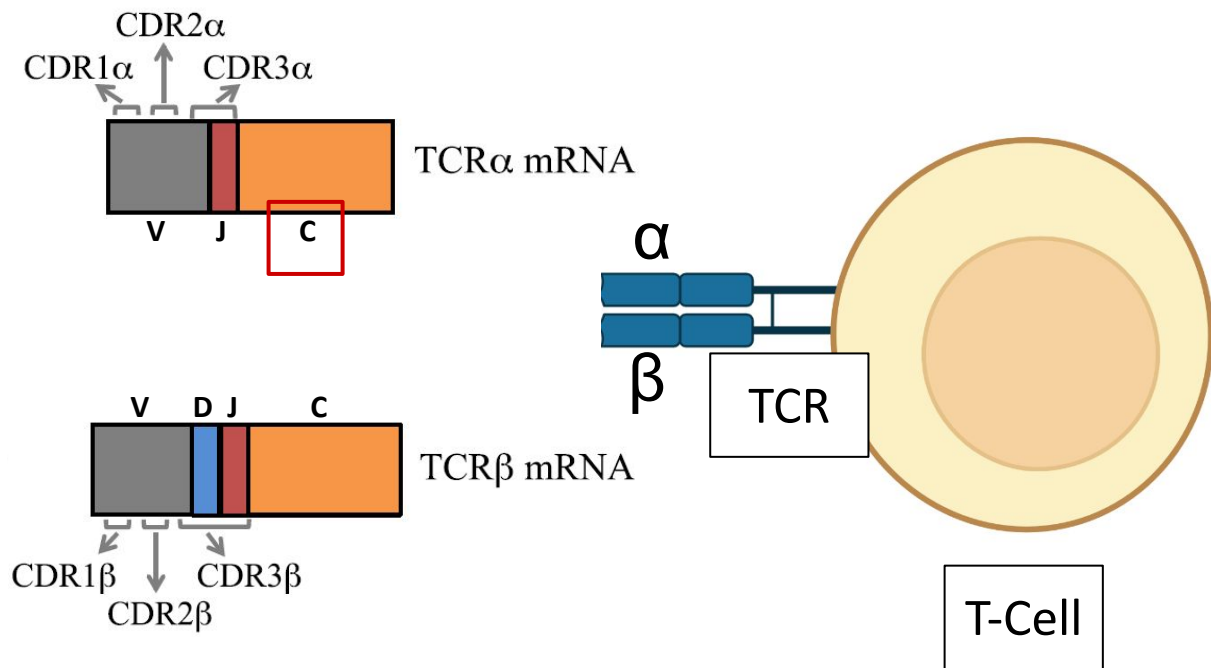
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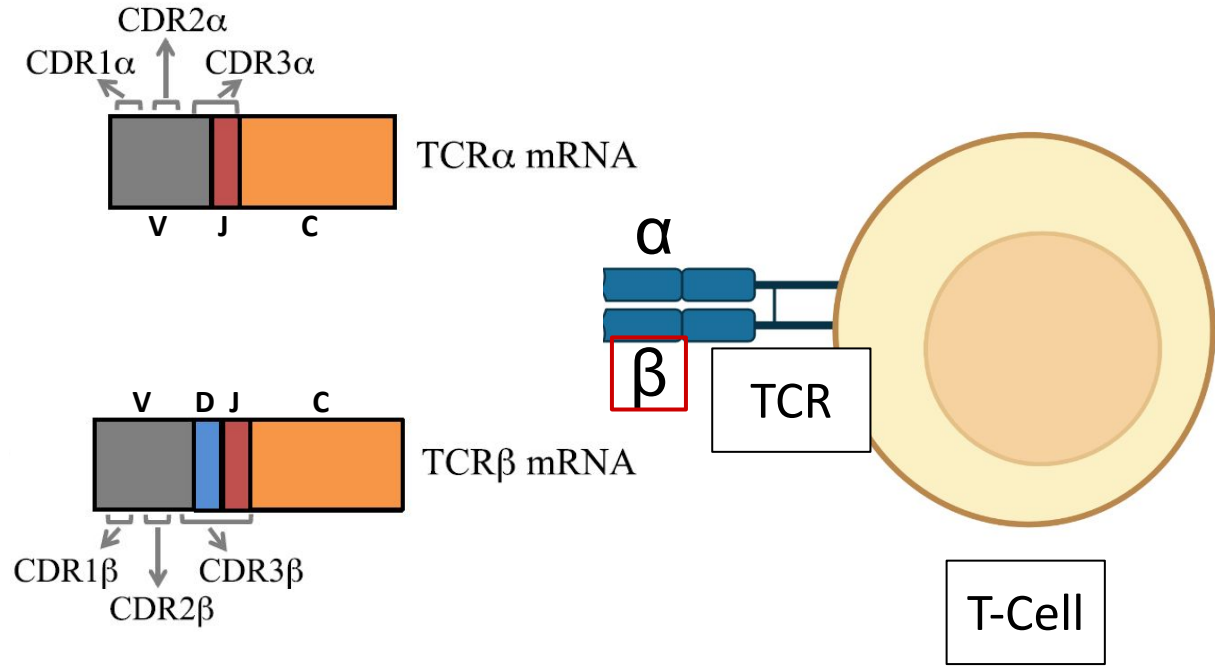
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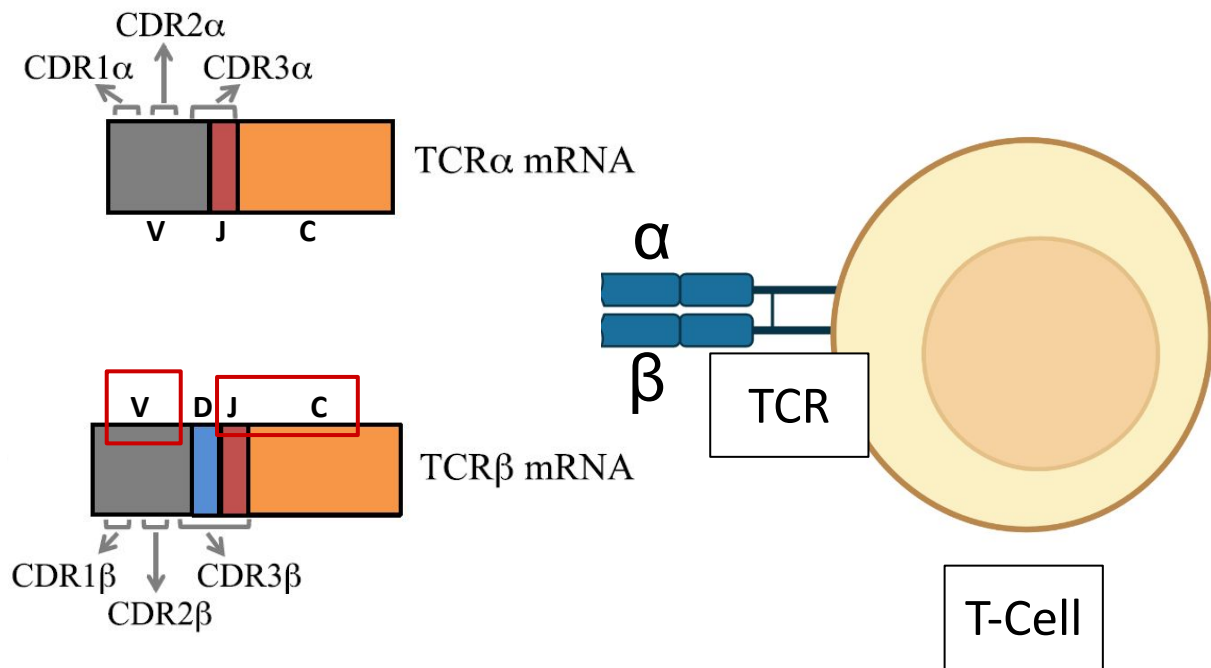
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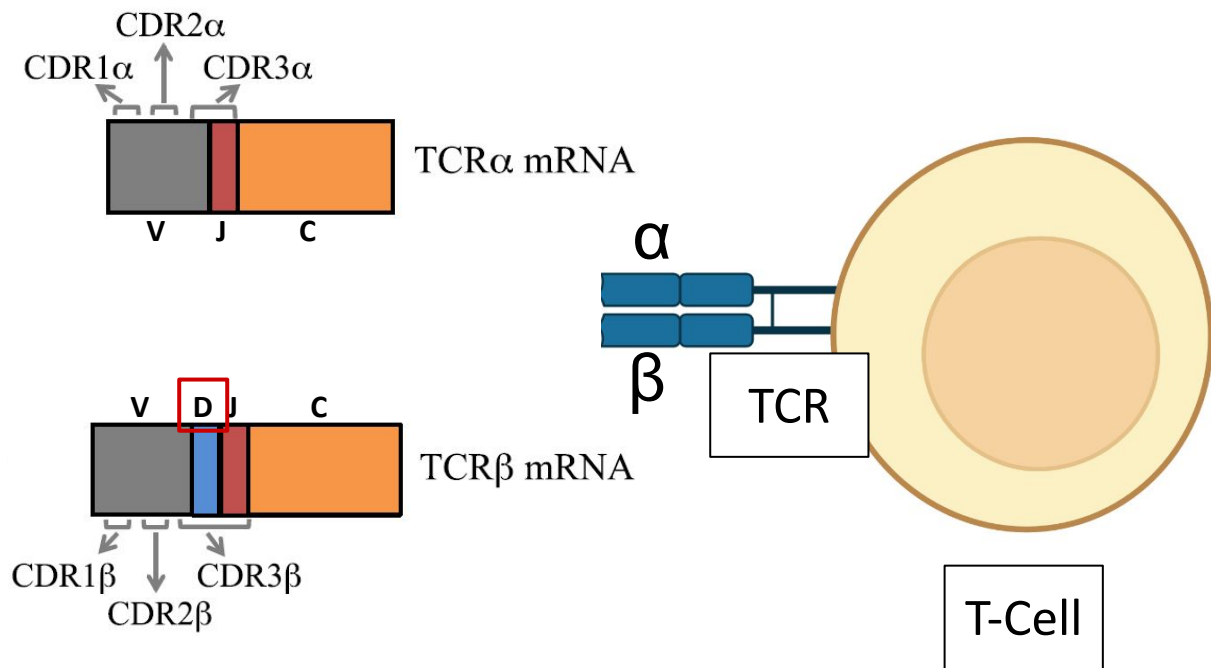
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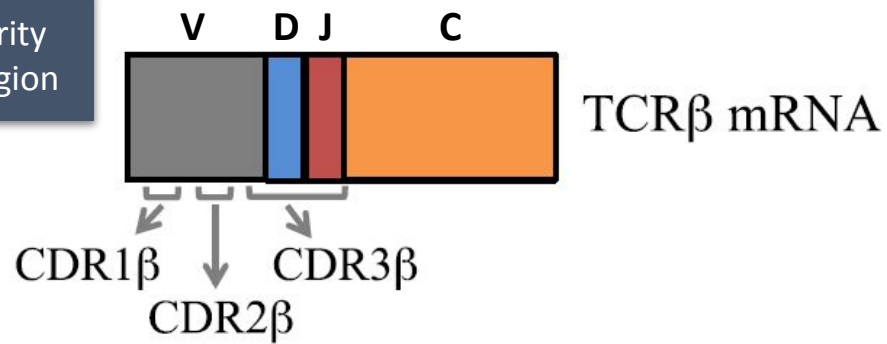
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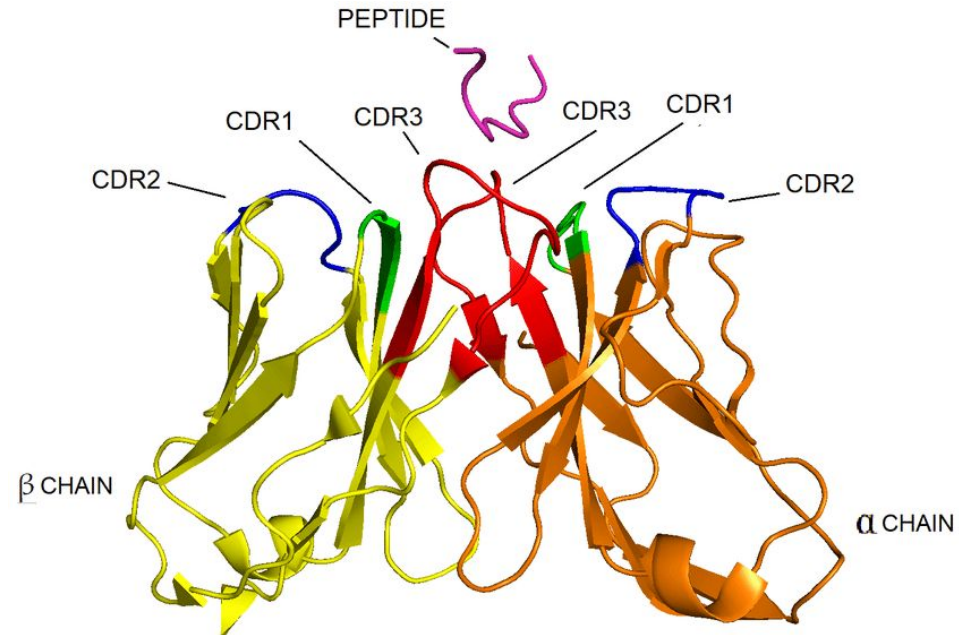


TCRmatch

Complementarity
determining region

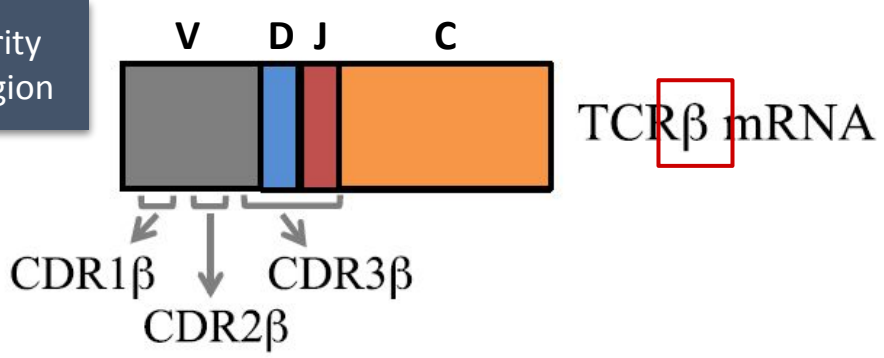


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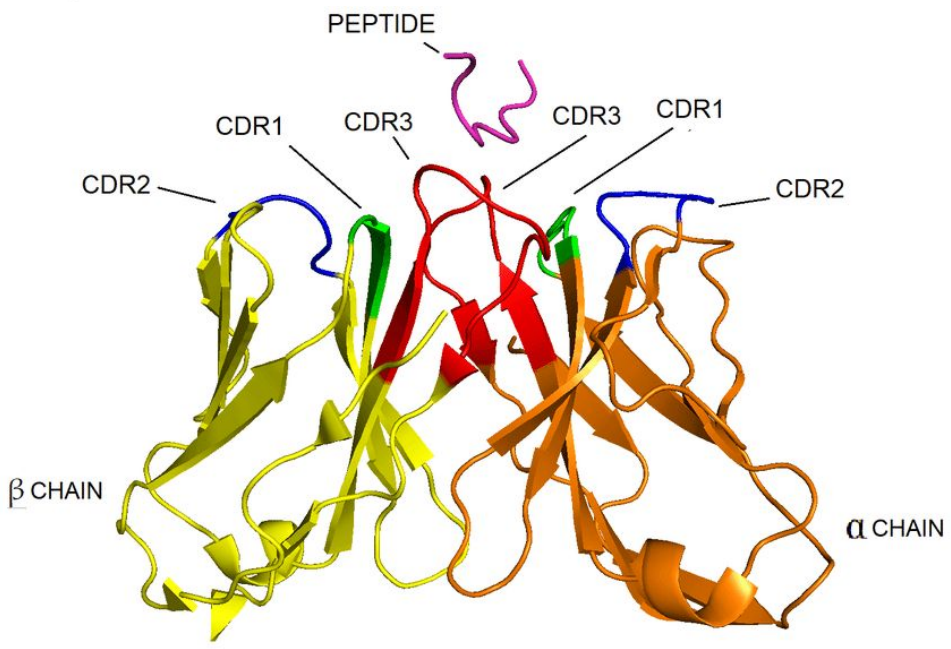


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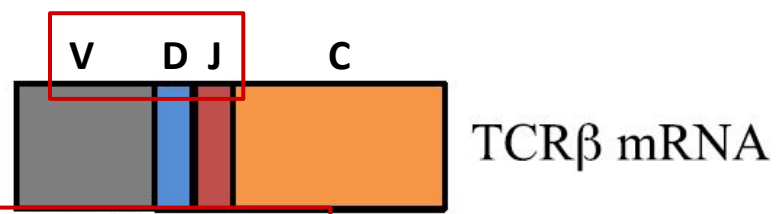
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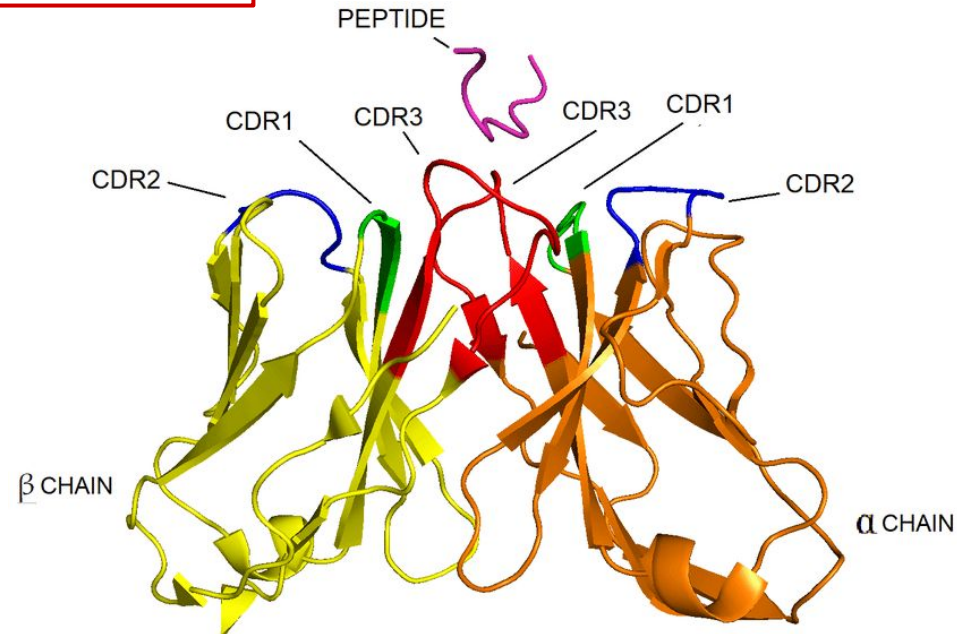
Cinelli, Mattia. (2018). Analysis of murine CDR3 β repertoires using machine learning techniques.

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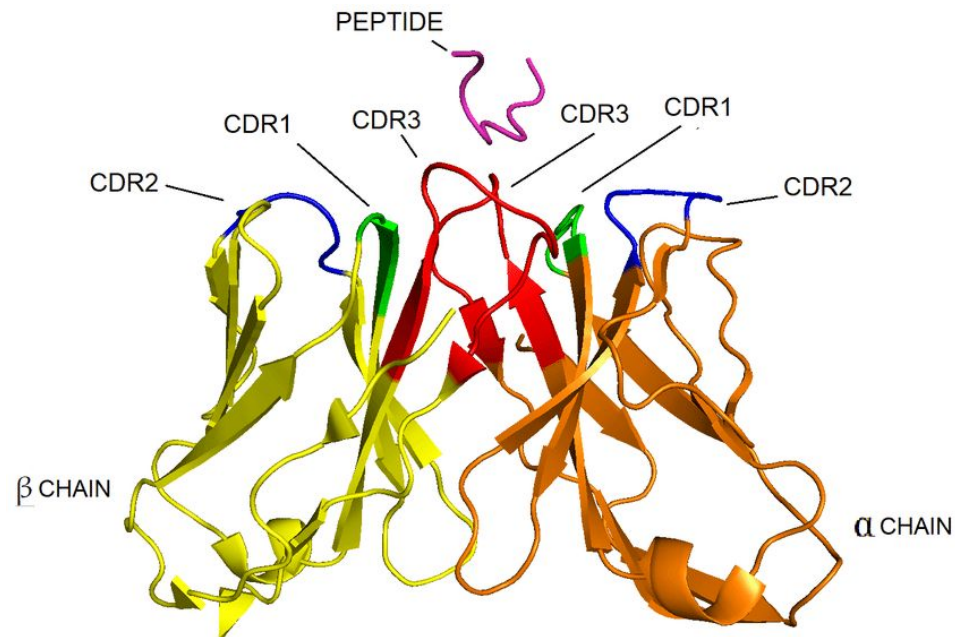
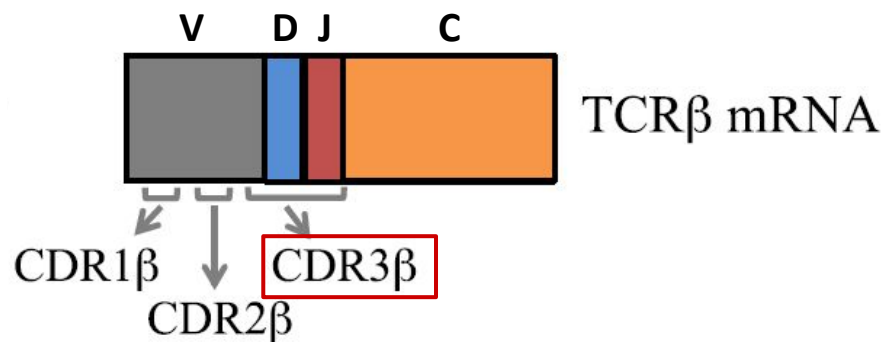


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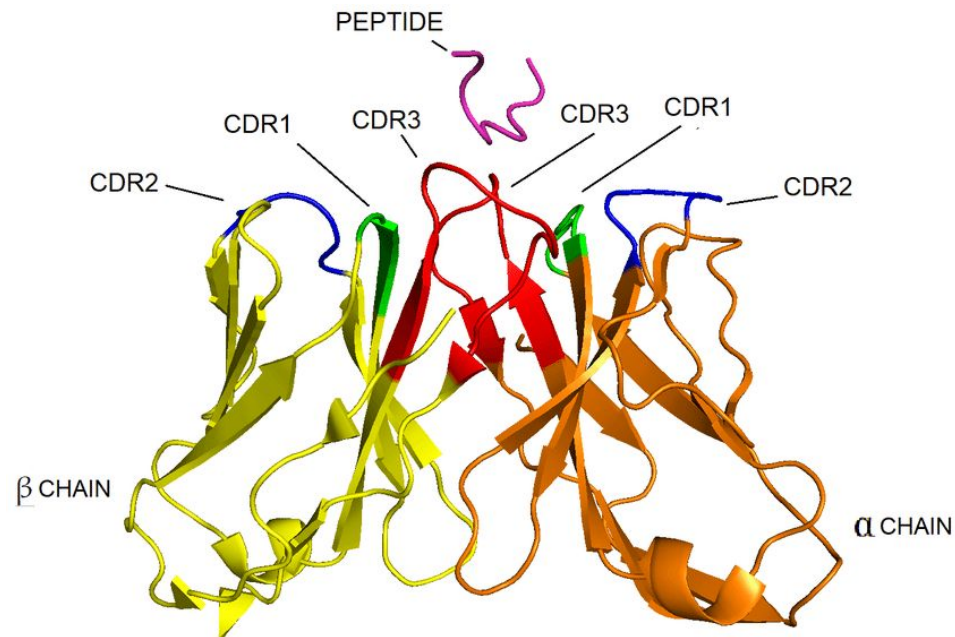
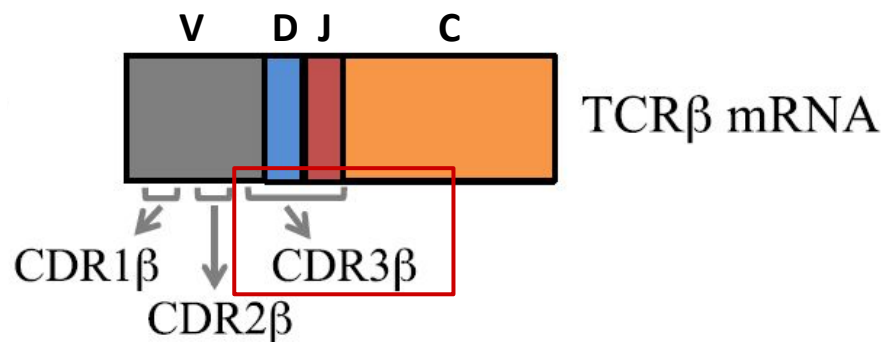
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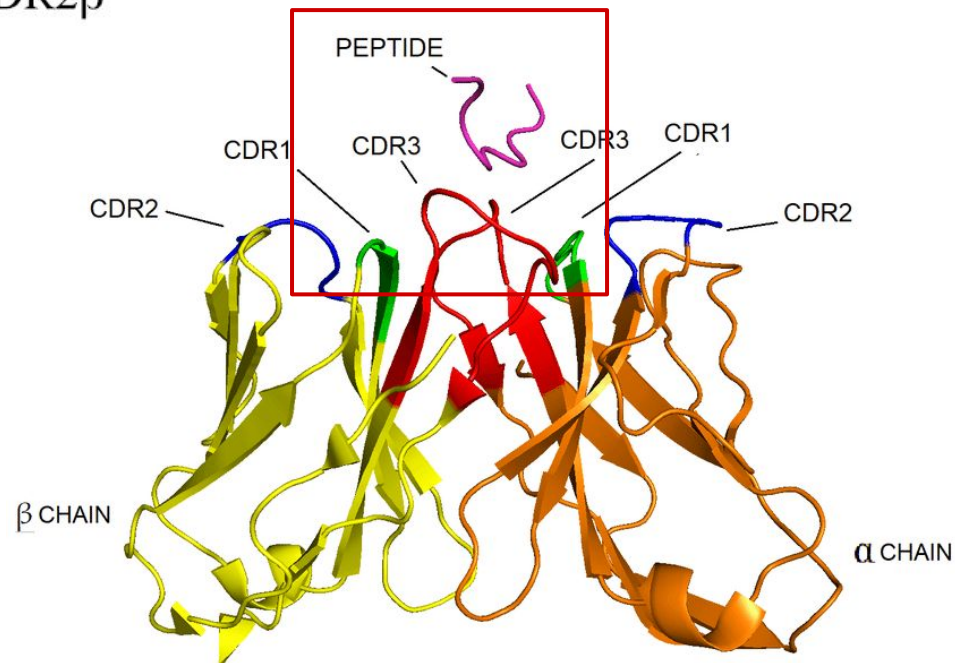
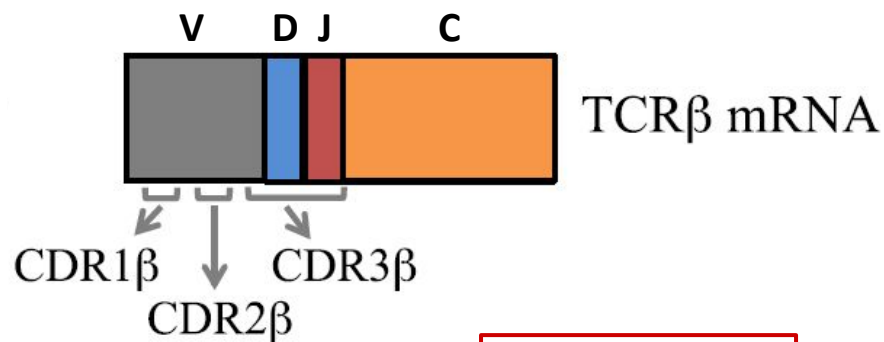
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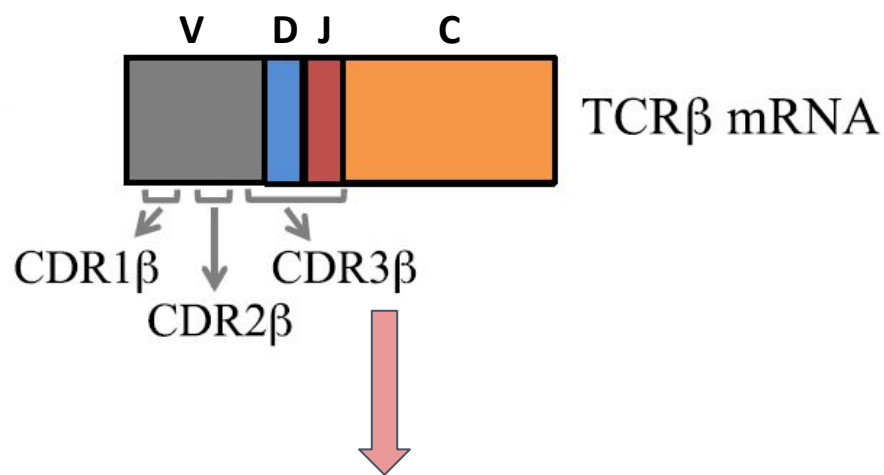
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Repertoire sequencing

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TCR sequencing does not directly reveal the epitope recognized by a given CDR3 β

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<http://www.iedb.org/>



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AND ANALYSIS RESOURCE

Help

More IEDB

Home

Specialized Searches

Analysis Resource

The IEDB has just launched its updated 3D viewers! Learn more via our help article [here](#).

Welcome

The Immune Epitope Database (IEDB) is a freely available resource funded by NIAID. It catalogs experimental data on antibody and T cell epitopes studied in humans, non-human primates, and other animal species in the context of infectious disease, allergy, autoimmunity and transplantation. The IEDB also hosts tools to assist in the prediction and analysis of epitopes.

[Learn More](#)

Upcoming Events & News

AAI Exhibitor Booth	May 6-10
FOCIS Exhibitor Booth	June 21-24
Virtual User Workshop	Oct 26-28

* register [here](#)

[IEDB SARS-CoV-2 Epitope Analysis Videos](#)

Summary Metrics

Peptidic Epitopes	1,539,170
Non-Peptidic Epitopes	3,146
T Cell Assays	443,509
B Cell Assays	1,332,364
MHC Ligand Assays	4,631,827
Epitope Source Organisms	4,234
Restricting MHC Alleles	970
References	23,297

START YOUR SEARCH HERE

Epitope ?

- Any
- Linear peptide
- Discontinuous
- Non-peptidic

Exact



Epitope Source ?

Organism

Ex: influenza, peanut

Antigen

Ex: core, capsid, myosin



Host ?

- Any
- Human
- Mouse
- Non-human primate
- Ex: dog, camel



Assay ?

- T Cell
- B Cell
- MHC Ligand

Ex: neutralization

Outcome: Positive Negative



MHC Restriction ?

- Any
- Class I
- Class II
- Non-classical
- Ex: HLA-A*02:01



Disease ?

- Any
- Infectious
- Allergic
- Autoimmune
- Ex: asthma



Reset

Search

Epitope Analysis Resource

T Cell Epitope Prediction ?

Scan an antigen sequence for amino acid patterns indicative of:

MHC I Binding

MHC II Binding

MHC I Processing (Proteasome, TAP)

MHC I Immunogenicity

B Cell Epitope Prediction ?

Predict linear B cell epitopes using:

[Antigen Sequence Properties](#)

Predict discontinuous B cell epitopes using antigen structure via:

[Discotope](#)

[ElliPro](#)

Epitope Analysis Tools ?

Analyze epitope sets of:

[Population Coverage](#)

[Conservation Across Antigens](#)

[Clusters with Similar Sequences](#)

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Epitope

Any
 Linear peptide

Assay

T Cell
 B Cell
 MHC Ligand

Host

Any
 Human
 Mouse
 Non-human primate
 Ex: dog, camel

Disease

Any
 Infectious
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**TCR sequence - Epitope sequence
(144,290 TCR sequences)**

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Scan an antigen sequence for amino acid patterns indicative of:

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- Immunogenicity

Antigen Sequence Properties

Predict discontinuous B cell epitopes using antigen structure via:

- Discotope
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Epitope Analysis Tools

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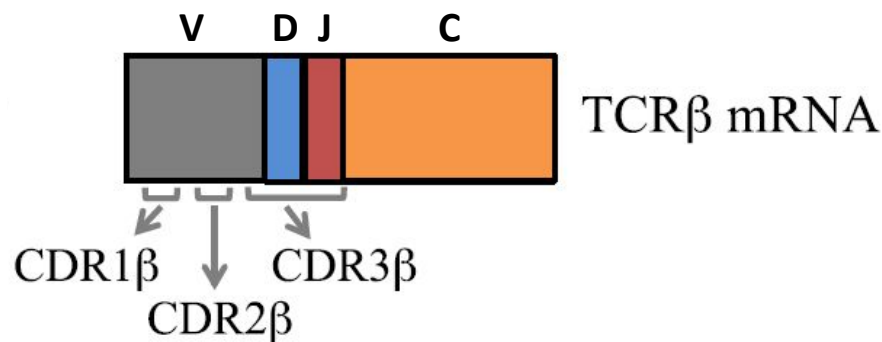
Solution: use the sequence of known TCRs to match the query,

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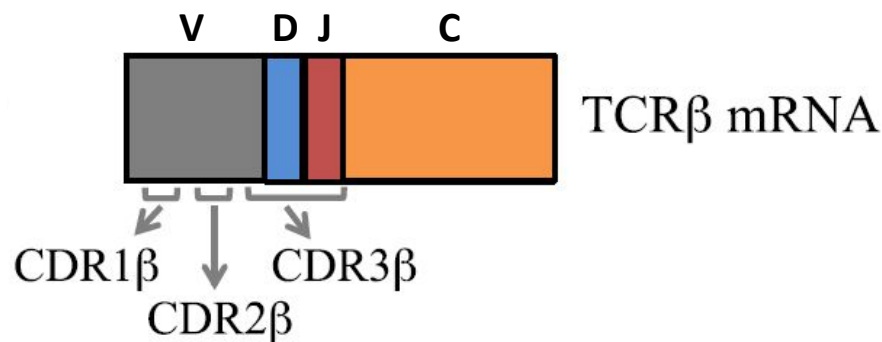


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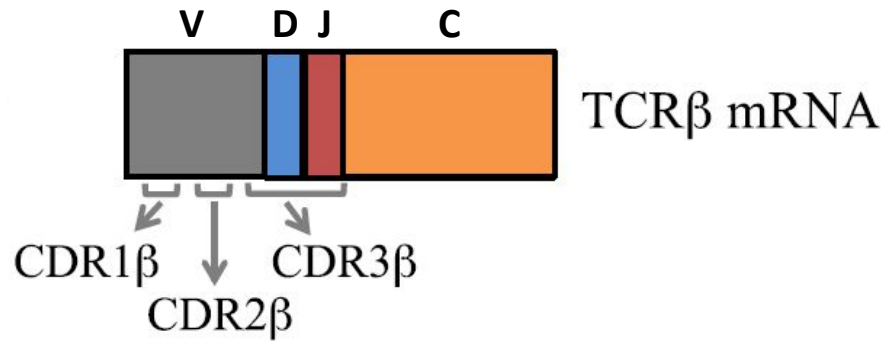


Repertoire sequencing

```
...CASSIRSSYEQYF...  
...CASSLEGYTEAFFF...  
...CASSSANYGYTFF...  
...CASSIRAAETQYFF...  
...CASSIRSSTEAFFF...  
...CASSSRSSYEQYF...
```

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ASSIRSSYEQY

IMMUNE EPITOPE DATABASE AND ANALYSIS RESOURCE

Home Specialized Searches Analysis Resource Help More IEDB

Welcome

The Immune Epitope Database (IEDB) is a freely available resource funded by NIAID. It catalogs experimental data on antibody and T cell epitopes studied in humans, non-human primates, and other animal species in the context of infectious disease, allergy, autoimmunity and transplantation. The IEDB also hosts tools to assist in the prediction and analysis of epitopes.

Learn More

Upcoming Events & News

Virtual User Workshops Oct 28-29 & Nov 3-4, 2021
* access recordings [here](#)

IEDB SARS-CoV-2 Epitope Analysis Videos
SARS-CoV-2 & Myocarditis Publication

Summary Metrics

Peptidic Epitopes	1,394,331
Non-Peptidic Epitopes	3,131
T Cell Assays	436,871
B Cell Assays	1,317,388
MHC Ligand Assays	4,183,021
Epitope Source Organisms	4,181
Restricting MHC Alleles	963
References	22,917

START YOUR SEARCH HERE

Epitope

Any
 Linear peptide
Exact
 Discontinuous
 Non-peptidic

Assay

T Cell
 B Cell
 MHC Ligand
Outcome: Positive Negative

Find

Epitope Source

Organism
Ex: Influenza, peanut

Antigen
Ex: core, capsid, myosin

MHC Restriction

Any
 Class I
 Class II
 Non-classical
Ex: HLA-A*02:01

Host

Any
 Human
 Mouse
 Non-human primate
Ex: dog, camel

Disease

Any
 Infectious
 Allergic
 Autoimmune
Ex: asthma

Reset Search

Epitope Analysis Resource

T Cell Epitope Prediction

Scan an antigen sequence for amino acid patterns indicative of:

- MHC I Binding
- MHC II Binding
- MHC I Processing (Proteasome, TAP)
- MHC I Immunogenicity

B Cell Epitope Prediction

Predict linear B cell epitopes using:

- Antigen Sequence Properties

Predict discontinuous B cell epitopes using antigen structure via:

- Discotope
- ElliPro

Epitope Analysis Tools

Analyze epitope sets of:

- Population Coverage
- Conservation Across Antigens
- Clusters with Similar Sequences

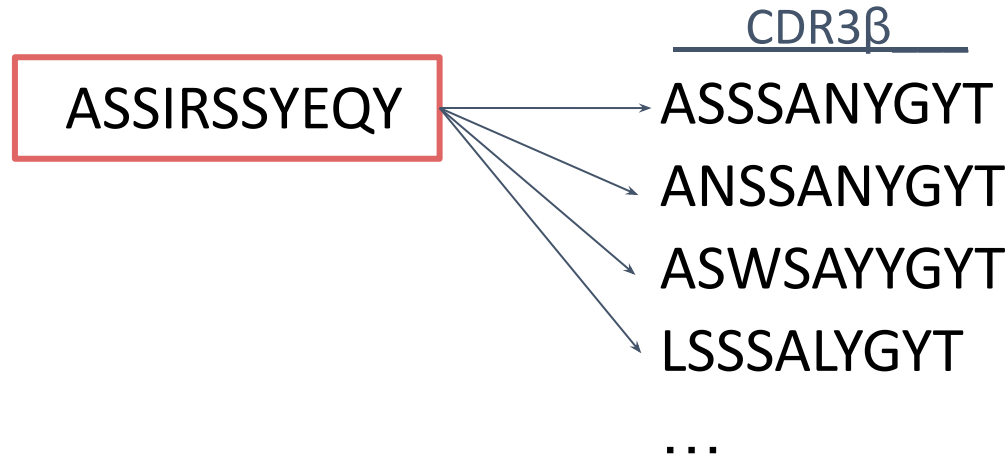
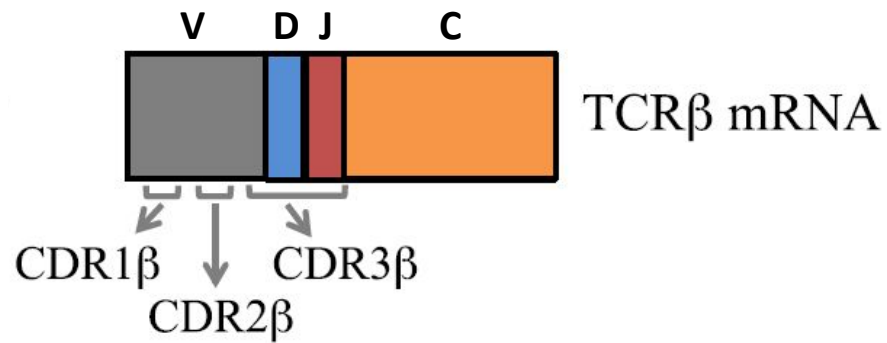
Provide Feedback | Help Request | Solutions Center | Tool Licensing Information

Supported by a contract from the National Institute of Allergy and Infectious Diseases, a component of the National Institutes of Health in the Department of Health and Human Services.

Last Updated: April 24, 2022

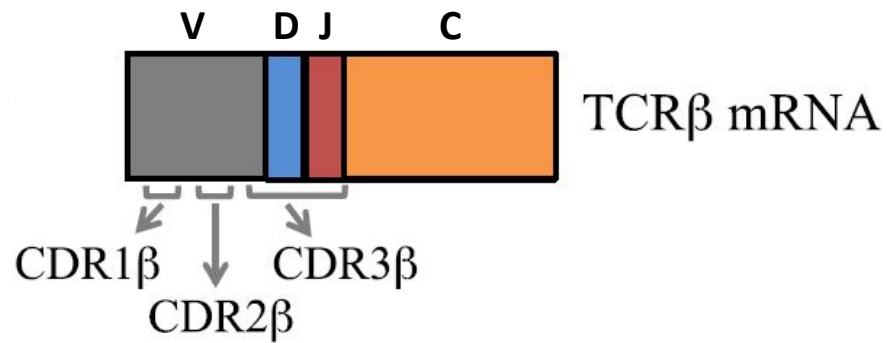
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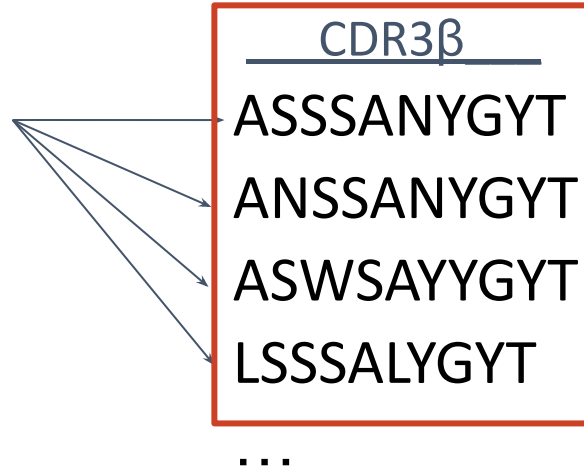


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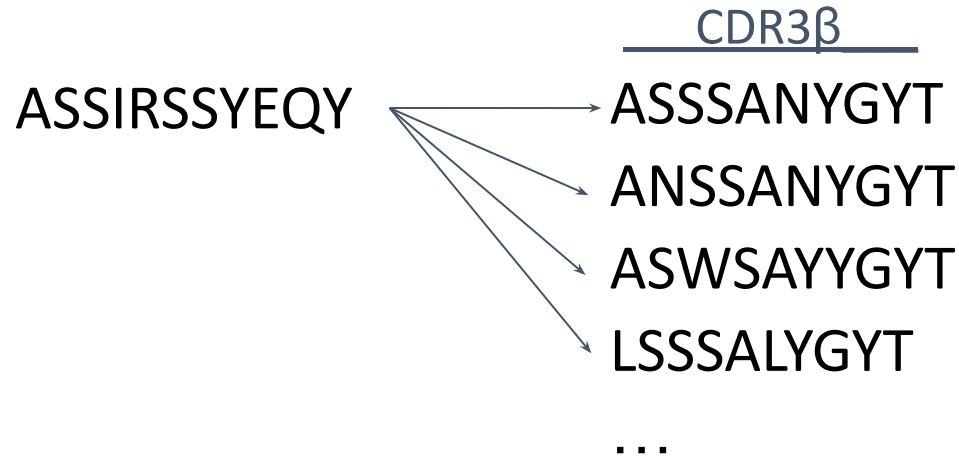
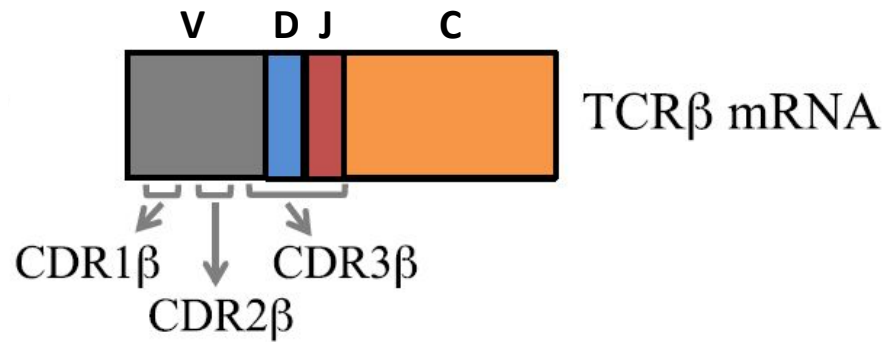


ASSIRSSYEQY



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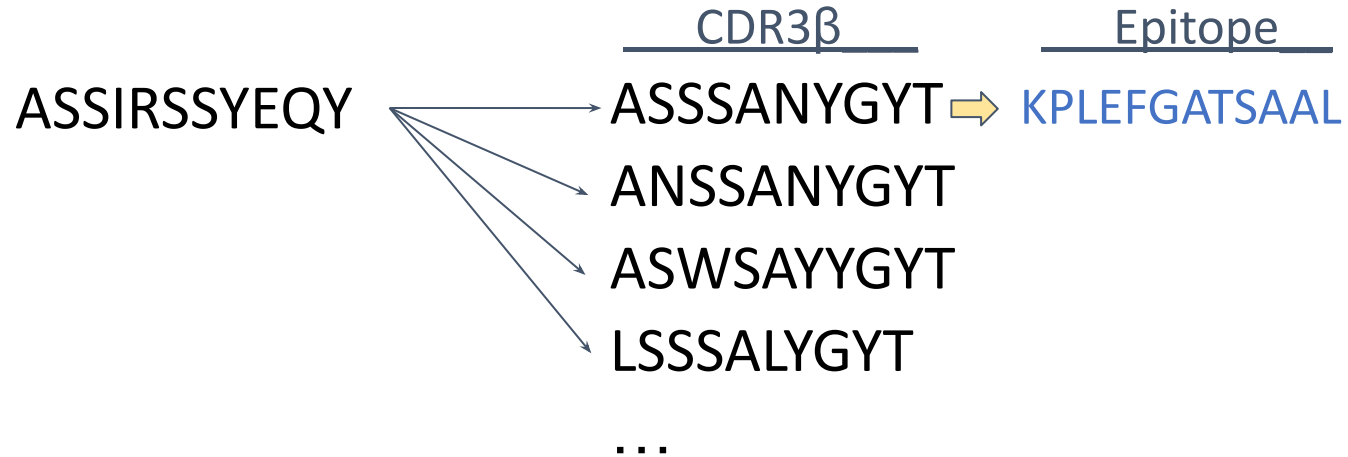
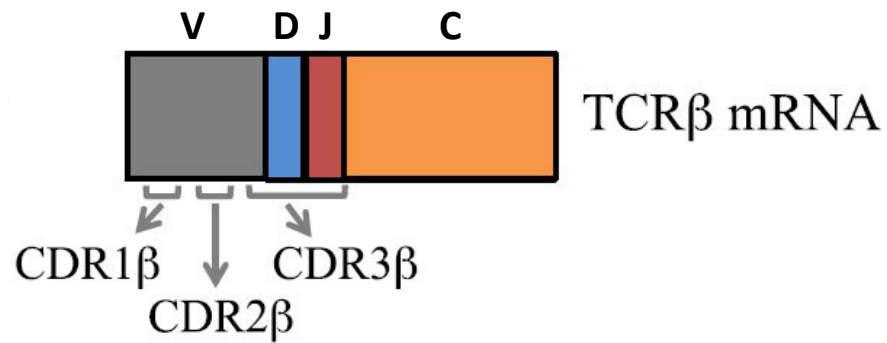
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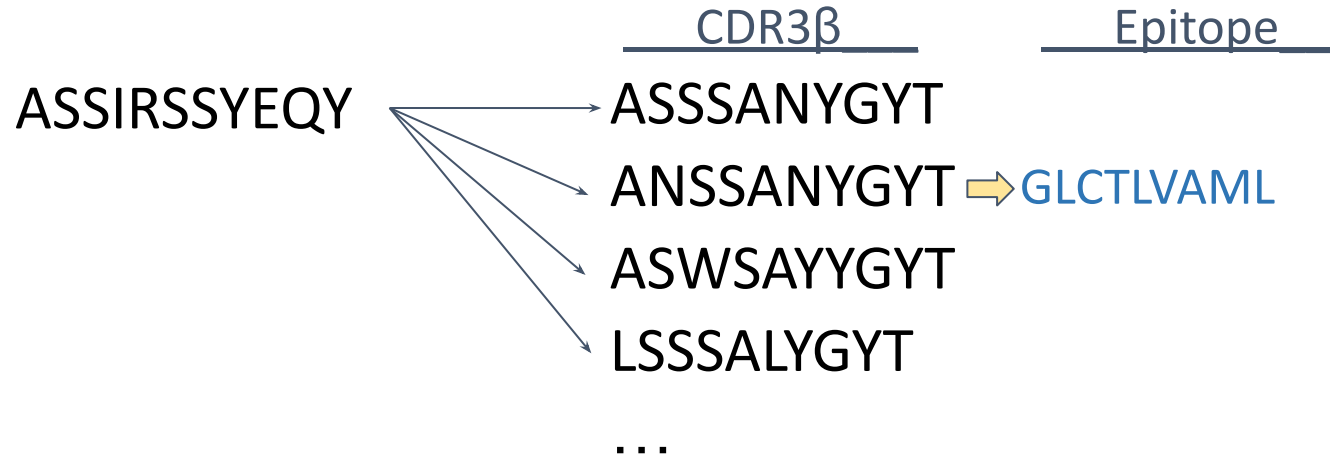
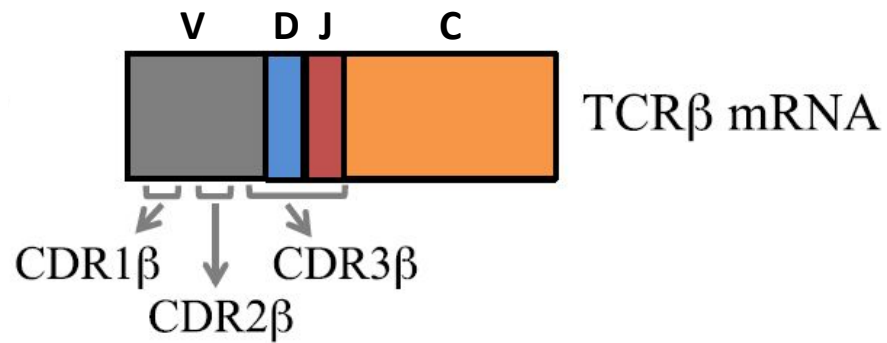
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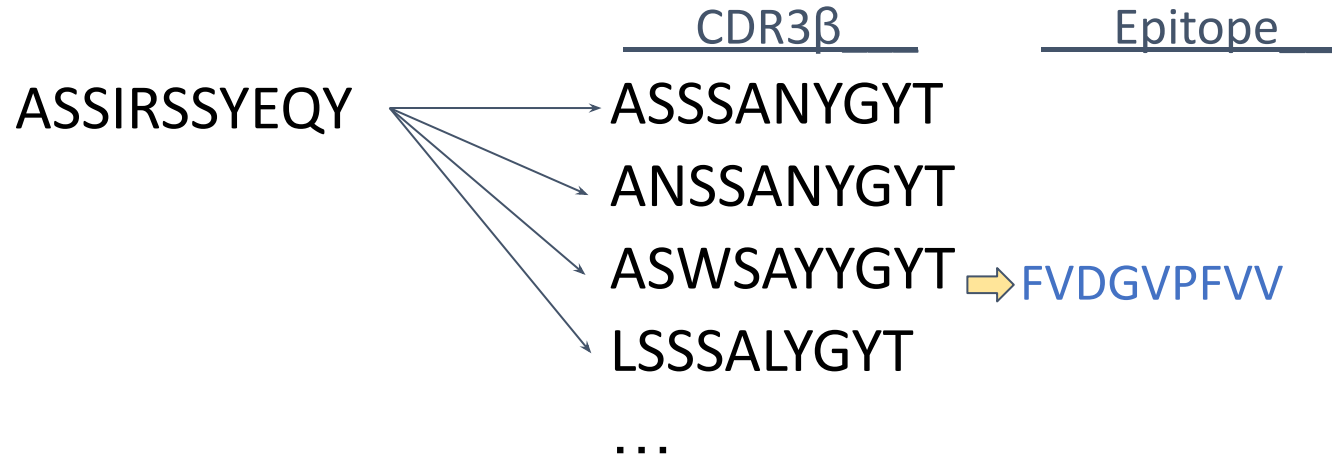
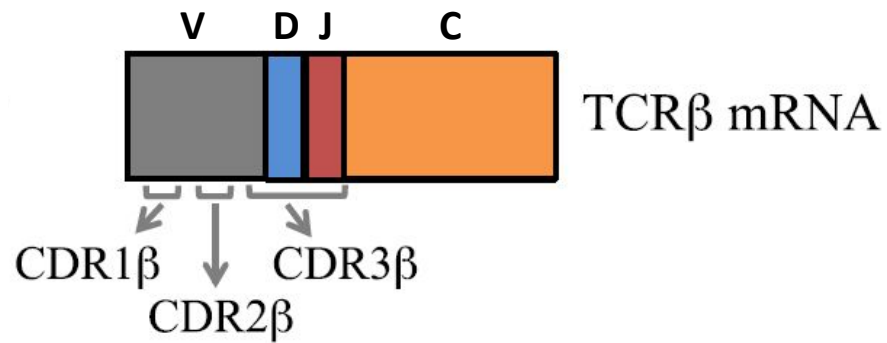
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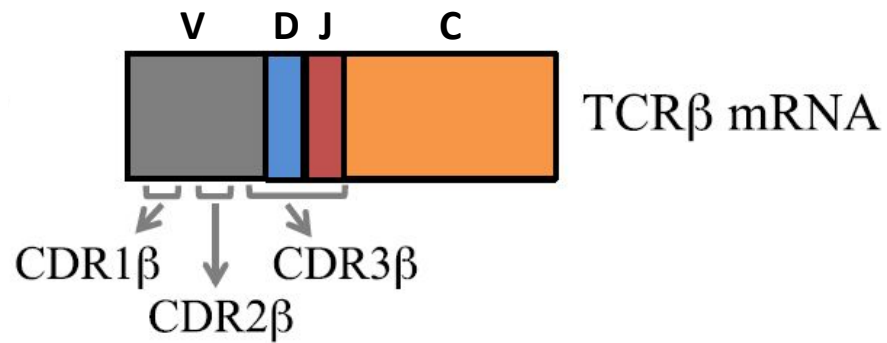
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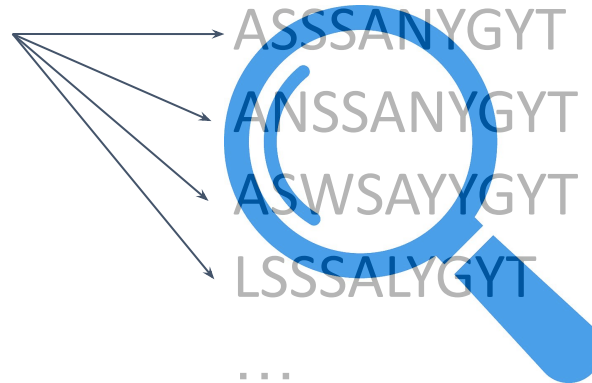


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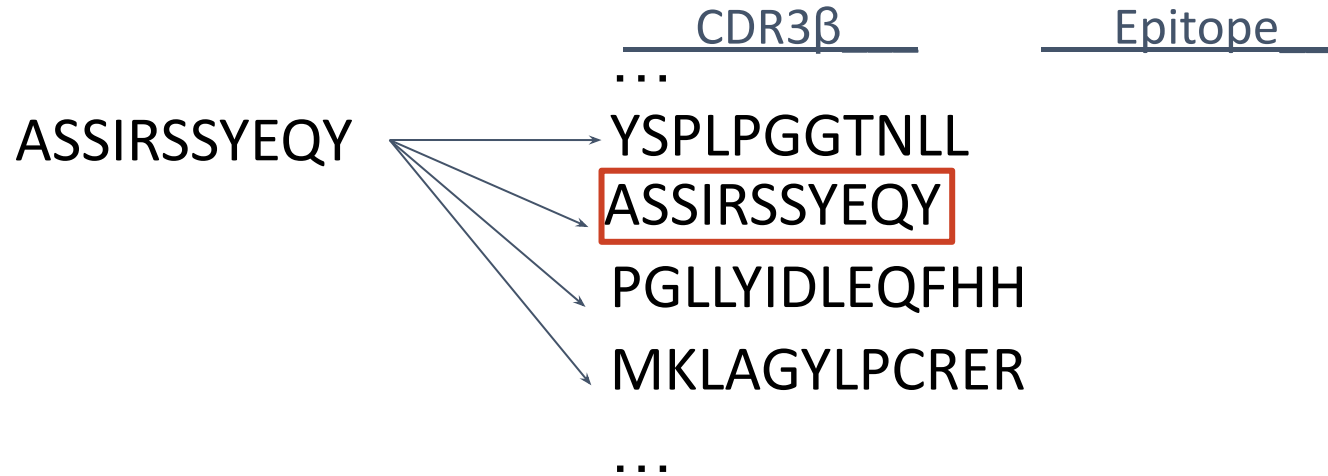
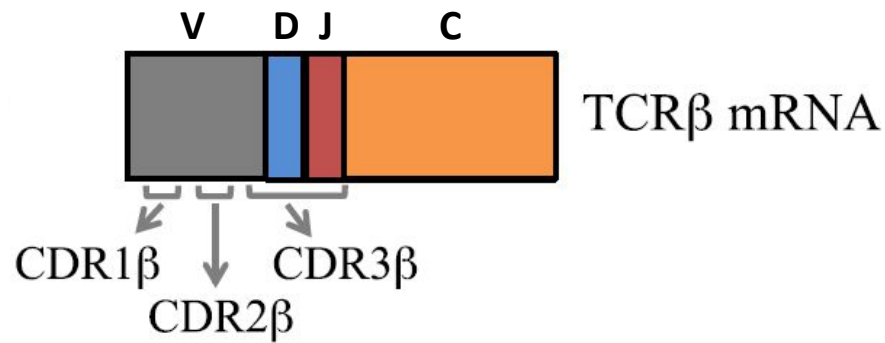


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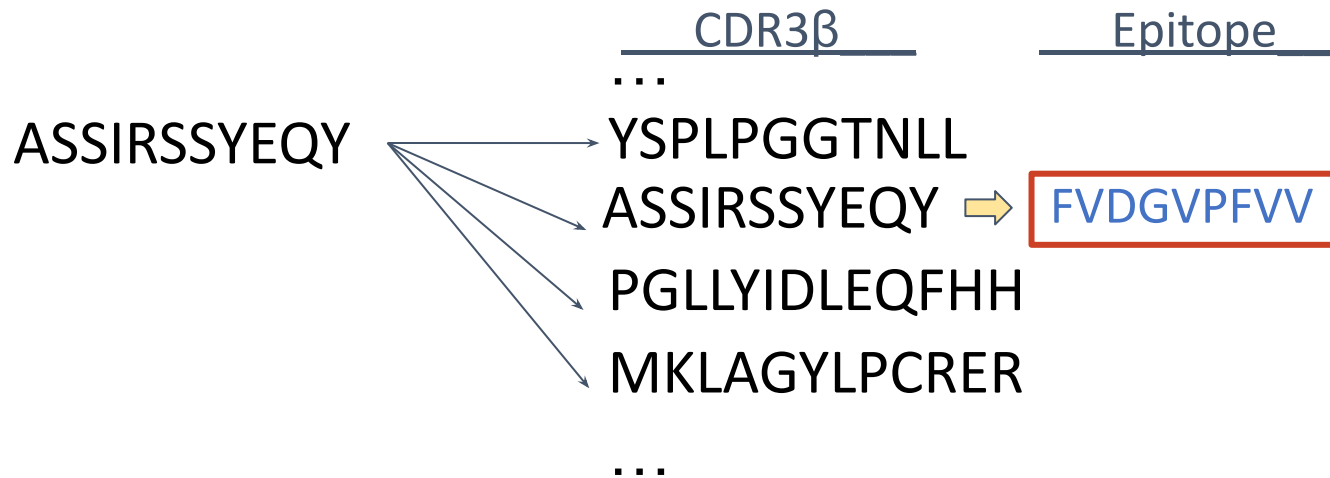
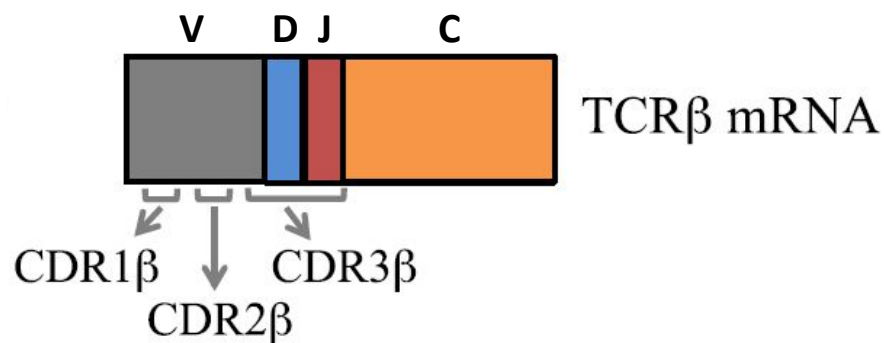
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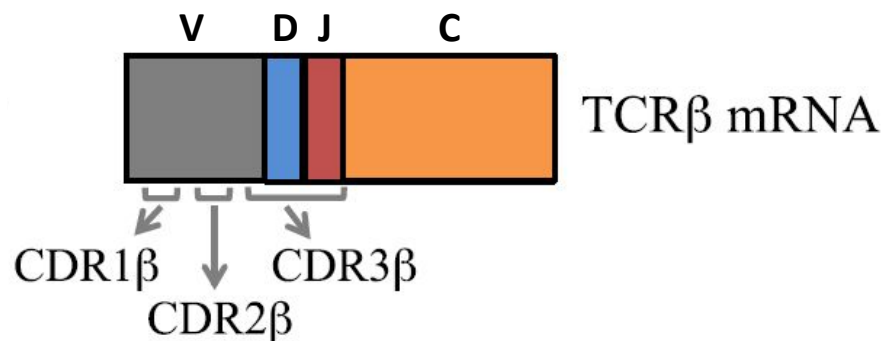
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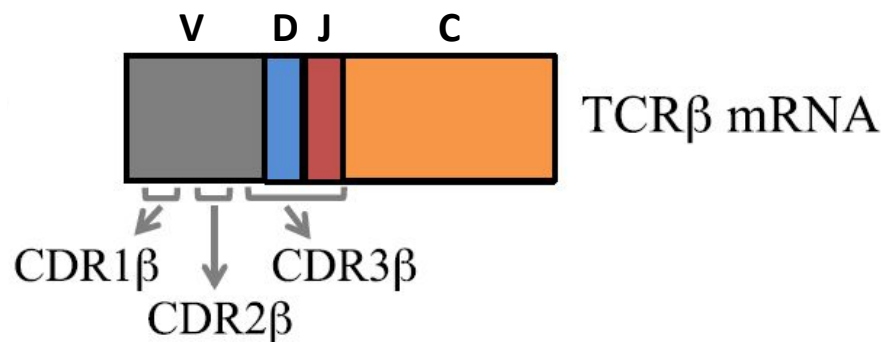
CDR3 β

Epitope

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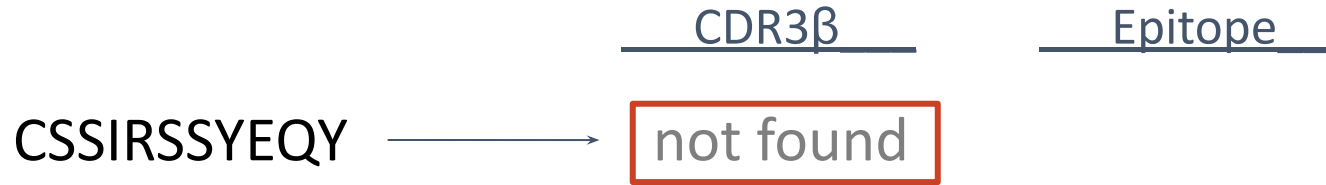
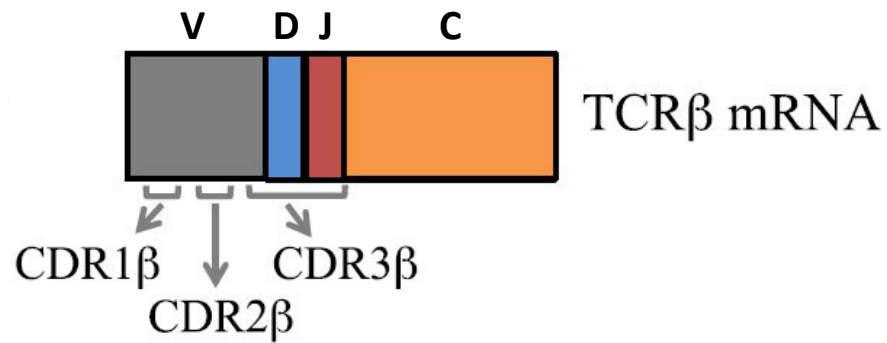
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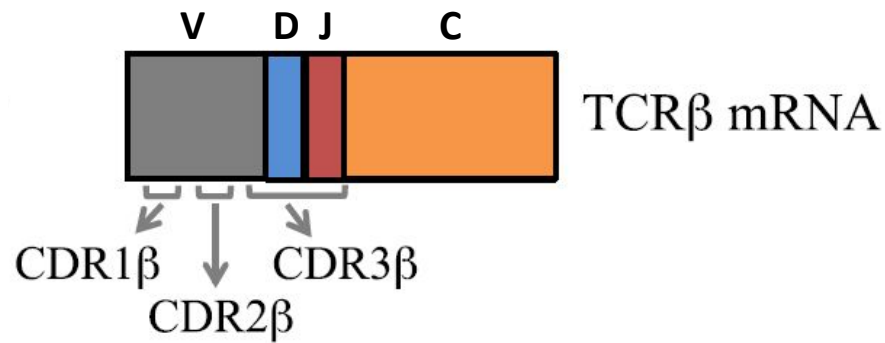
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CDR3 β

not found



Epitope

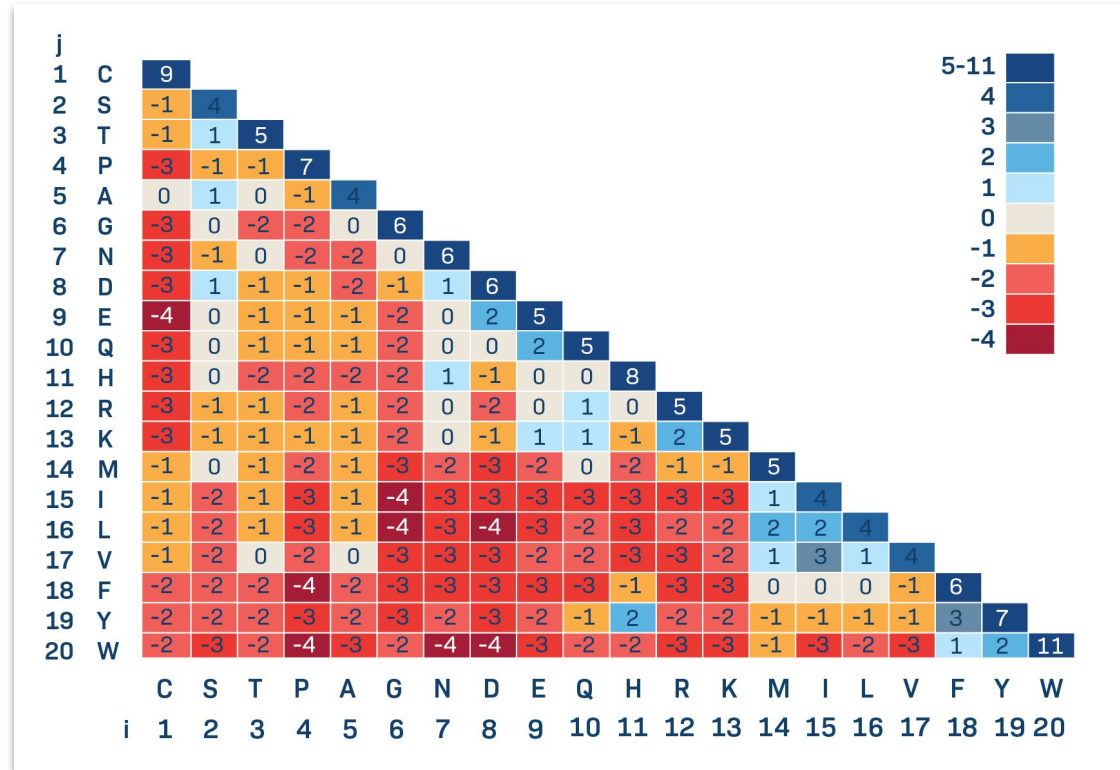
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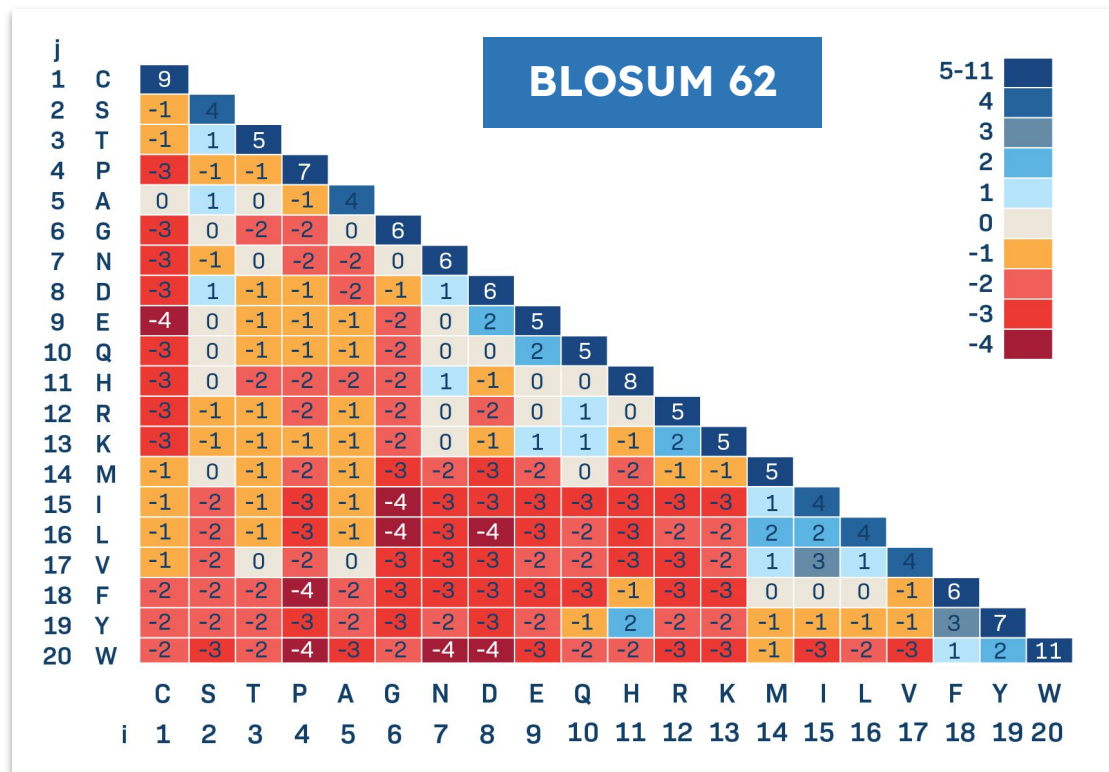


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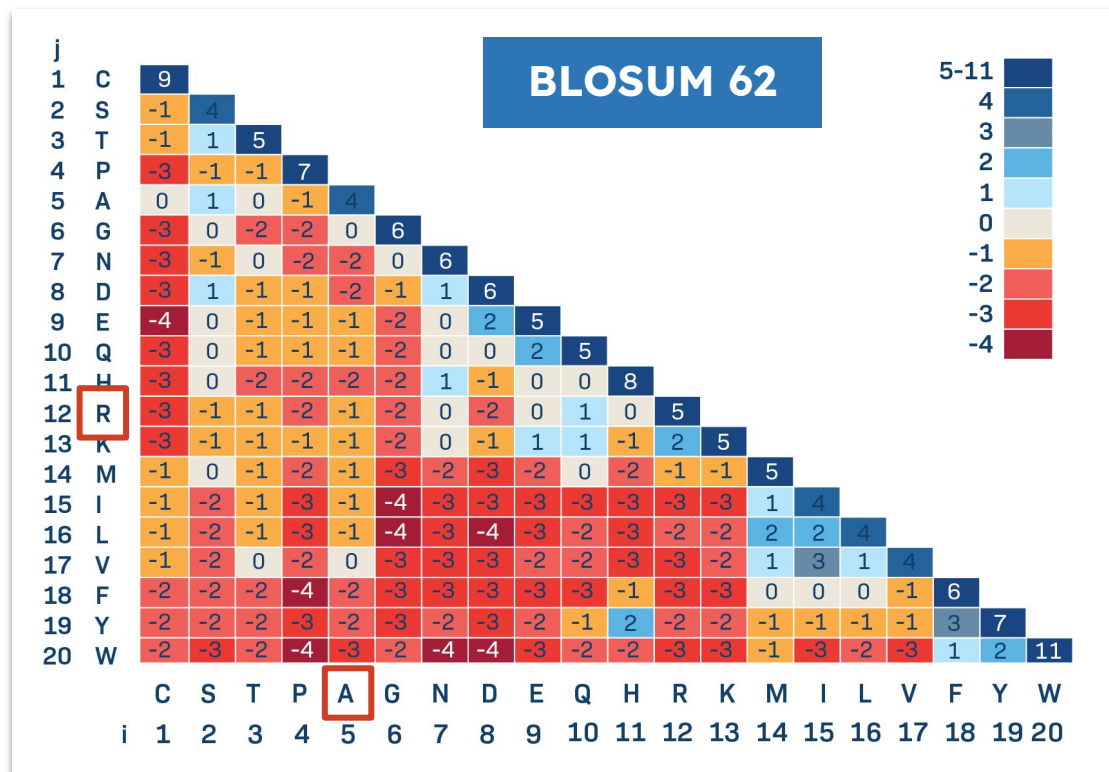


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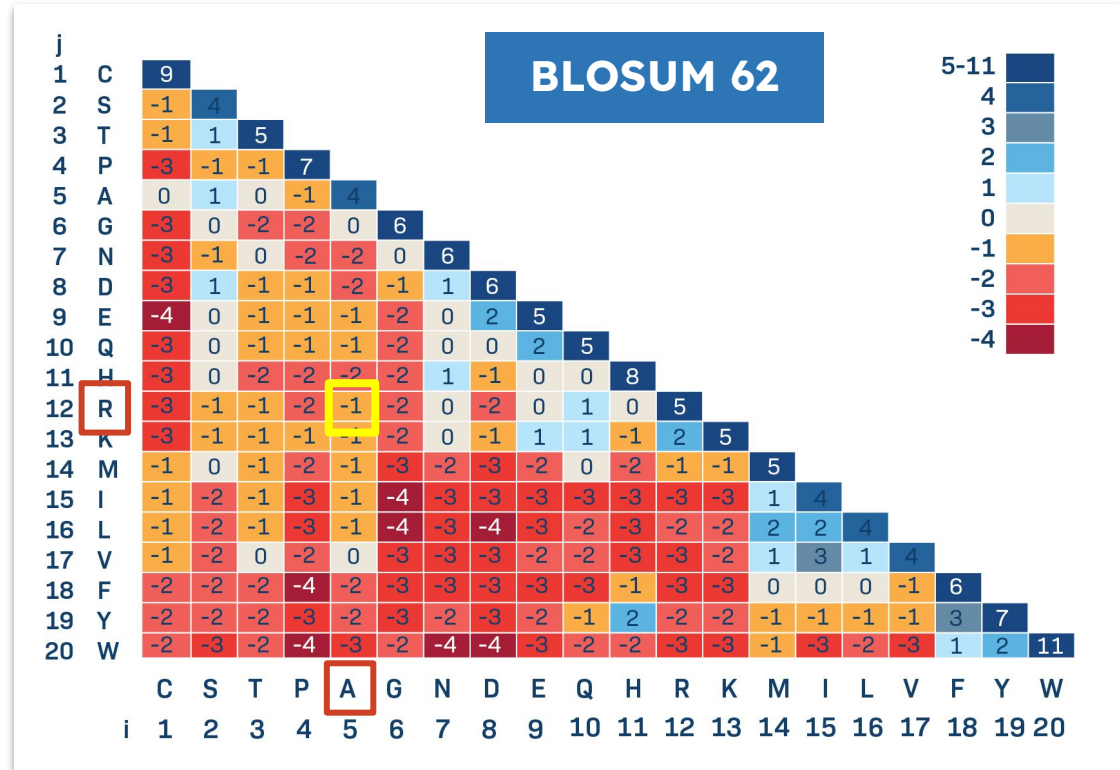


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Where did the BLOSUM62 alignment score matrix come from?

Sean R Eddy

Many sequence alignment programs use the BLOSUM62 score matrix to score pairs of aligned residues. Where did BLOSUM62 come from?

Back in the good old days, so many things were easier to understand. I once disassembled the engine of my 1972 MG just to see how it worked, but now I won't touch the squirrel's nest of technology that's inside my modern Honda Civic. Likewise, in the early days of sequence comparison, alignment scores were straightforward stuff that anybody could tweak. The first sequence comparisons just assigned -1 per mismatch and -1 per insertion/deletion, and if you didn't like that, you could make up whatever scores you thought gave you better-looking alignments. Those days are gone. Look inside a modern amino acid score matrix, and you'll see a squirrel's nest of 400 numbers. These highly tuned matrices, which go by industrialized acronyms like BLOSUM62 and PAM250, no longer seem to have any user serviceable parts inside. Blame probability theory.

Alignment scores are log-odds scores

What we want to know is whether two sequences are homologous (evolutionarily related) or not, so we want an alignment score that reflects that. Theory says that if you want to compare two hypotheses, a good score is a log-odds score: the loga-

ment score is the sum of individual log-odds scores for each aligned residue pair. Those individual scores make up a 20×20 score matrix. The equation for calculating a score $s(a,b)$ for aligning two residues a and b is:

$$s(a,b) = \frac{1}{\lambda} \log \frac{p_{ab}}{f_a f_b}$$

The numerator (p_{ab}) is the likelihood of the hypothesis we want to test: that these two residues are correlated because they're

The definition of 'conservative substitution' in a score matrix is purely statistical. It has nothing directly to do with amino acid structure or biochemistry.

homologous. Thus, p_{ab} are the target frequencies: the probability that we expect to observe residues a and b aligned in homologous sequence alignments. The denominator ($f_a f_b$) is the likelihood of a null

chance ($p_{ab} > f_a f_b$), then the odds ratio is greater than one and the score is positive. Operationally, we say that positive scores mean conservative substitutions, and negative scores indicate nonconservative substitutions. This definition of 'conservative substitution' in a score matrix is purely statistical. It has nothing directly to do with amino acid structure or biochemistry.

This explains some details in BLOSUM62 that may seem counterintuitive at first glance. For instance, tryptophan (W/W) pairs score +11, while leucine (L/L) pairs only score +4; why shouldn't all identities get the same score? The rarer the amino acid is, the more surprising it would be to see two of them align together by chance. In the homologous alignment data that BLOSUM62 was trained on, leucine/leucine (L/L) pairs were in fact more common than tryptophan/tryptophan (W/W) pairs ($p_{L,L} = 0.0371$, $p_{W,W} = 0.0065$), but tryptophan is a much rarer amino acid ($f_L = 0.099$, $f_W = 0.013$). Run those numbers (with BLOSUM62's original $\lambda = 0.347$) and you get +3.8 for L/L and +10.5 for W/W, which were rounded to +4 and +11.

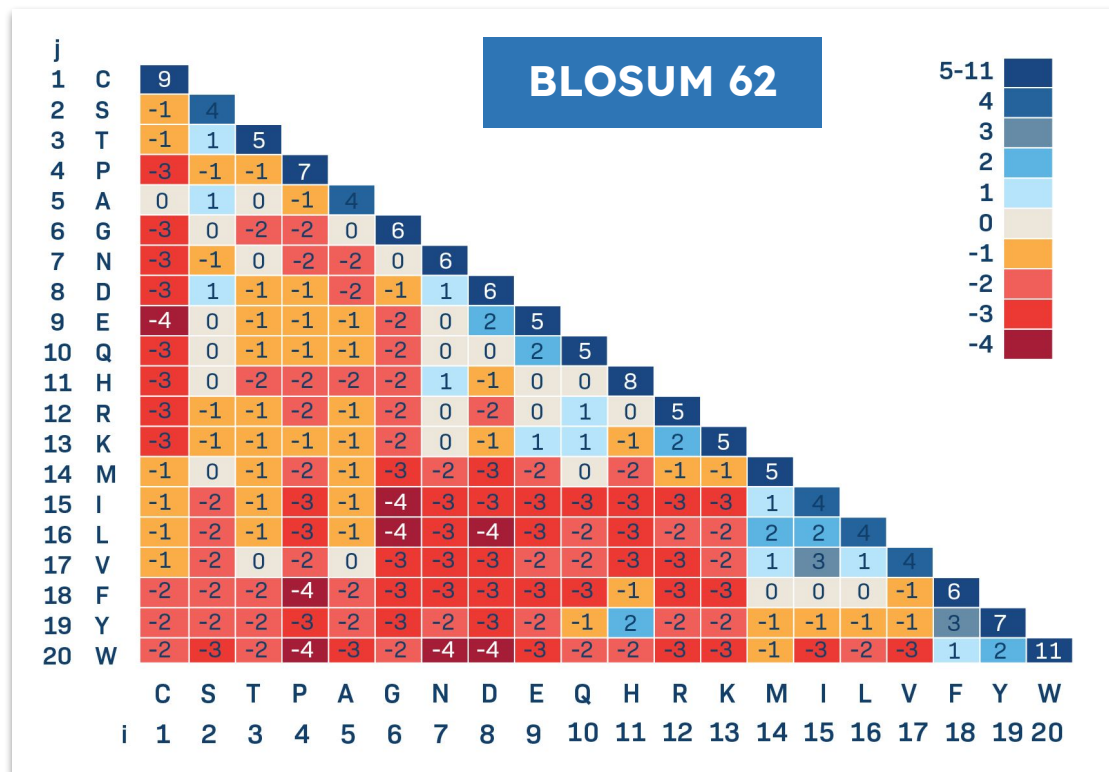
Another example is that BLOSUM62 awards a +1 to an apparently nonconser-

CSSIRSSYEQY

not found

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CSSIRSSYEQY



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Epitope

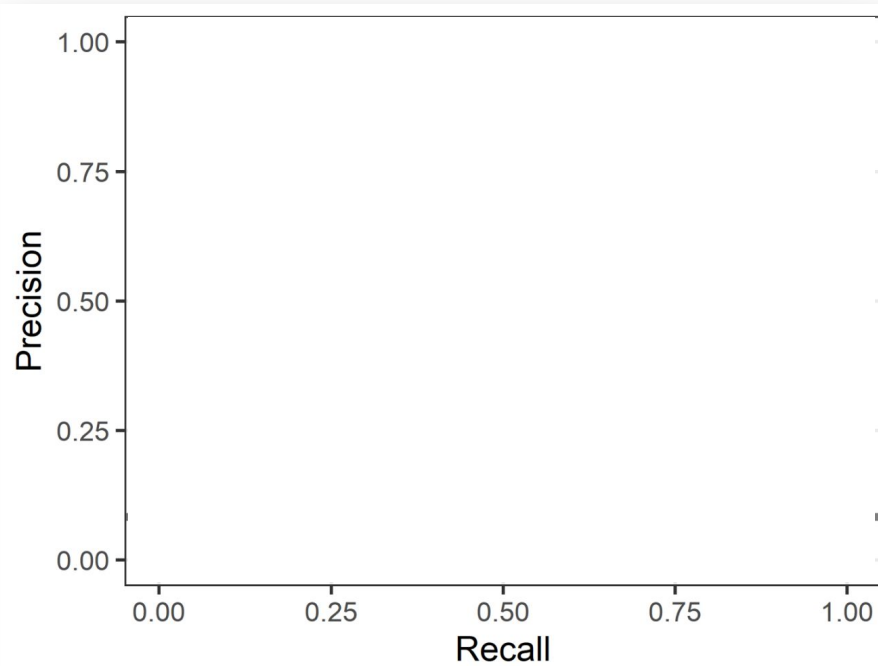
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Metric	Description
Alignment Score	Alignment score divided by length of alignment
Identity Alignment	Percent identity within length of alignment
Identity Long	Percent identity within length of longer sequence
Identity Short	Percent identity within length of shorter sequence
Levenshtein distance	Minimum number of edits (substitutions, insertions, and deletions) necessary to transform one sequence into another
TCRdist	Similarity-weighted mismatch distance between two sequences
TCRMatch (MAIT Match)	Comprehensive comparison of all possible k-mers using BLOSUM62 observed frequency matrix

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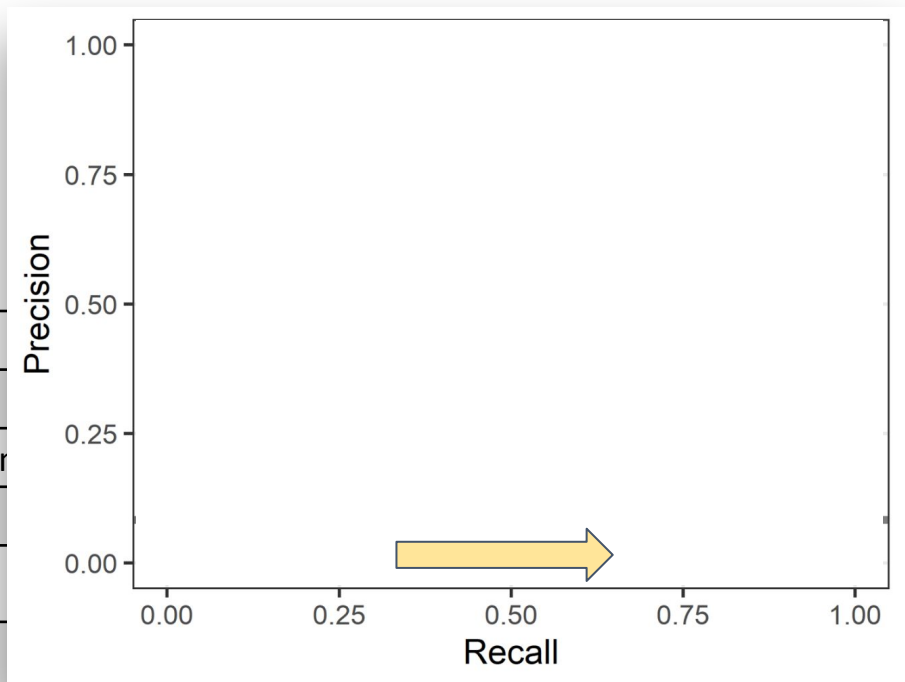
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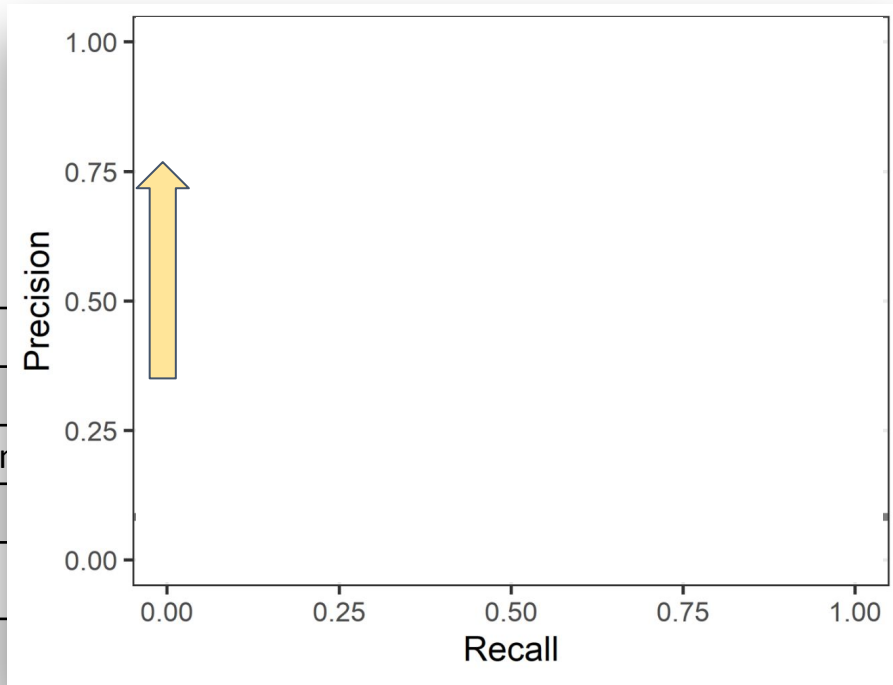
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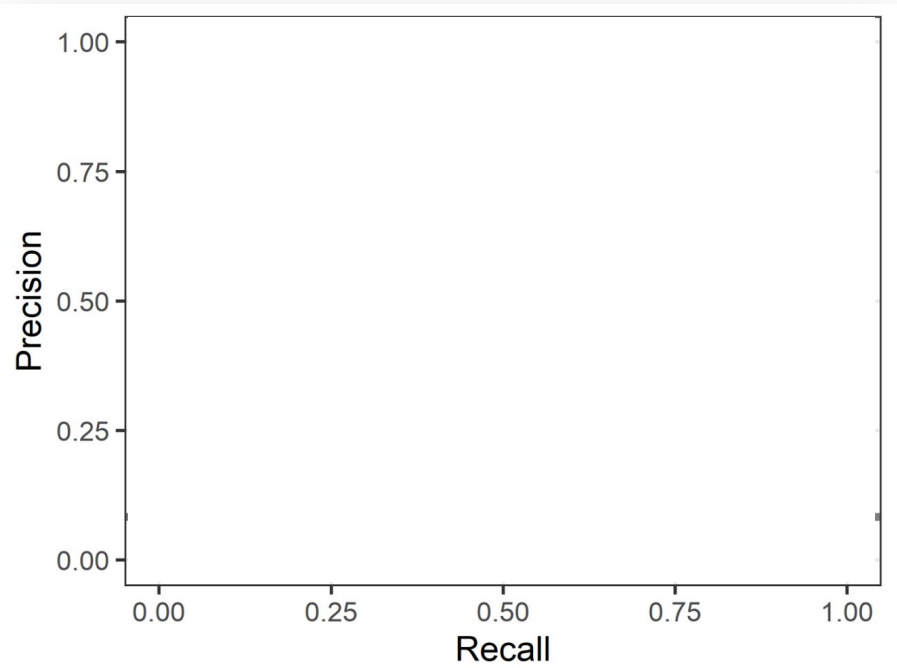
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TCRmatch

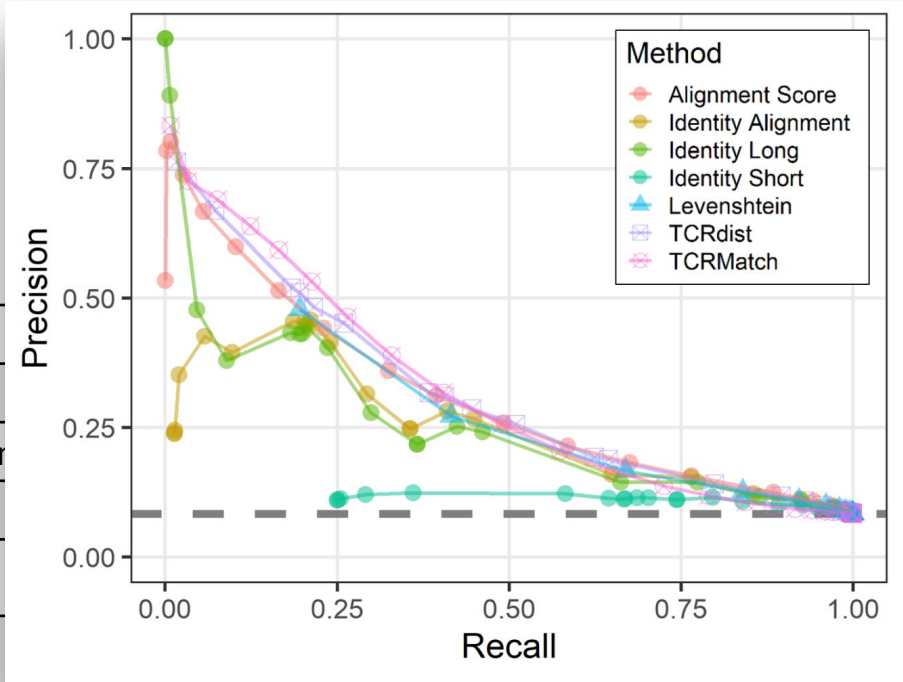
- MHC presenting an antigen to a T-Cell
- T-cell receptor: α/β units
- Somatic recombination
- Each chain: 3 CDRs
- CDR3 β
 - Most variable
 - Directly interacts with epitope
- Repertoire sequencing
- Which epitope interacts with *this specific* TCR?
- TCRmatch: searches IEDB for a similar CDR3 β
- How to find the most similar sequences?

Metric	
Alignment Score	
Identity Alignment	
Identity Long	
Identity Short	
Levenshtein distance	Minimum number of edits (substitutions, insertions, and deletions) necessary to transform one sequence into another
TCRdist	Similarity-weighted mismatch distance between two sequences
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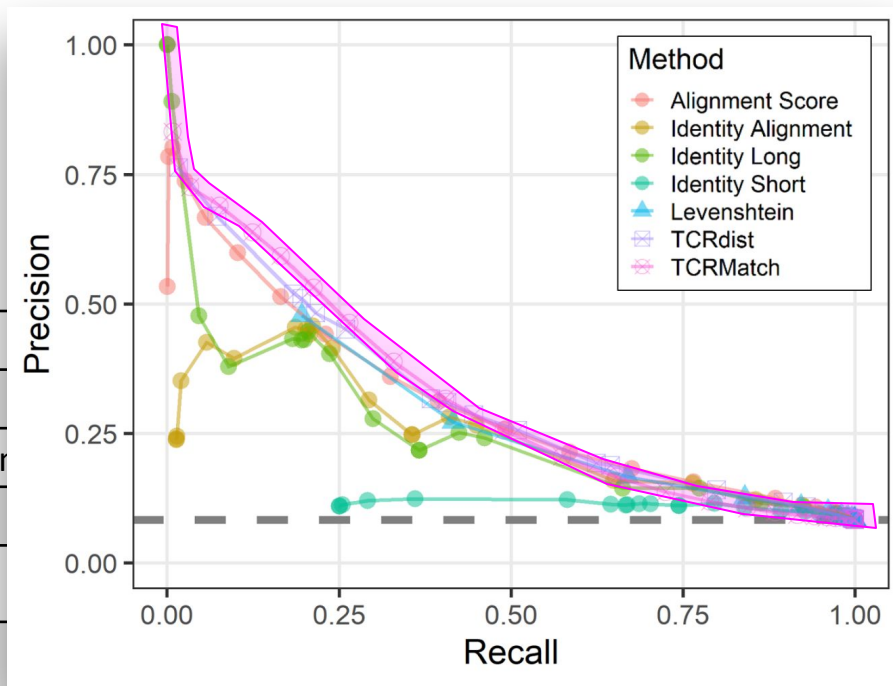


Metric	
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Identity Alignment	
Identity Long	
Identity Short	
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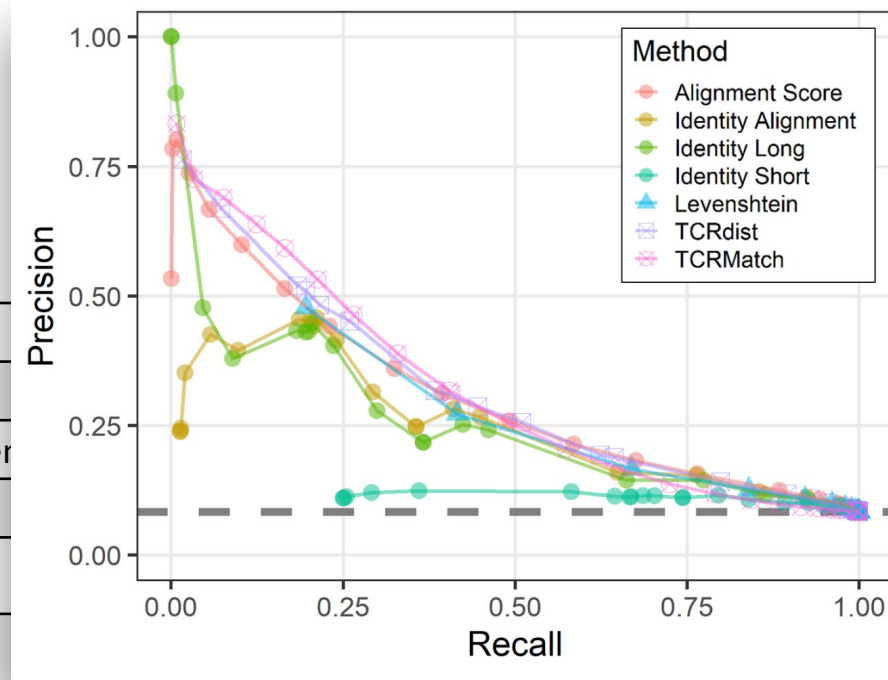
Metric	
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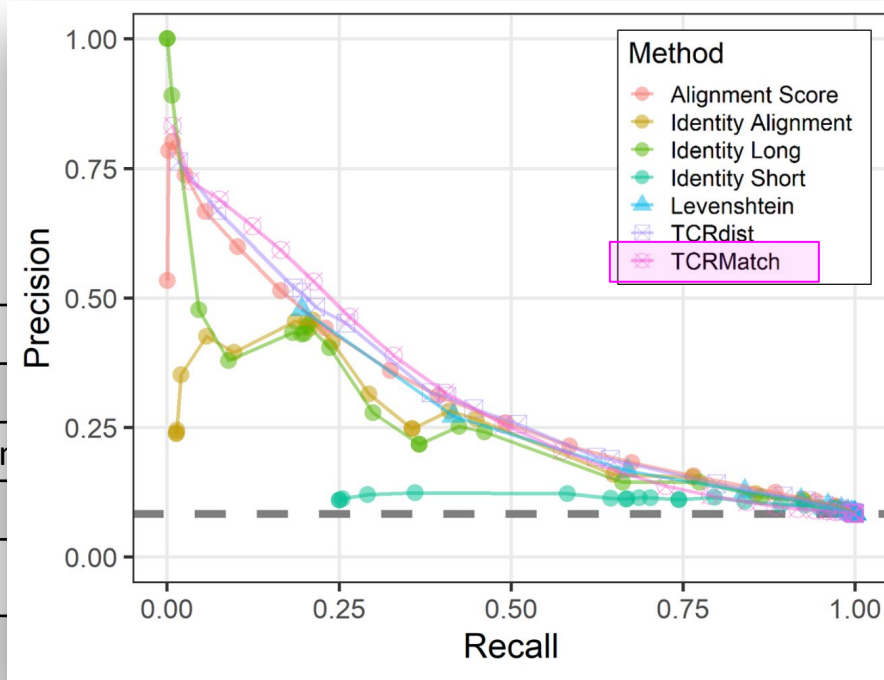
Metric	
Alignment Score	
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Levenshtein distance	Minimum number of edits (substitutions, insertions, and deletions) necessary to transform one sequence into another
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TCRmatch

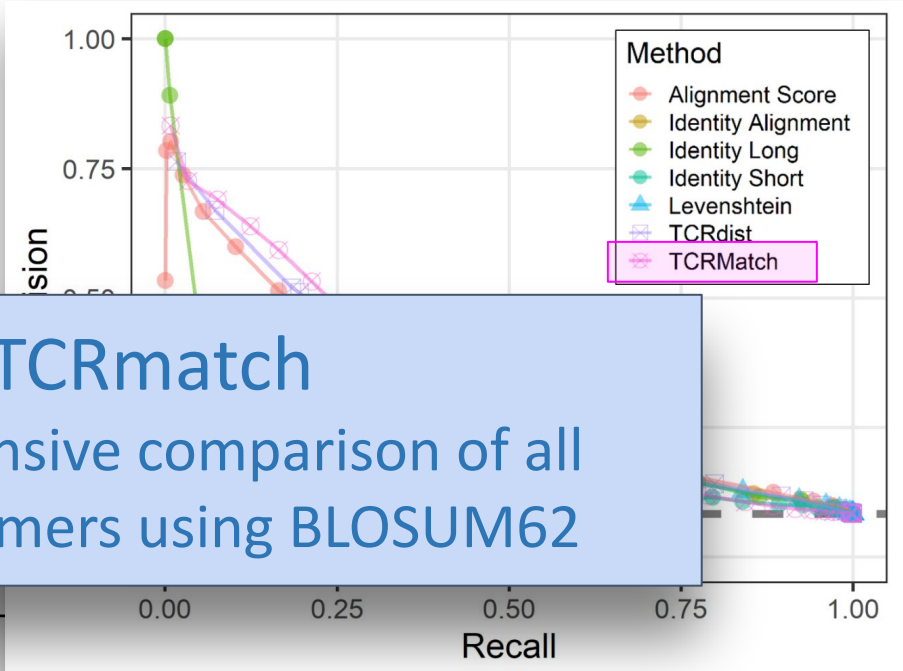
- MHC presenting an antigen to a T-Cell
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- Each chain: 3 CDRs
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TCRmatch

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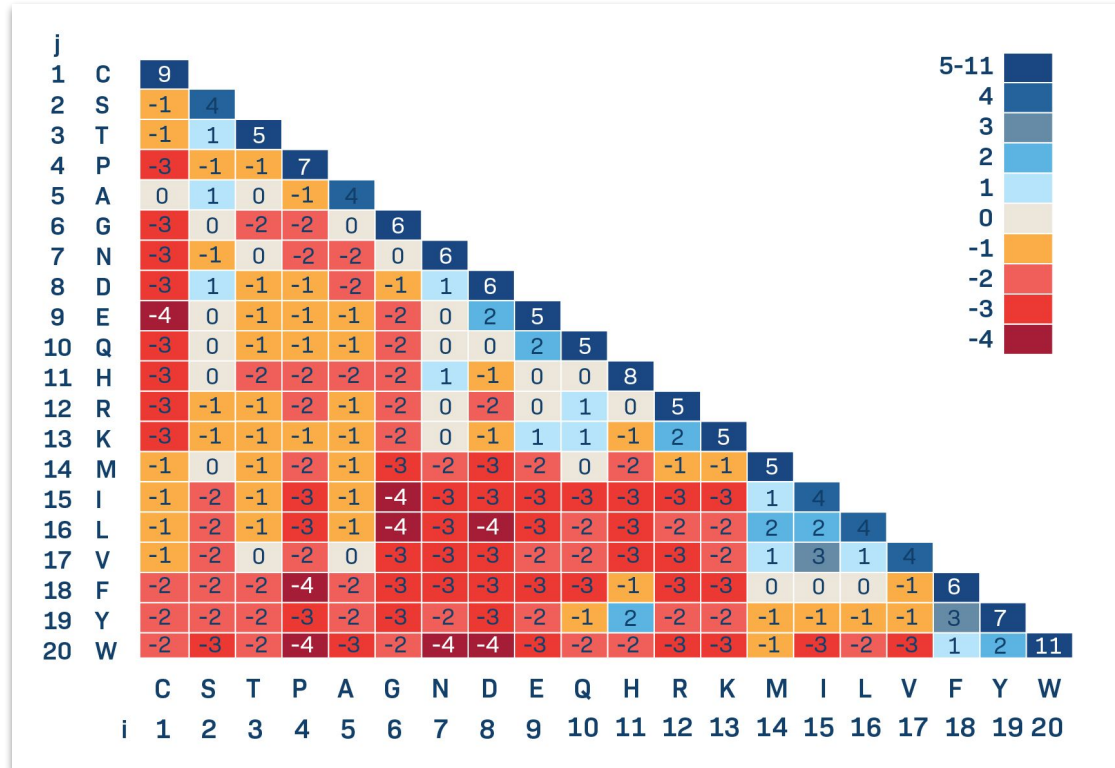


TCRmatch
 Comprehensive comparison of all possible k-mers using BLOSUM62

Levenshtein distance	Minimum number of edits (substitutions, insertions, and deletions) necessary to transform one sequence into another
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TCRmatch

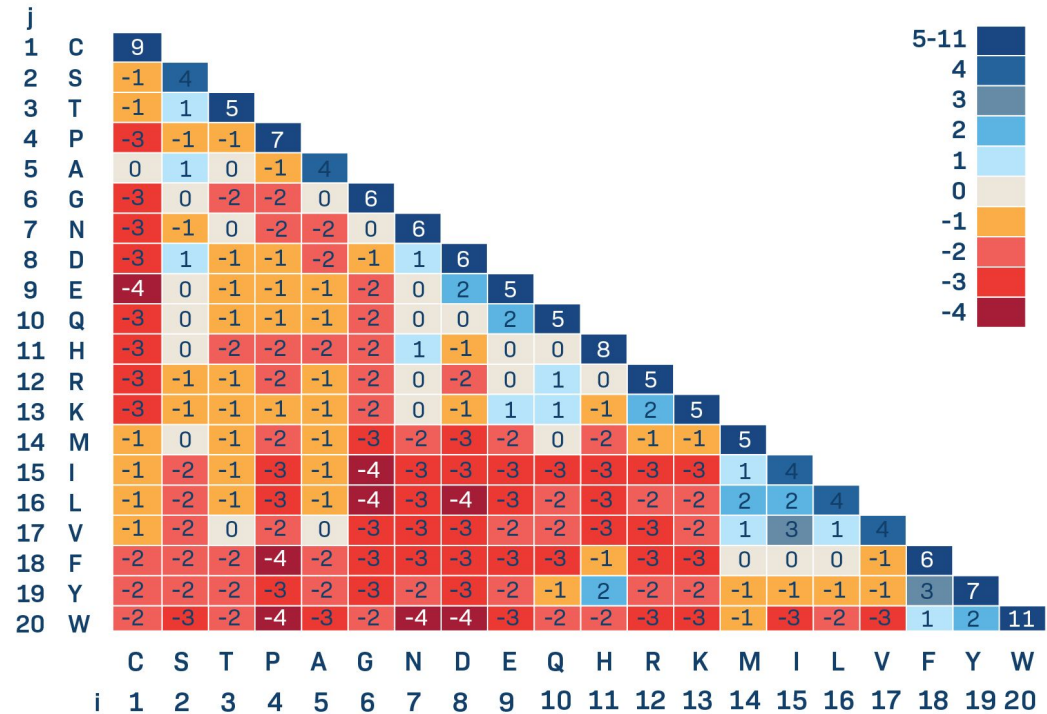
ASSSANYGYT
ASSIRAAETQY



TCRmatch

ASSSANYGYT

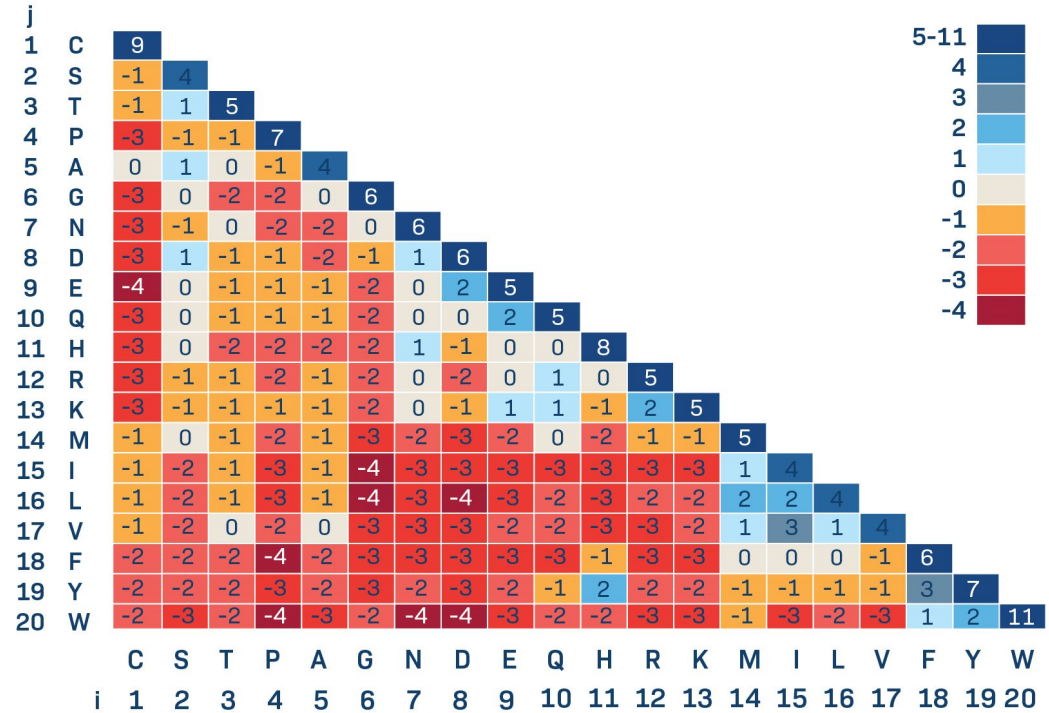
ASSIRAAETQY



TCRmatch

ASSSANYGYT

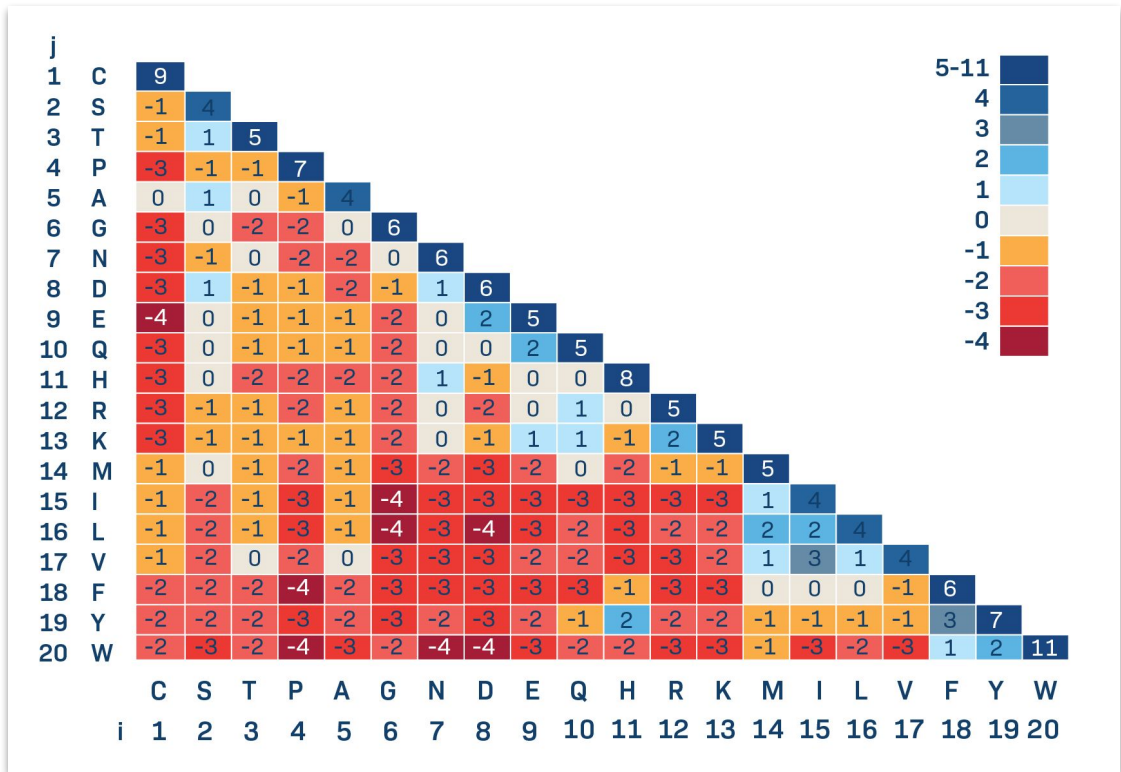
ASSIRAAETQY



TCRmatch

$$k = 1$$

ASSSANYGYT
ASSIRAAETQY

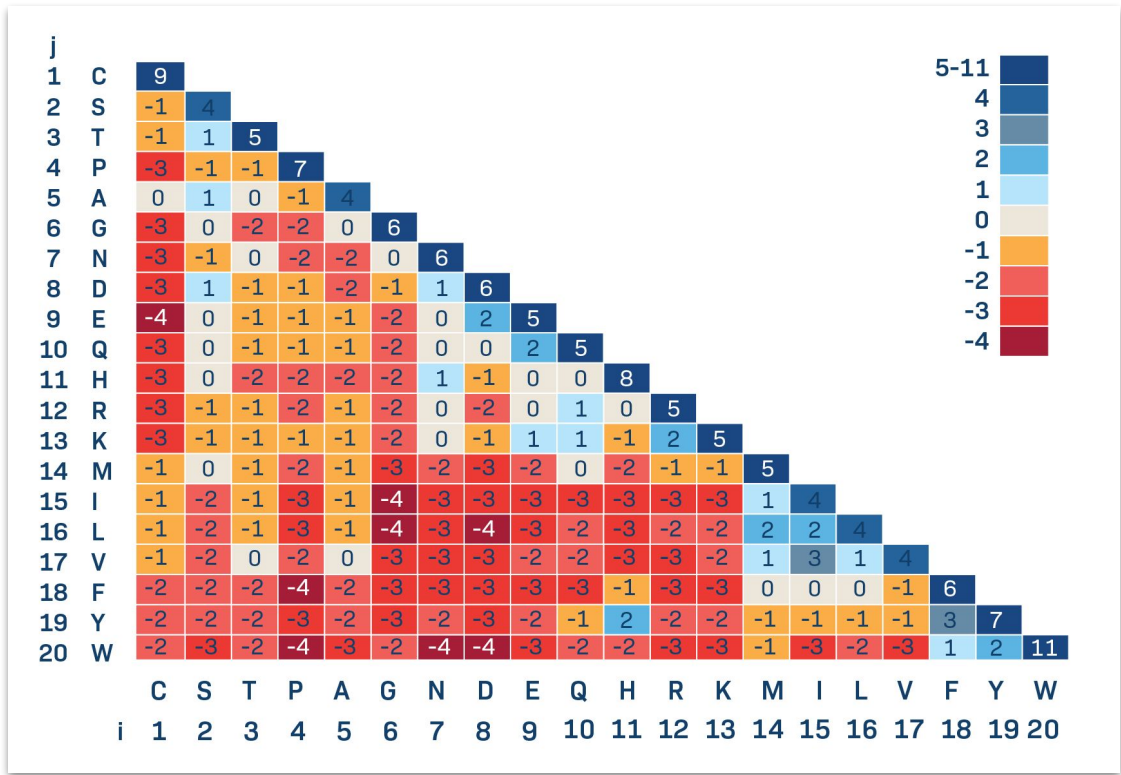


TCRmatch

$$k = 1$$

ASSSANYGYT

ASSIRAAETQY

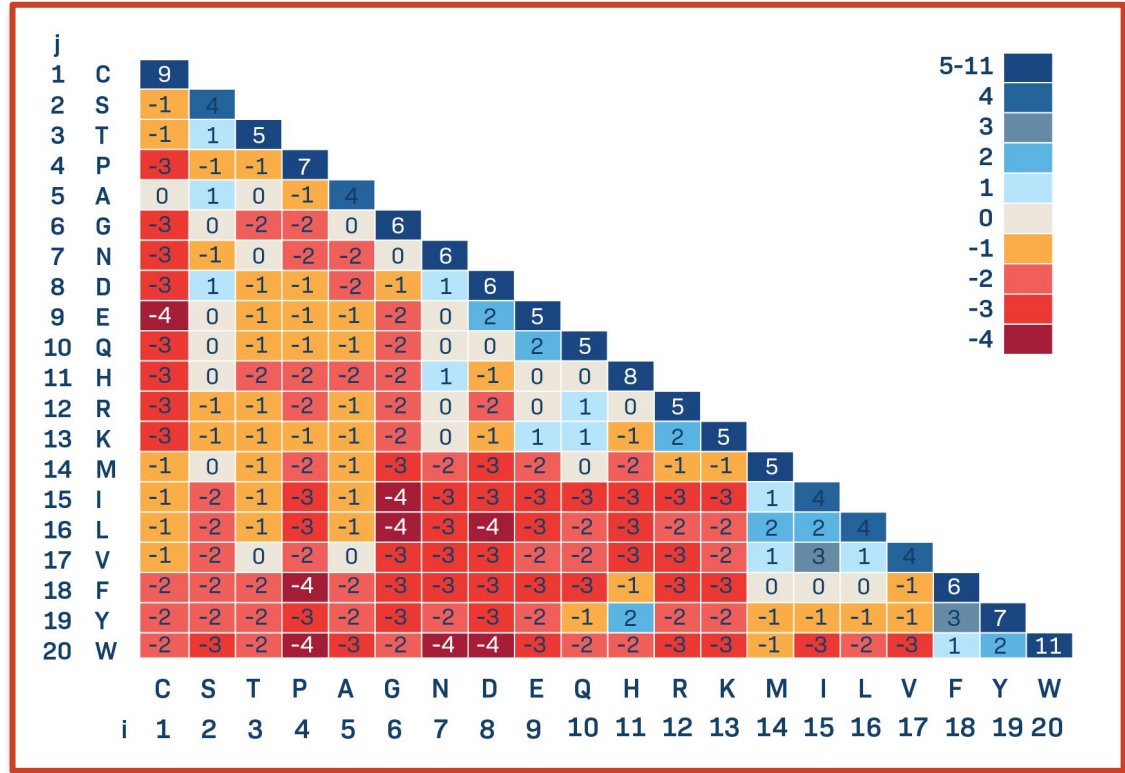


TCRmatch

$$k = 1$$

ASSSANYGYT

ASSIRAAETQY

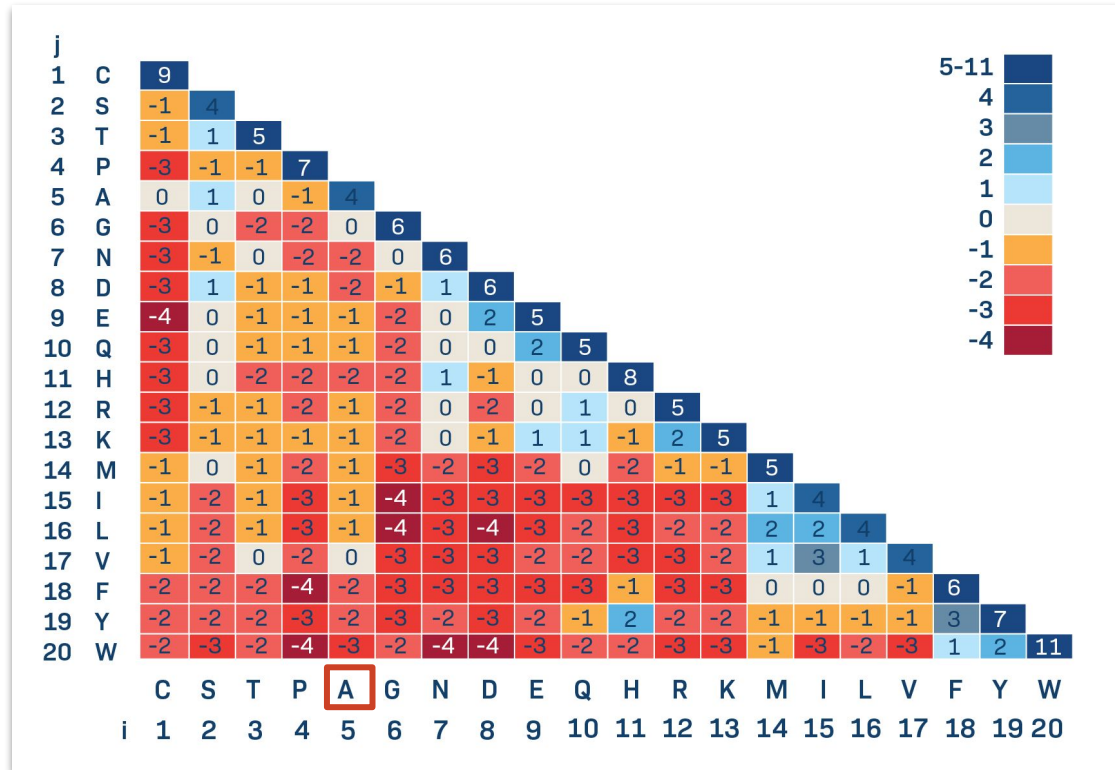


TCRmatch

$$k = 1$$

ASSSANYGYT

ASSIRAAETQY

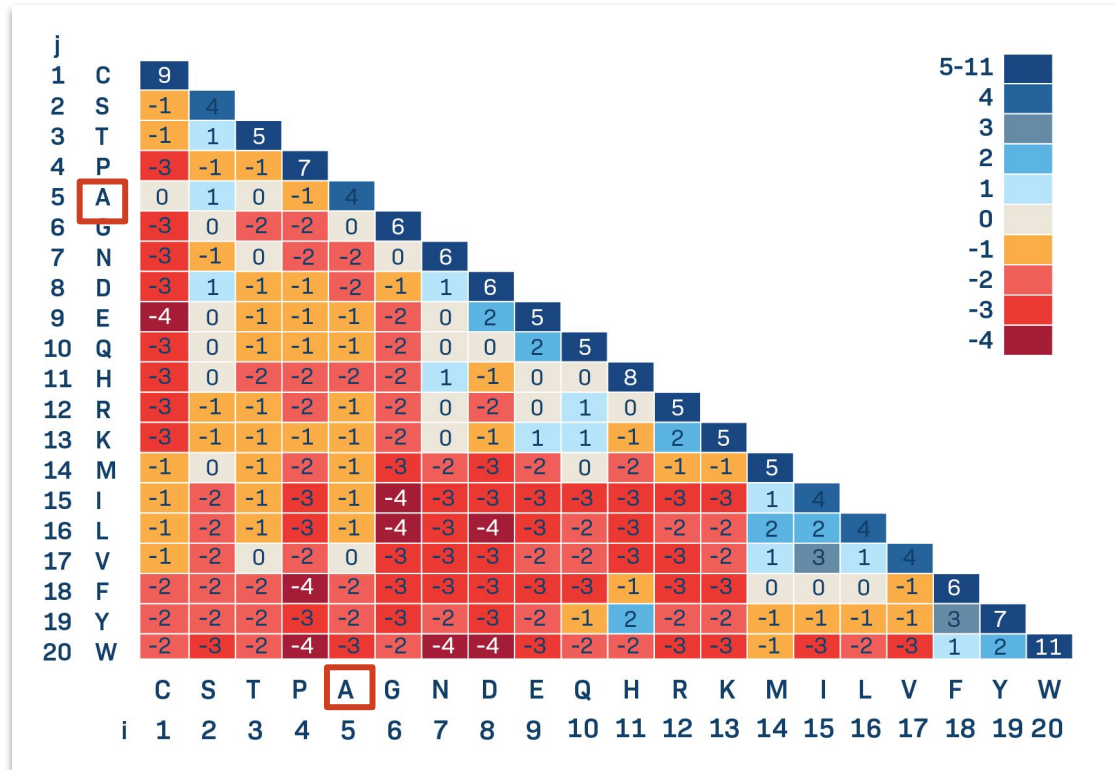


TCRmatch

$$k = 1$$

ASSSANYGYT

ASSIRAAETQY

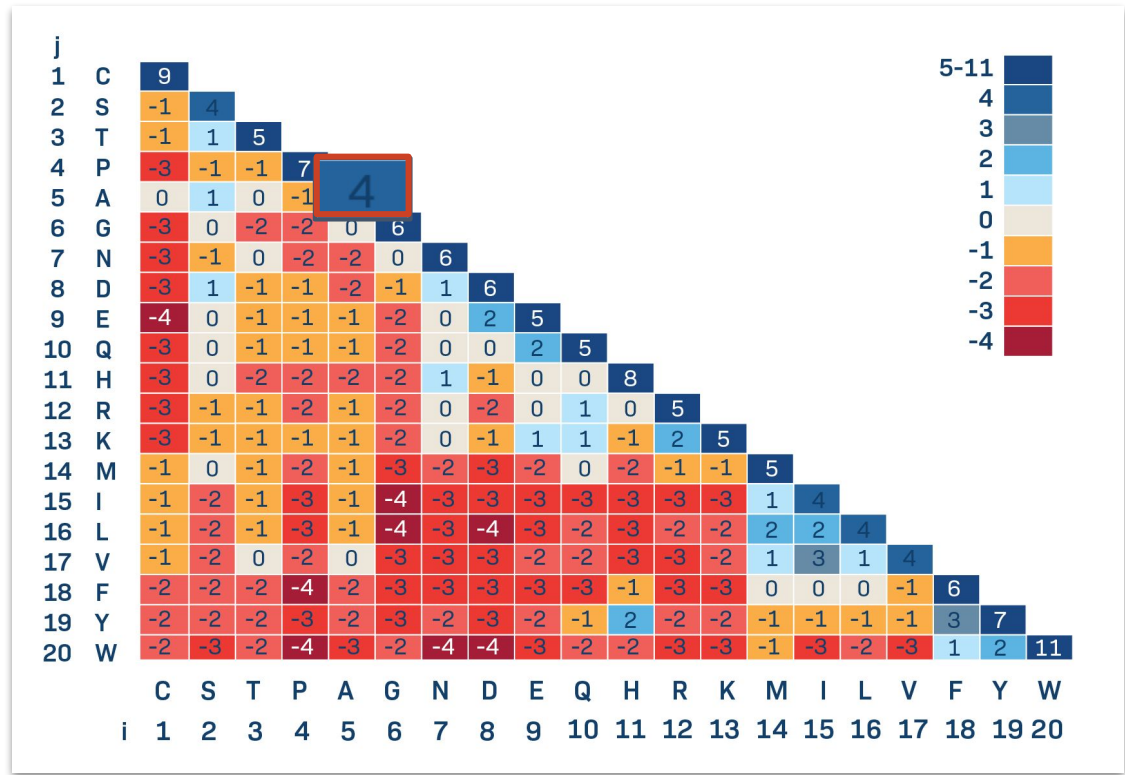


TCRmatch

$$k = 1$$

ASSSANYGYT

ASSIRAAETQY

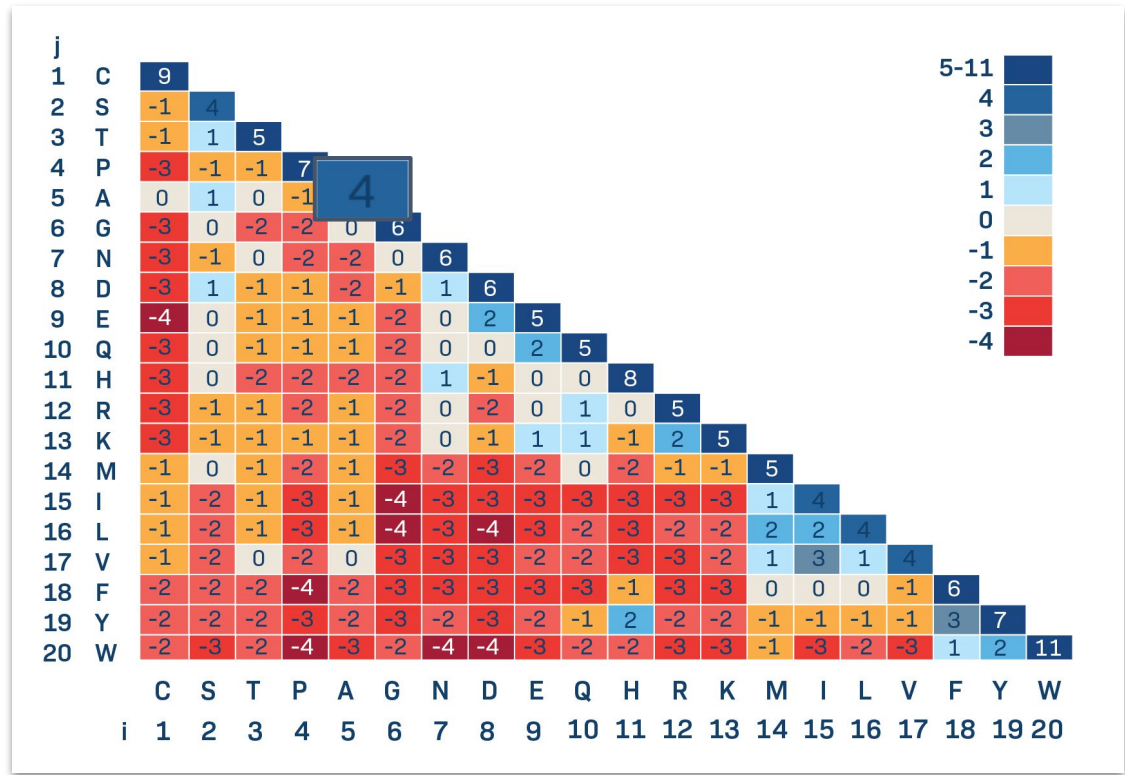


TCRmatch

$$k = 1$$

ASSSANYGYT

ASSIRAAETQY

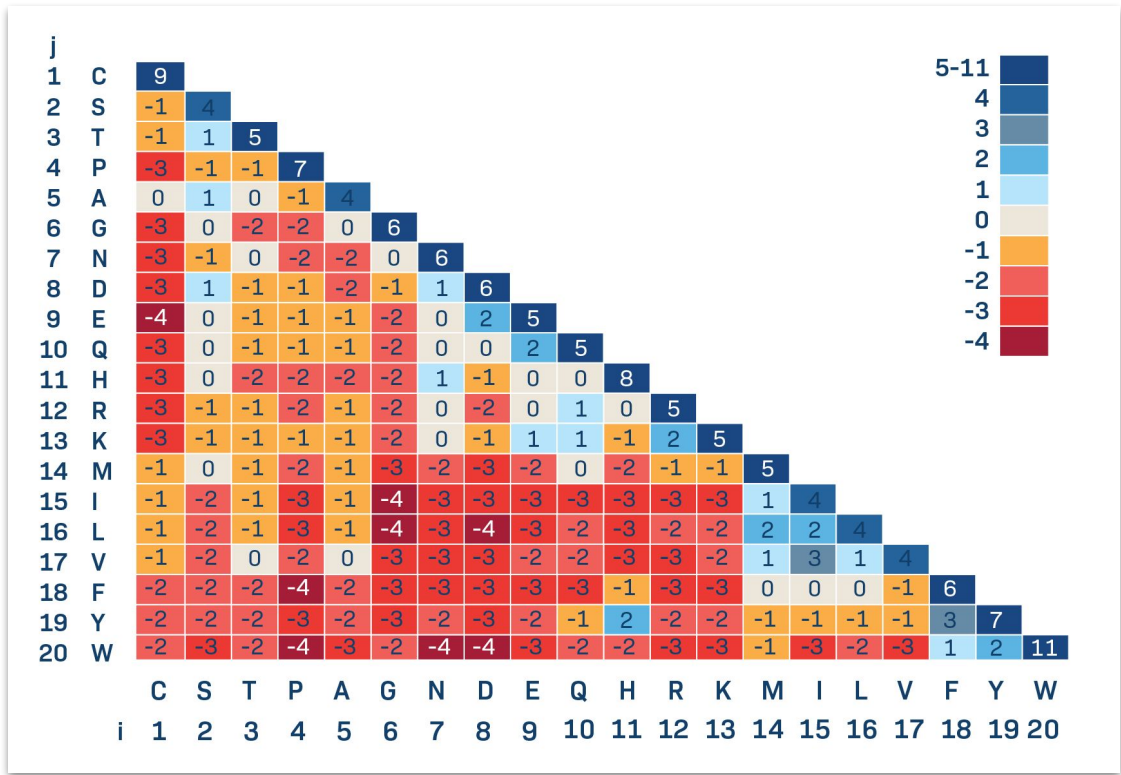


TCRmatch

$$k = 1$$

ASSSANYGYT

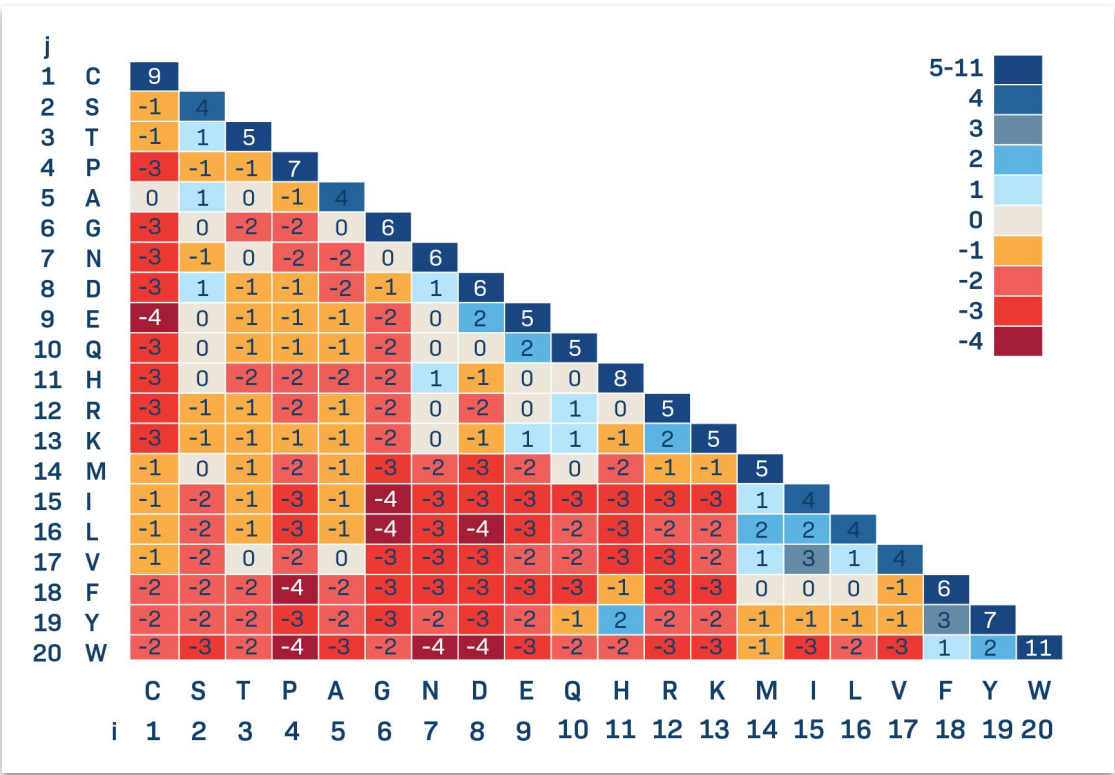
ASSIRAAETQY



TCRmatch

$$k = 1$$

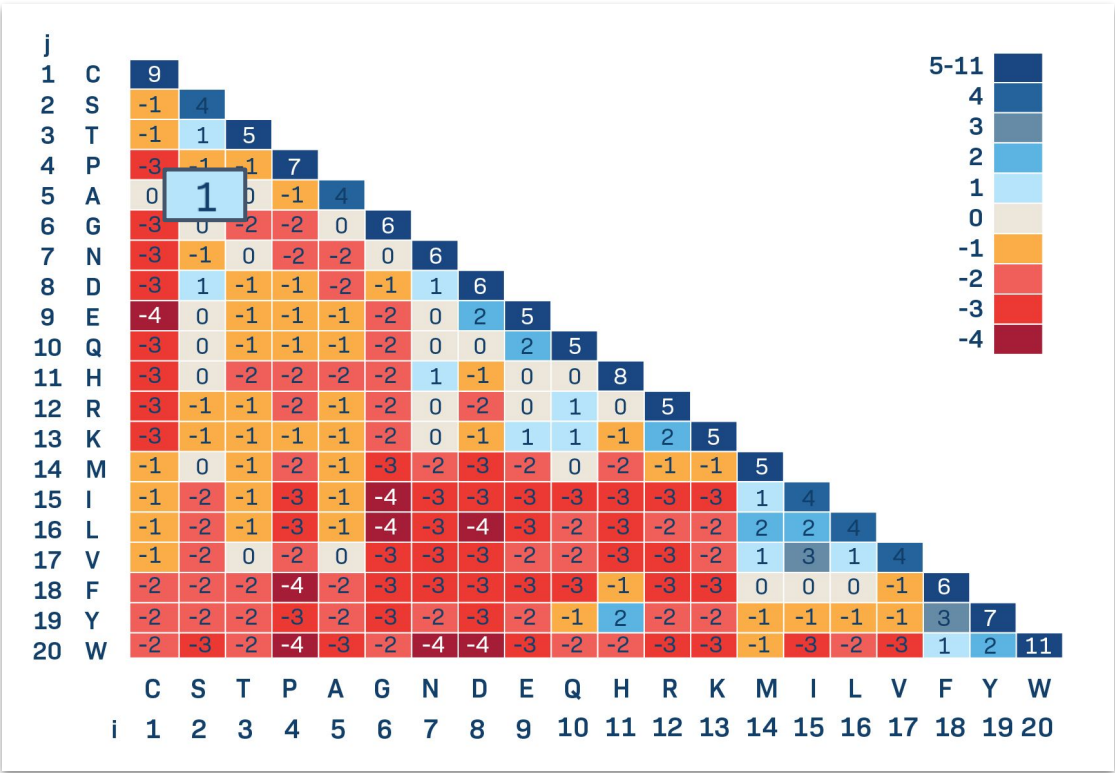
ASSSANYGYT
ASSIRAAETQY



TCRmatch

$$k = 1$$

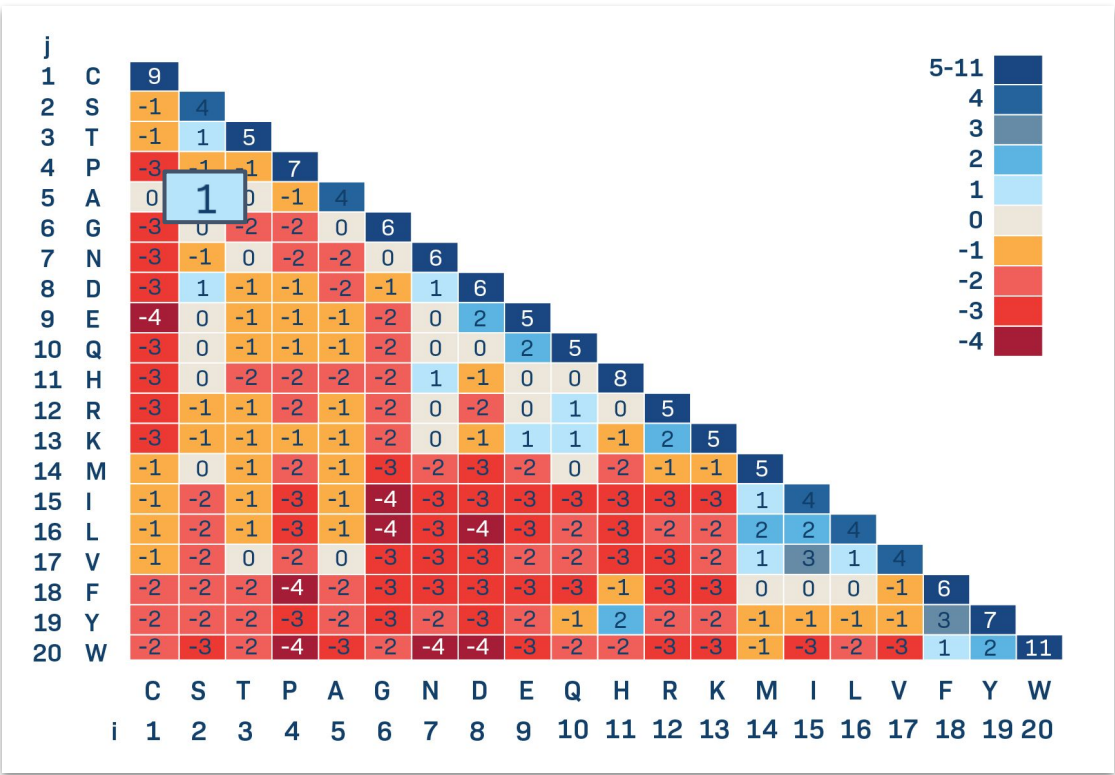
ASSSANYGYT
ASSIRAAETQY



TCRmatch

$$k = 1$$

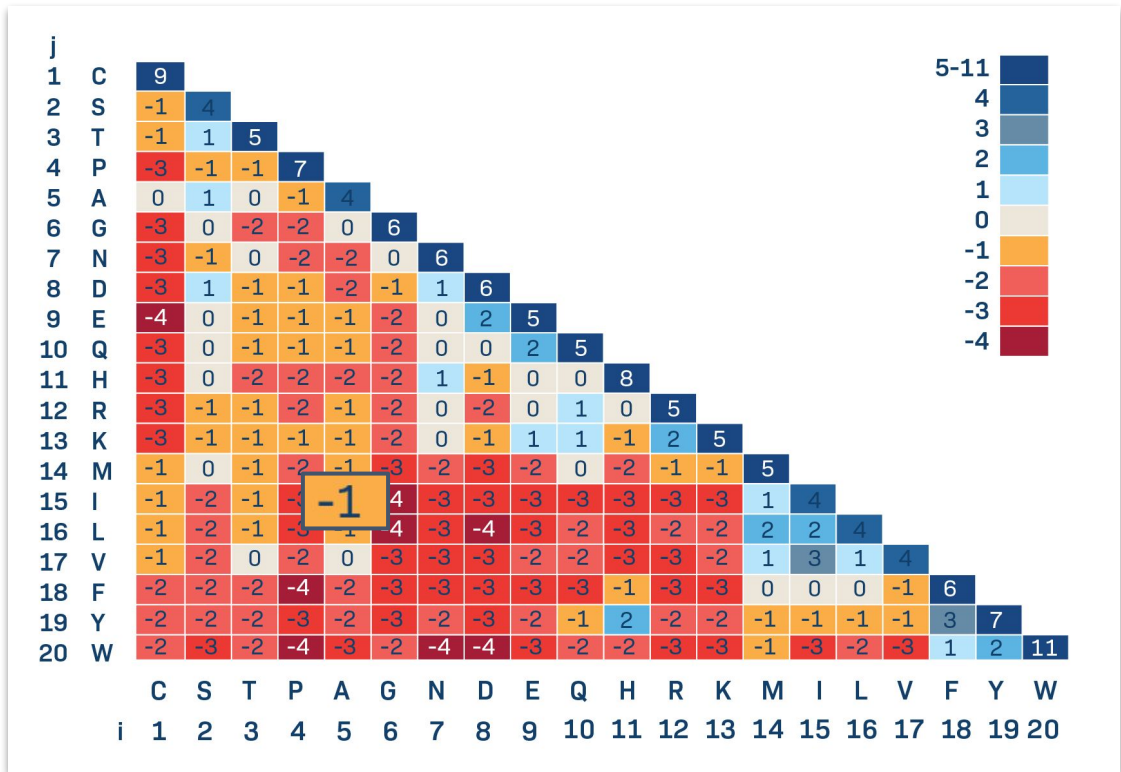
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ASSIRAAETQY



TCRmatch

$$k = 1$$

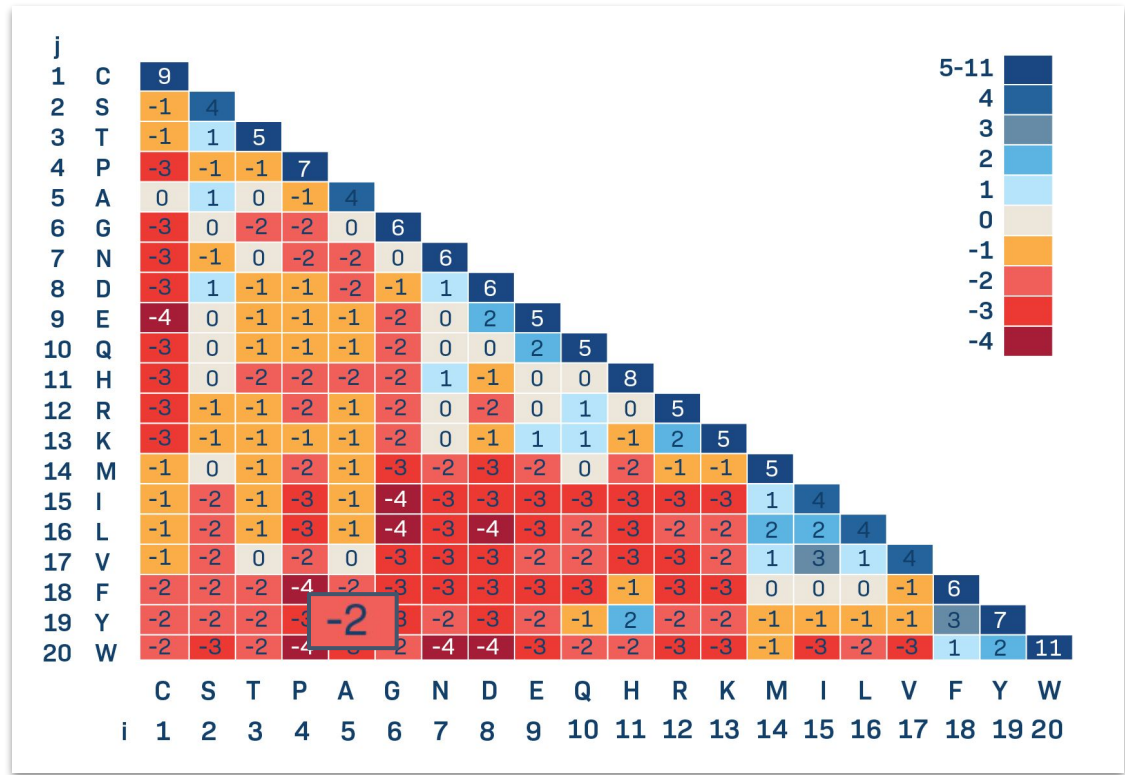
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ASSIRAAETQY



TCRmatch

$$k = 1$$

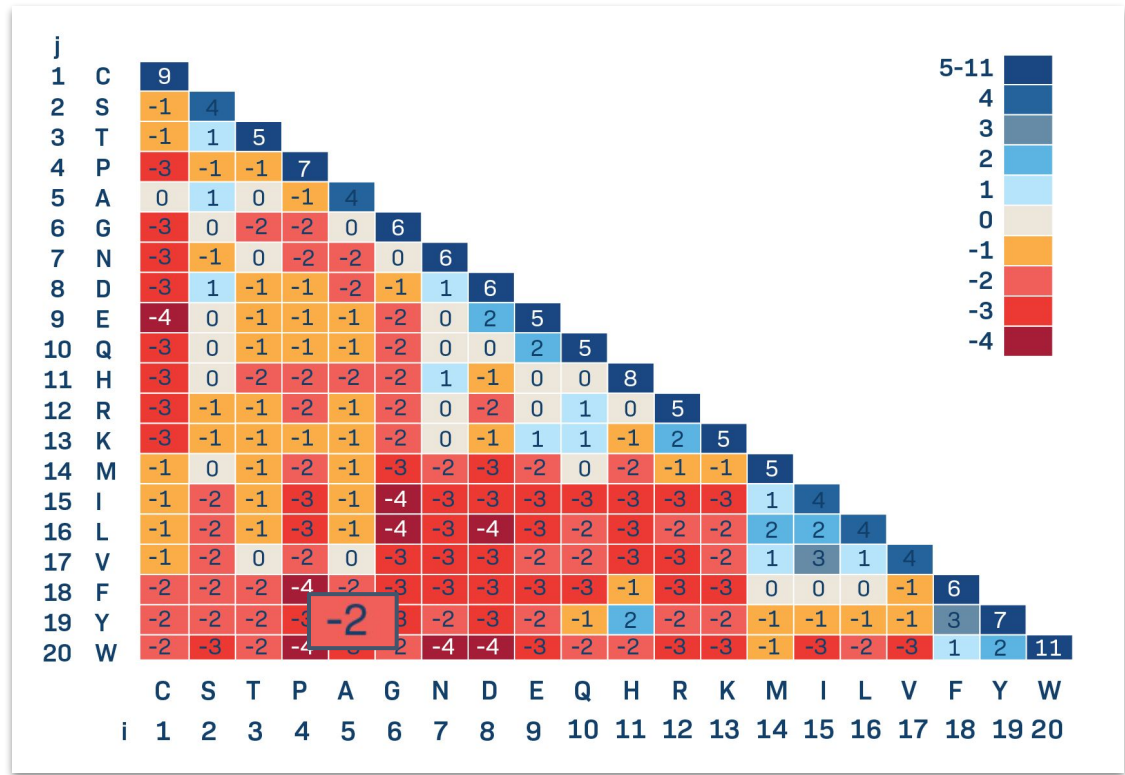
ASSSANYGYT
ASSIRAAETQY
(...)



TCRmatch

$$k = 1$$

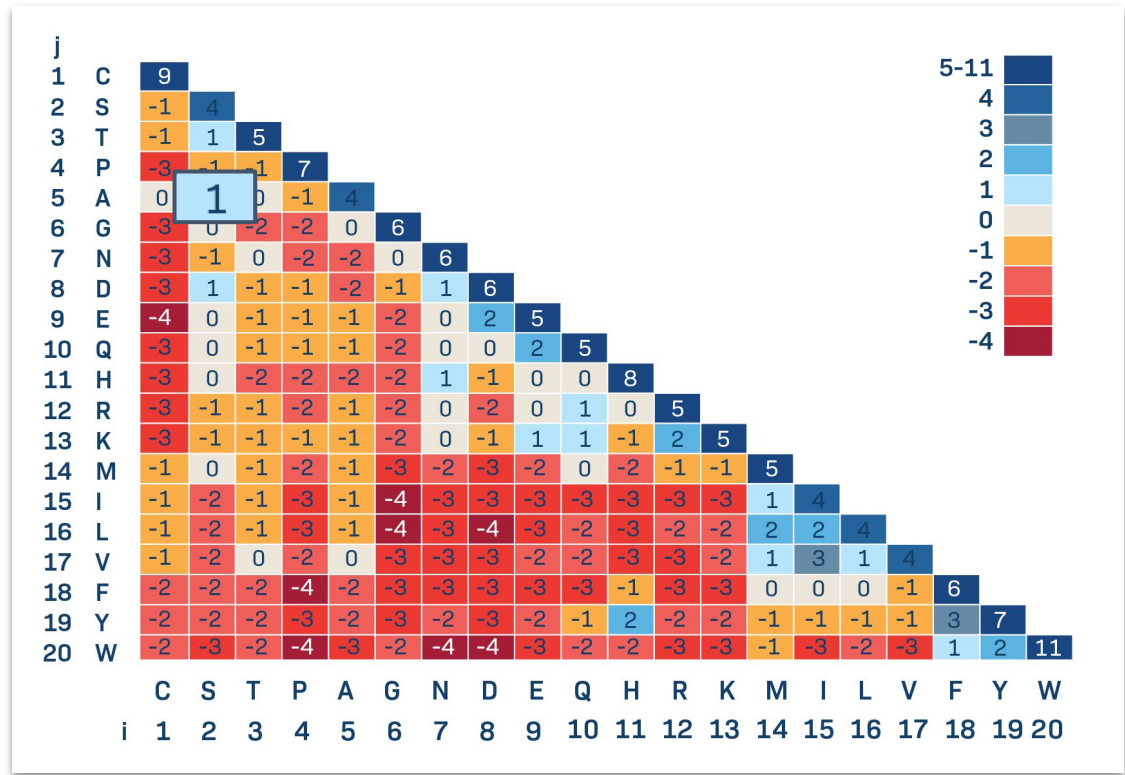
ASSSANYGYT
ASSIRAAETQY
(...)



TCRmatch

$$k = 1$$

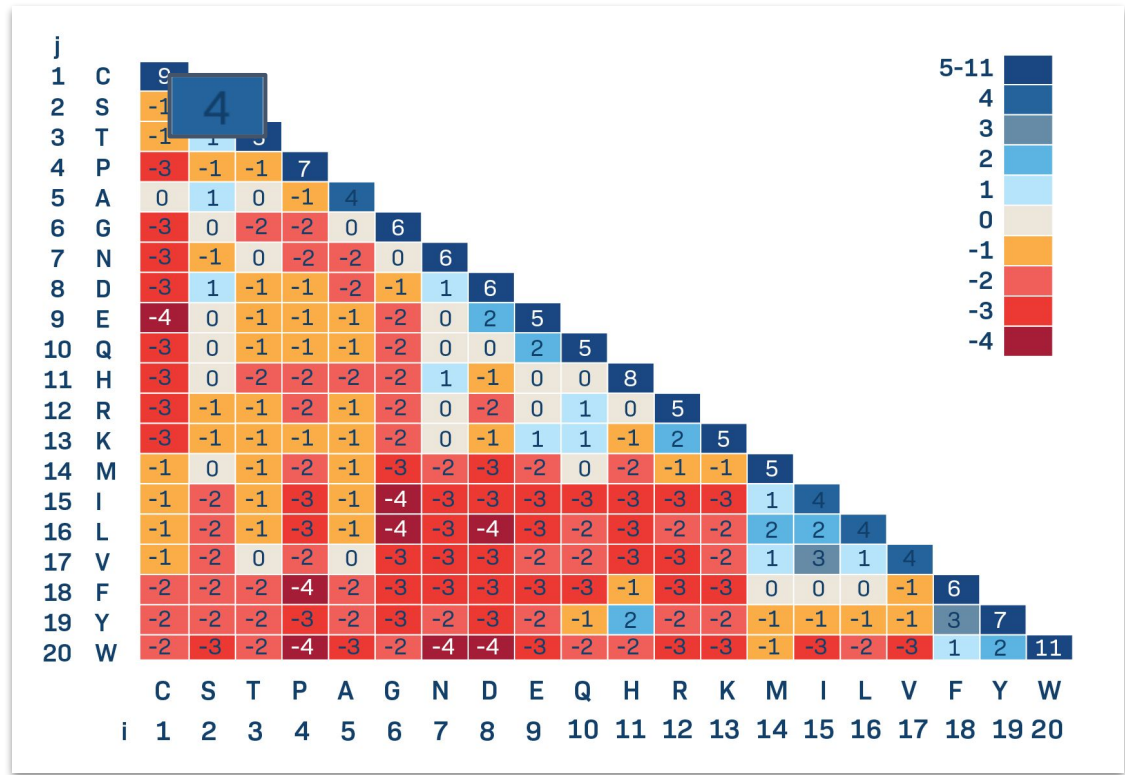
ASSSANYGYT
ASSIRAAETQY
(...)



TCRmatch

$$k = 1$$

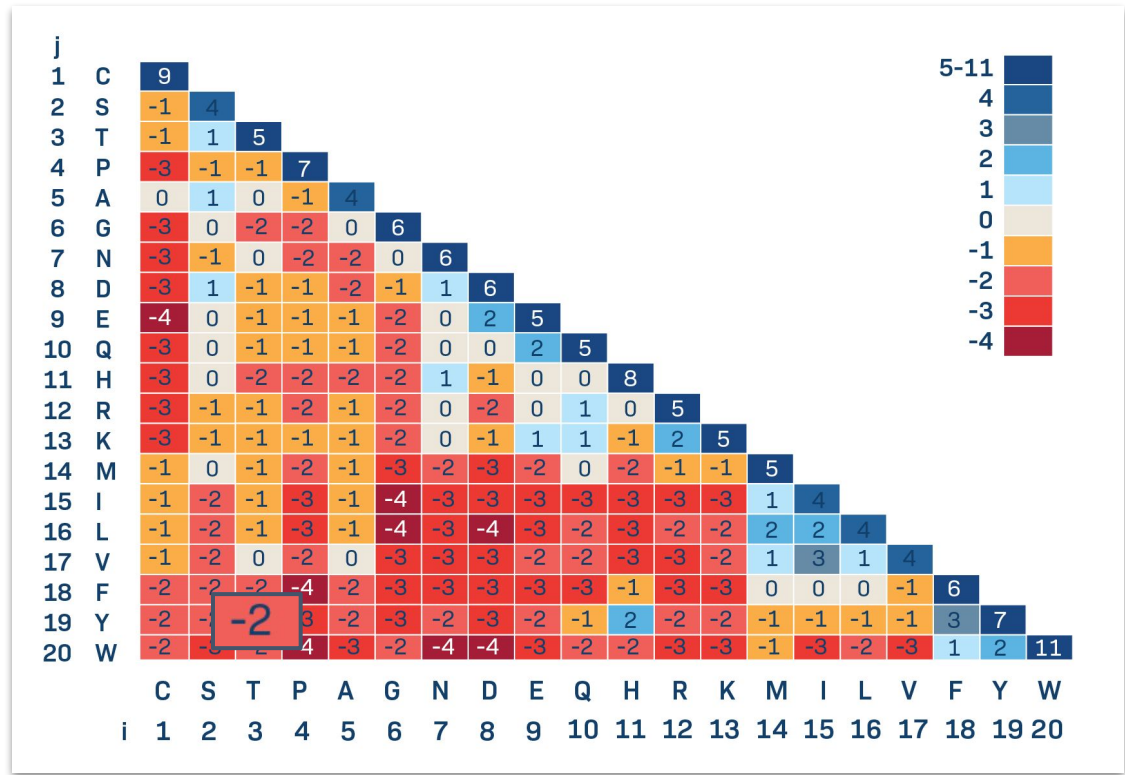
ASSSANYGYT
ASSIRAAETQY
(...)



TCRmatch

$$k = 1$$

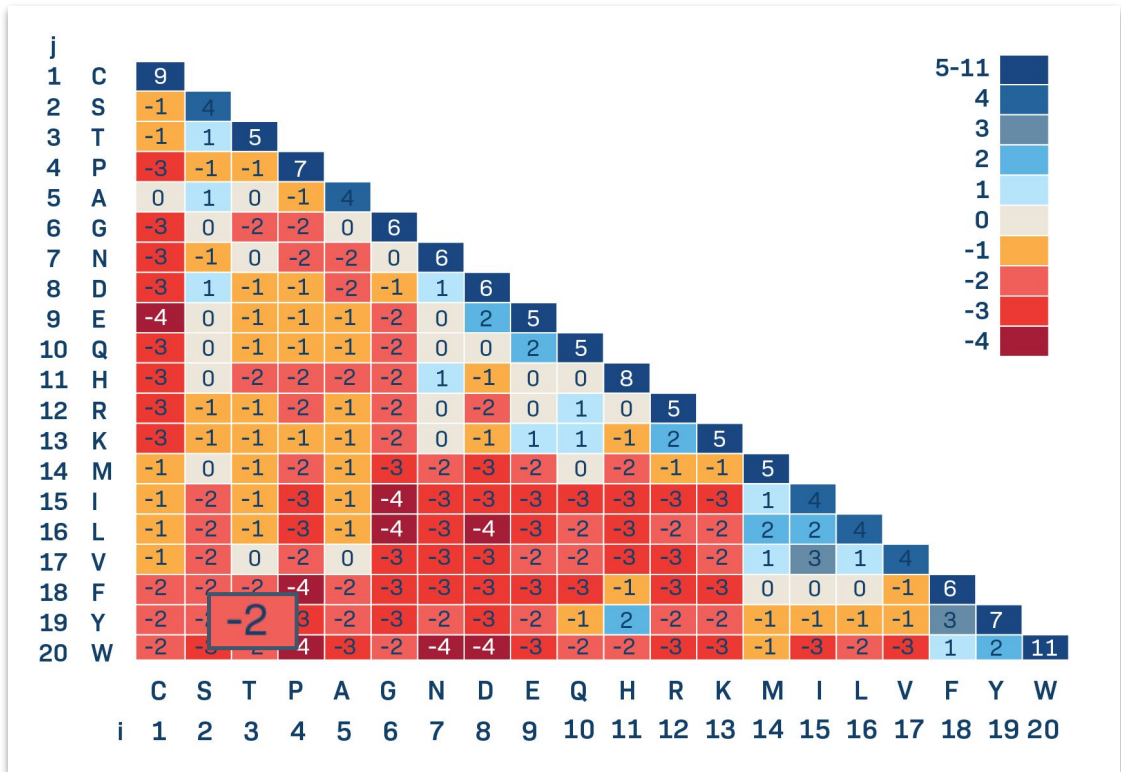
ASSSANYGYT
ASSIRAAETQY
(...)



TCRmatch

$$k = 1$$

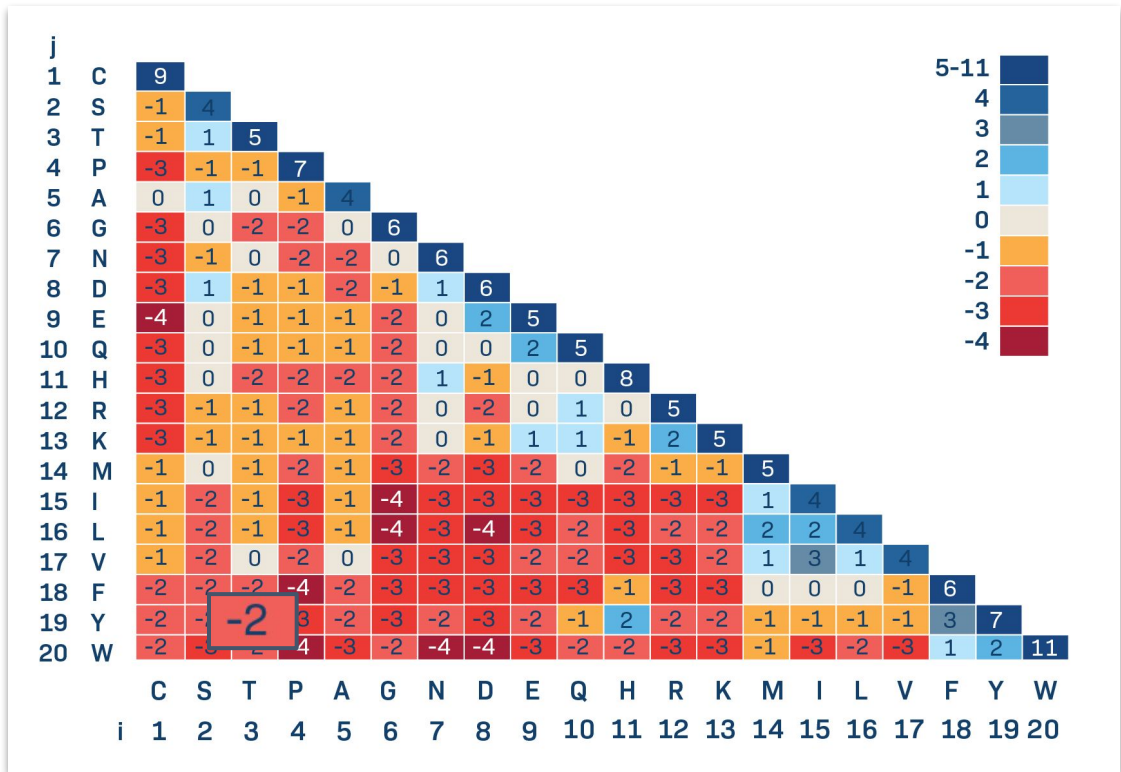
ASSSANYGYT
ASSIRAAETQY
(...)



TCRmatch

$$k = 2$$

ASSSANYGYT
ASSIRAAETQY
(...)

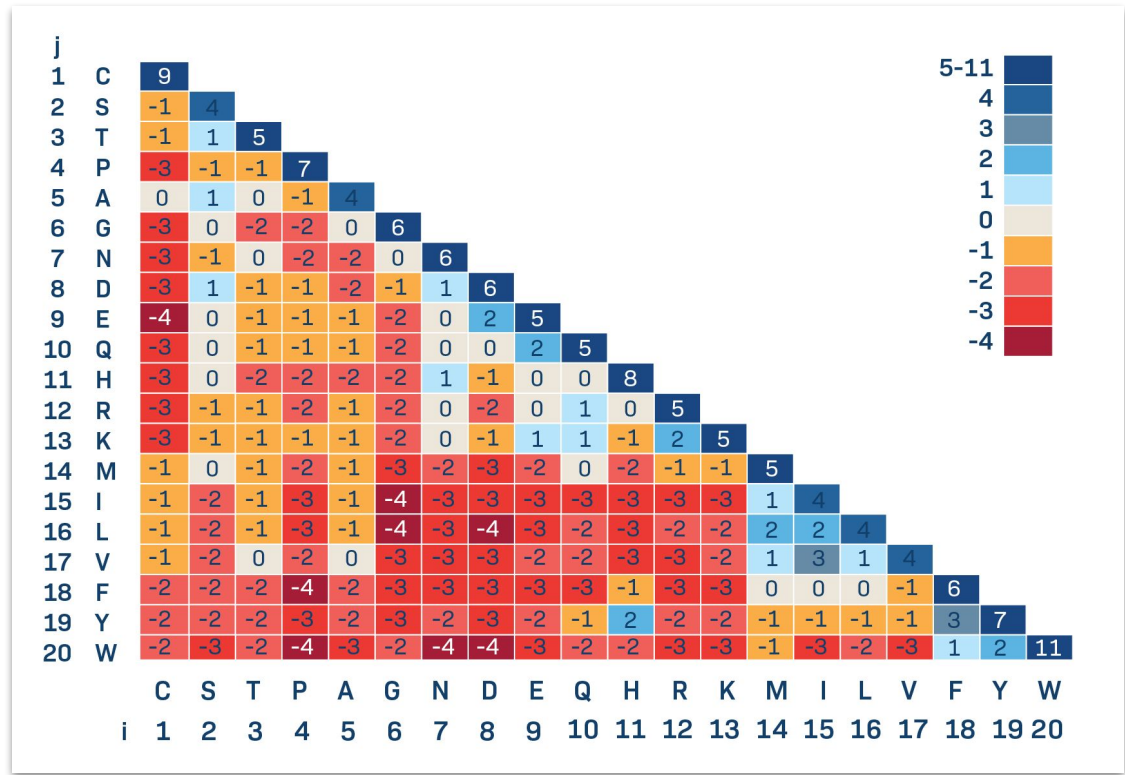


TCRmatch

$$k = 2$$

ASSSANYGYT

ASSIRAAETQY

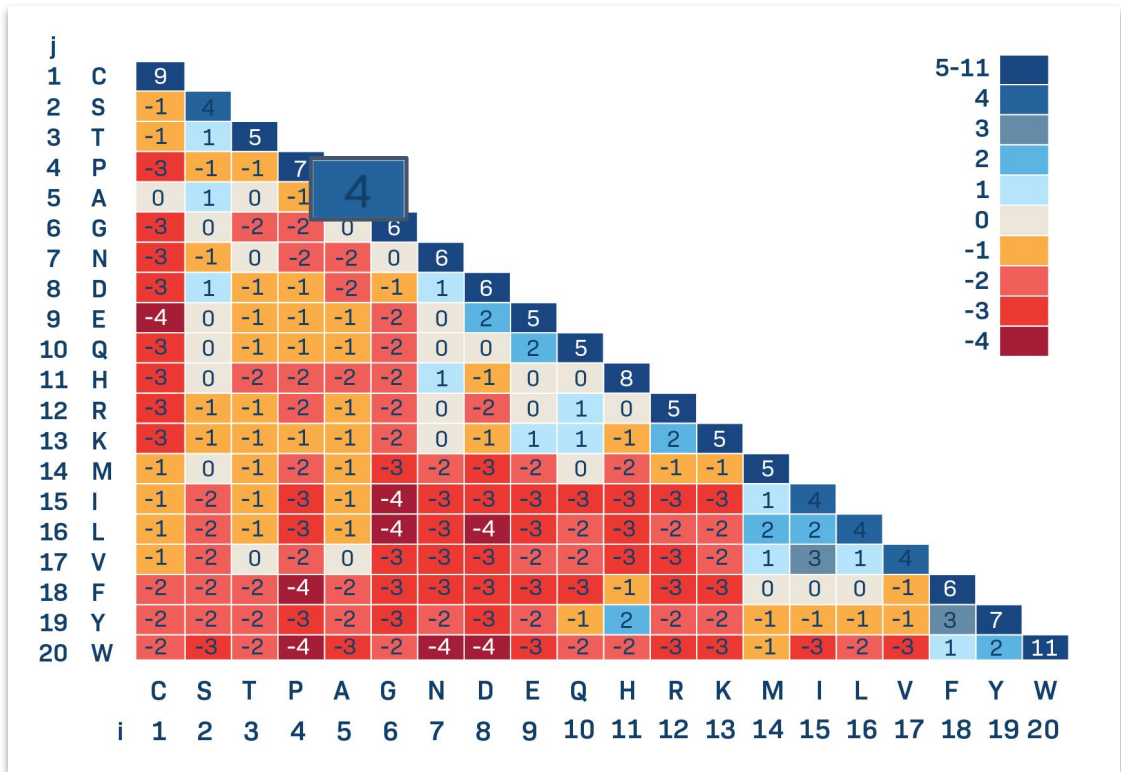


TCRmatch

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ASSSANYGYT

ASSIRAAETQY

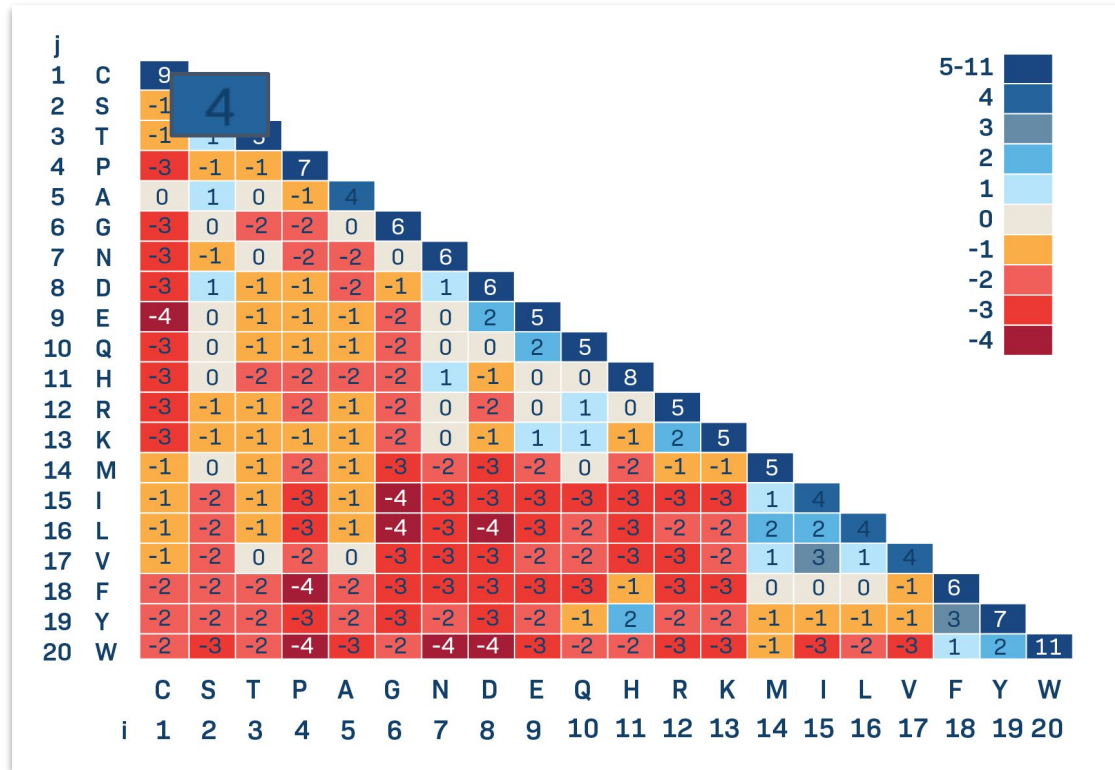


TCRmatch

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ASSSANYGYT

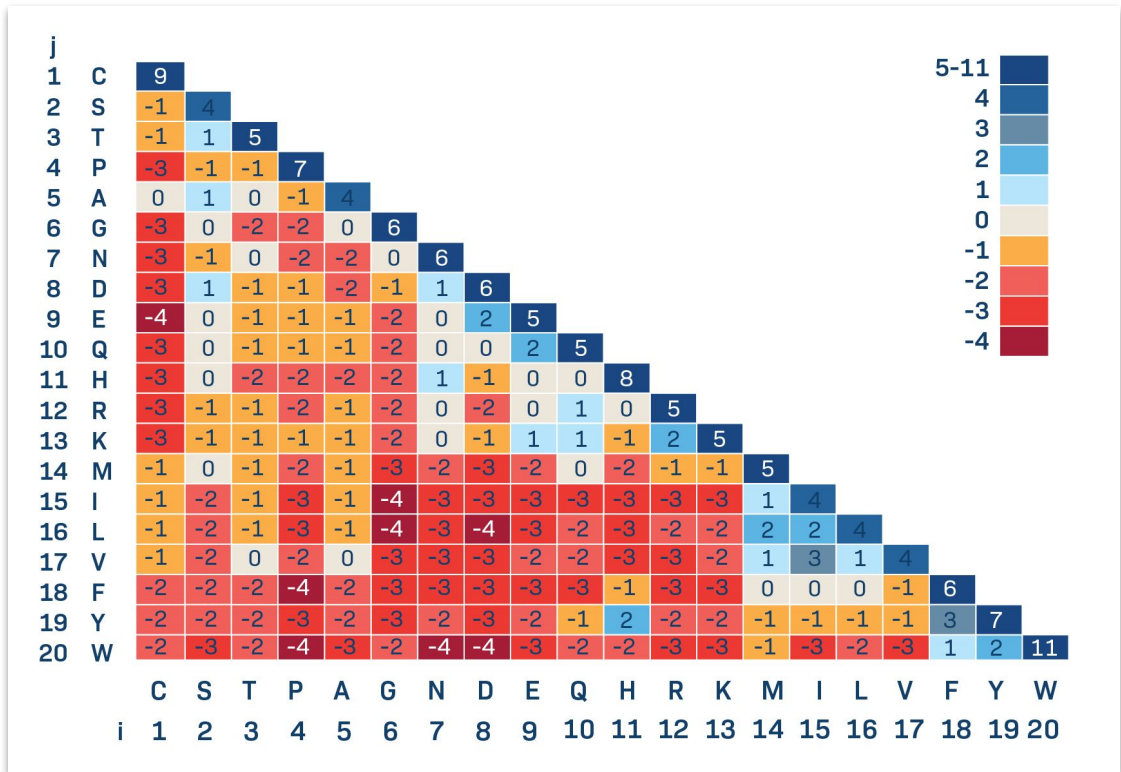
ASSIRAAETQY



TCRmatch

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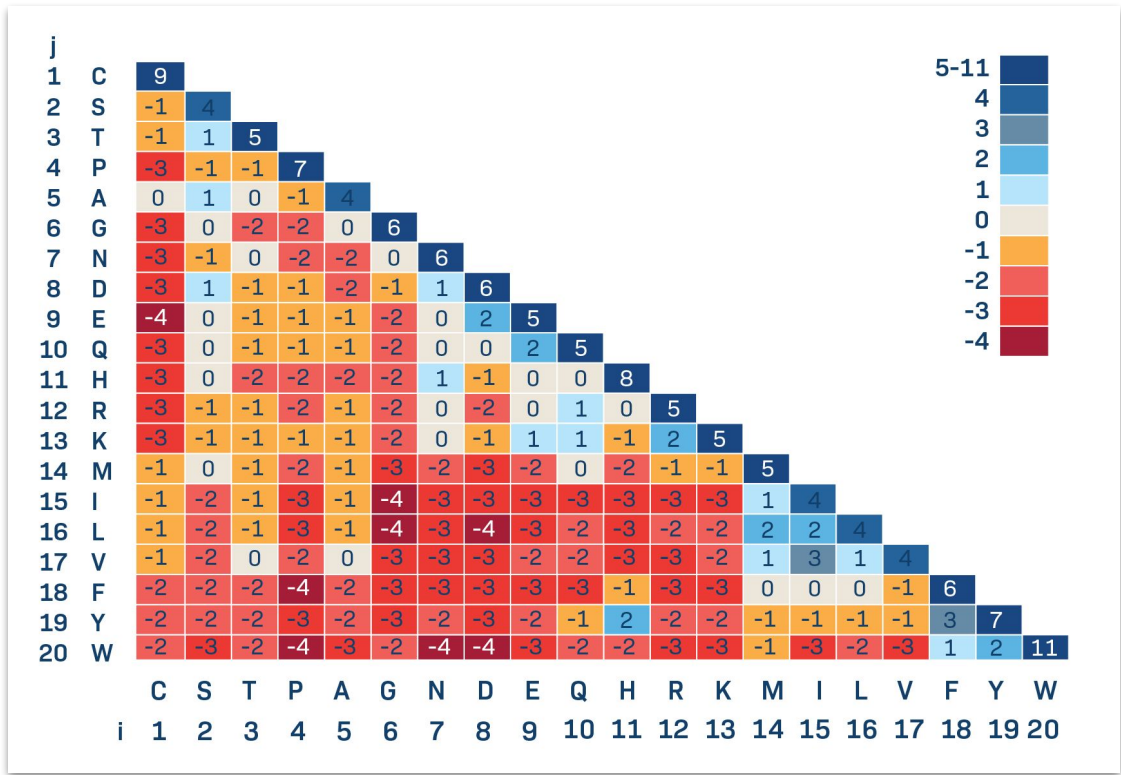
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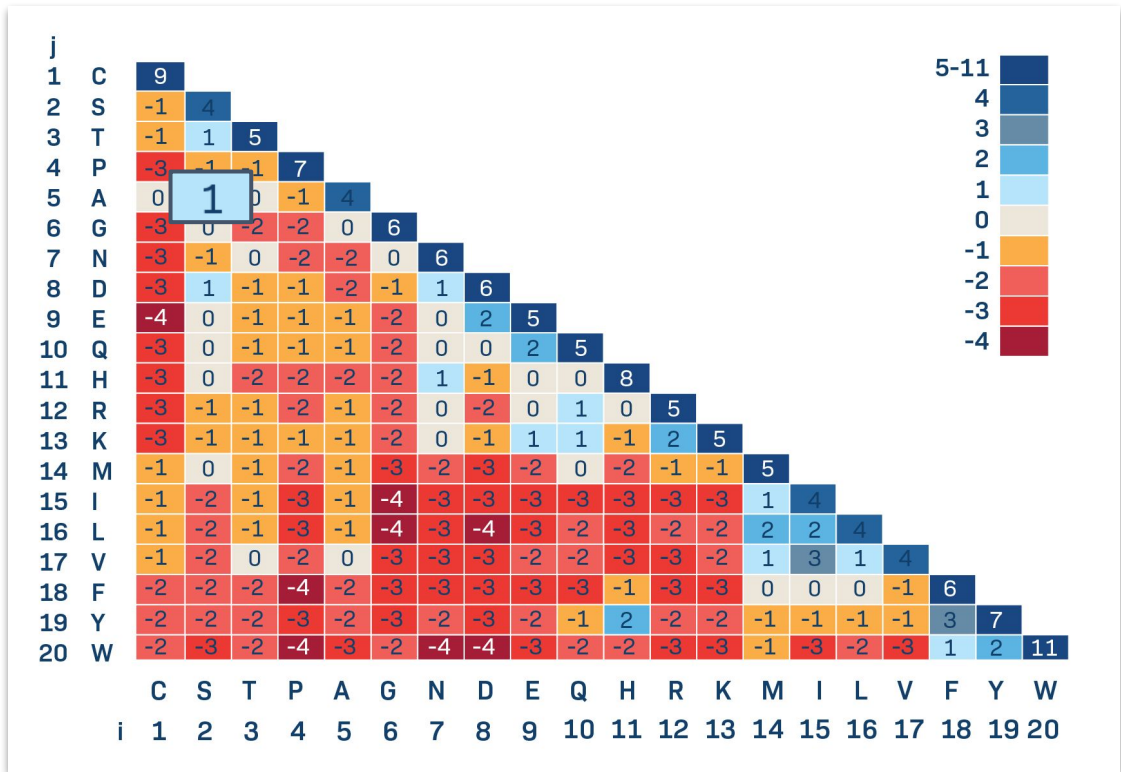
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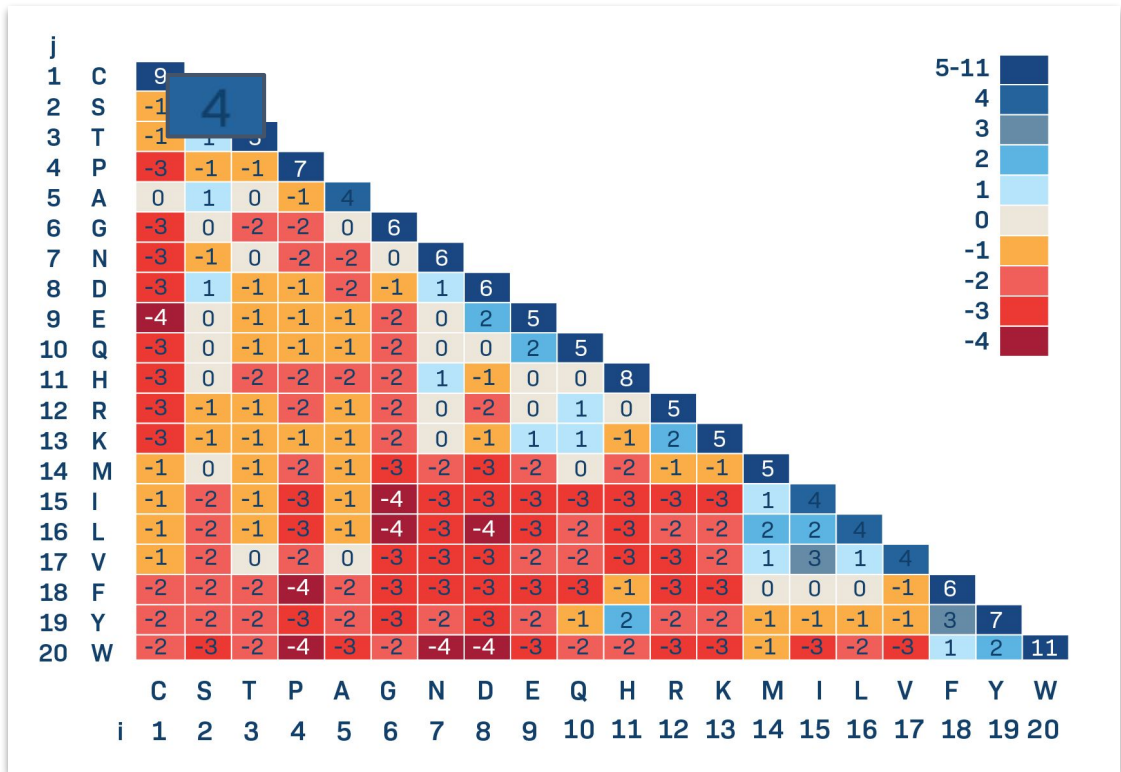
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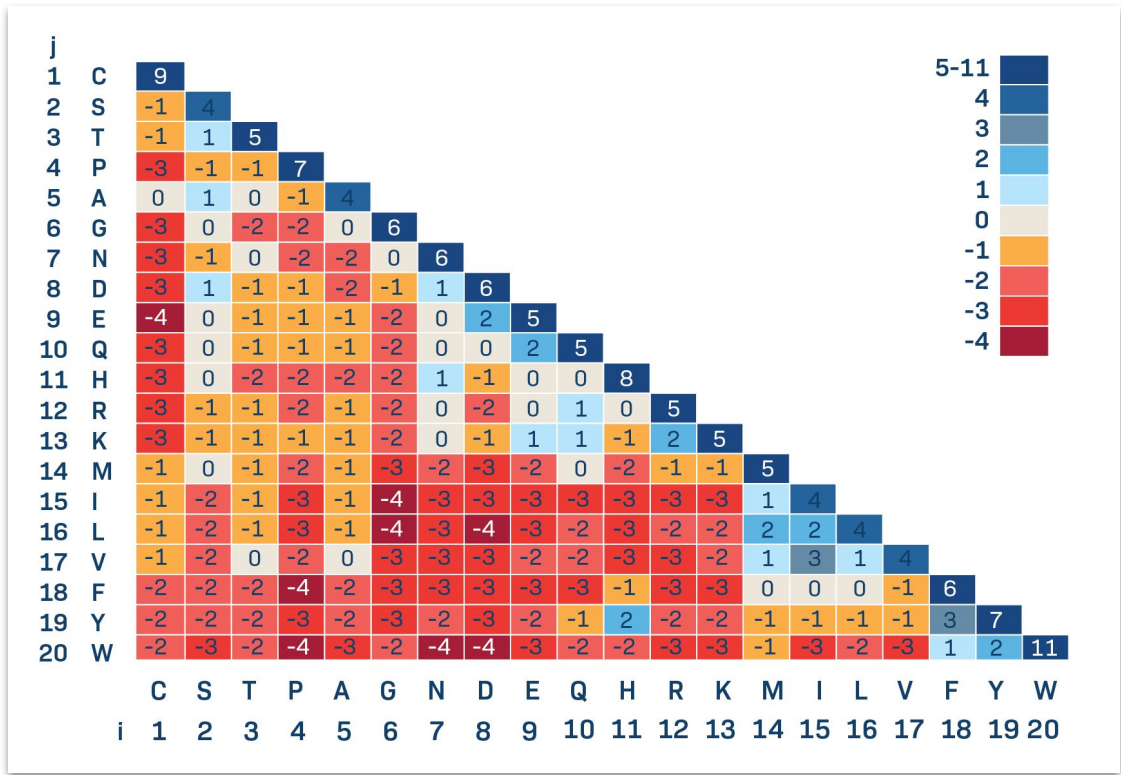
ASSSANYGYT
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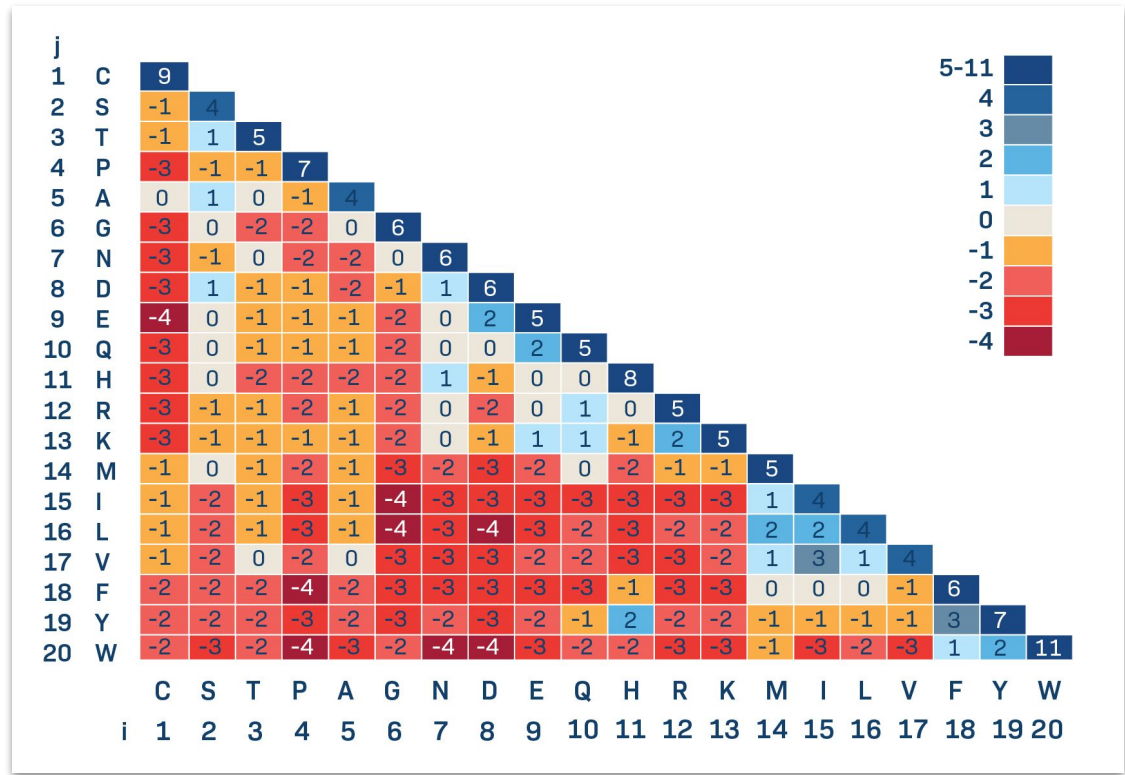
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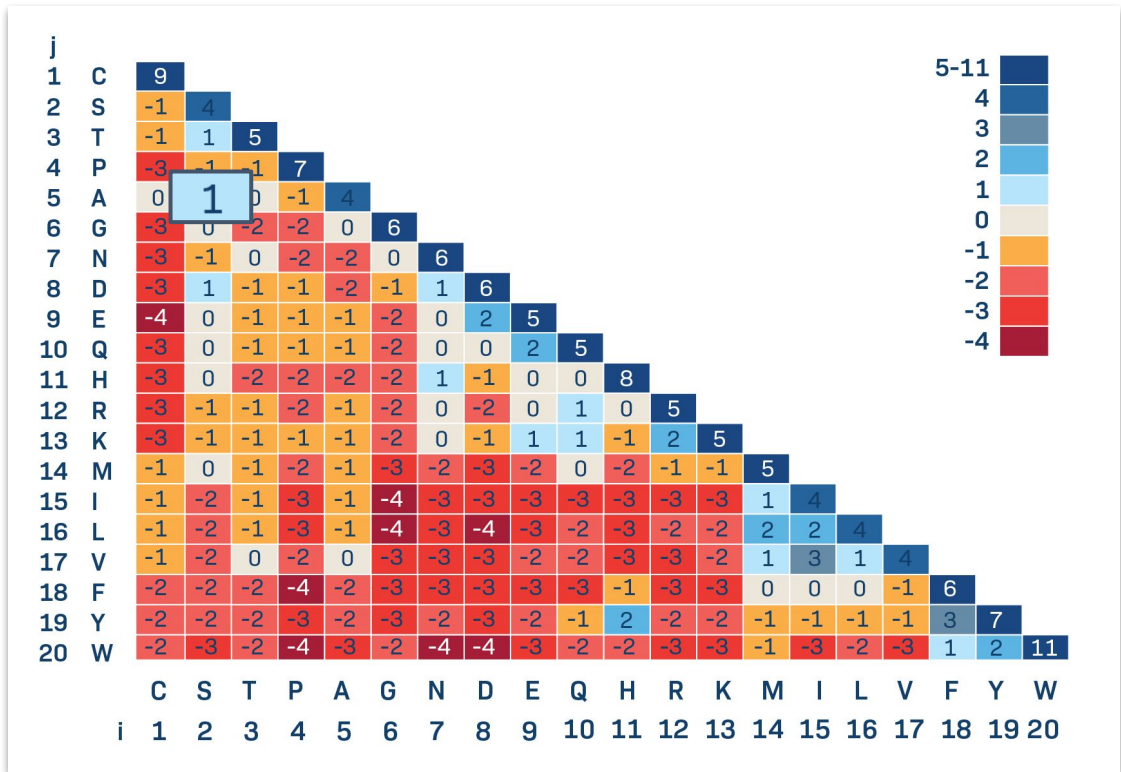
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TCRmatch

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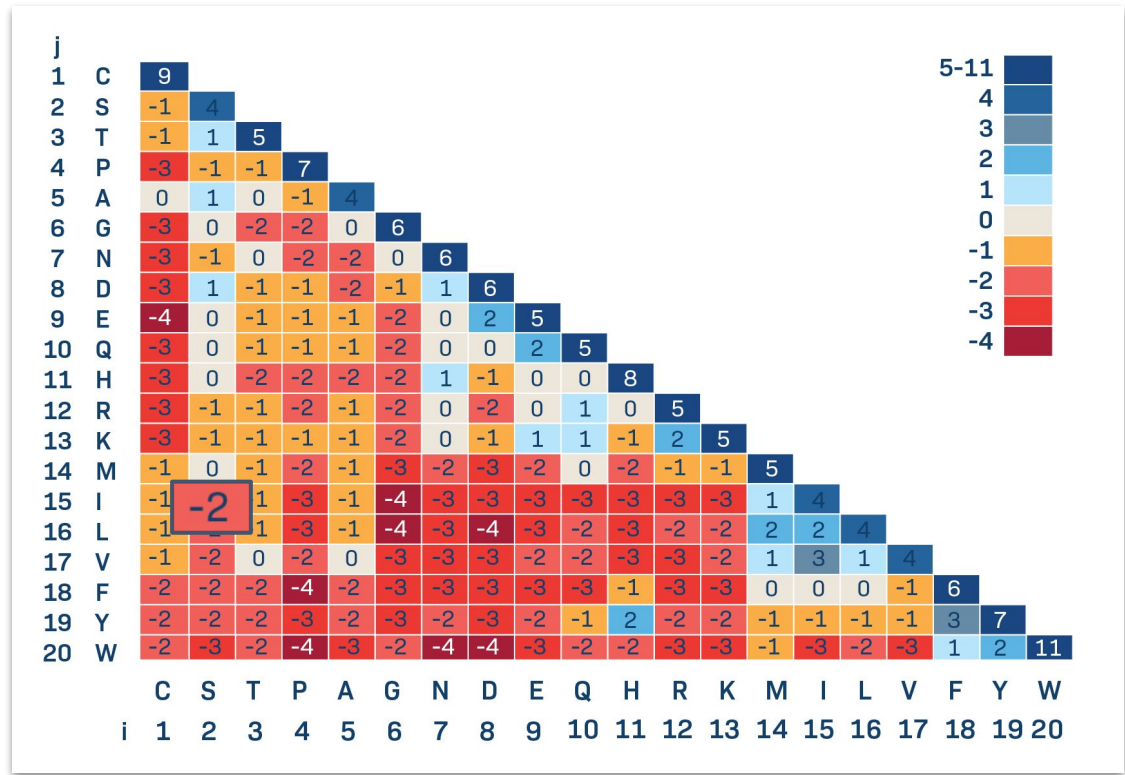
ASSSANYGYT
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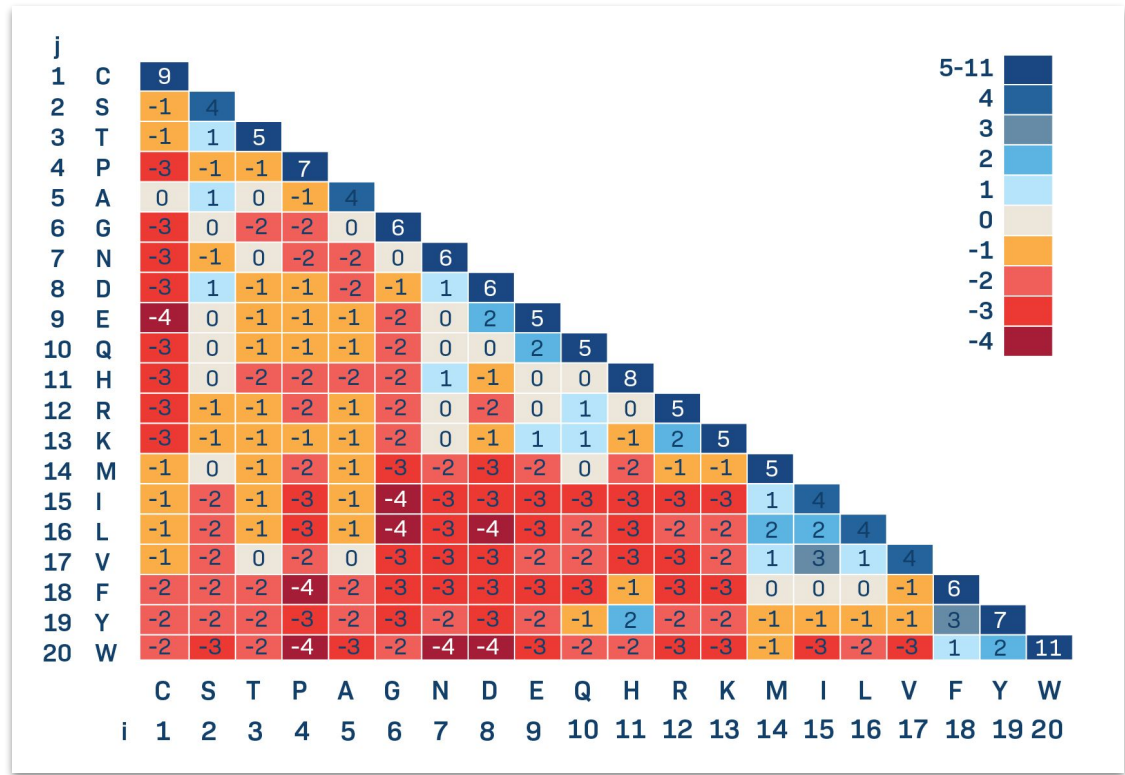
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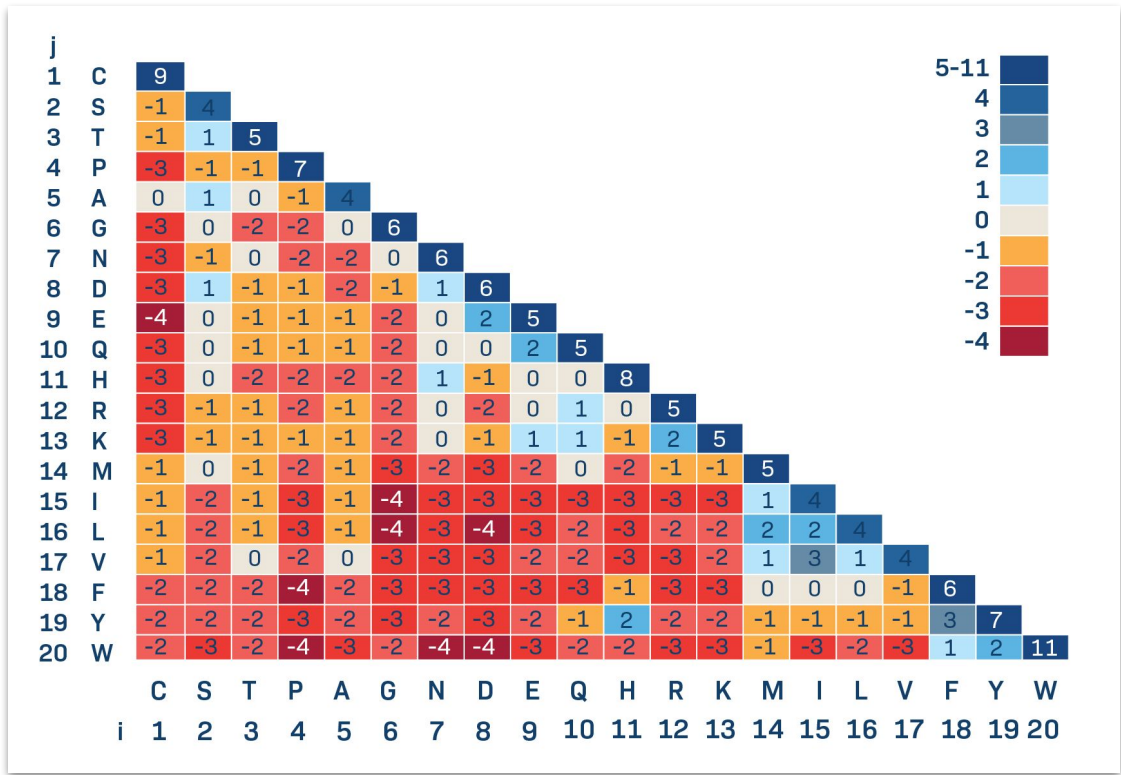
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TCRmatch

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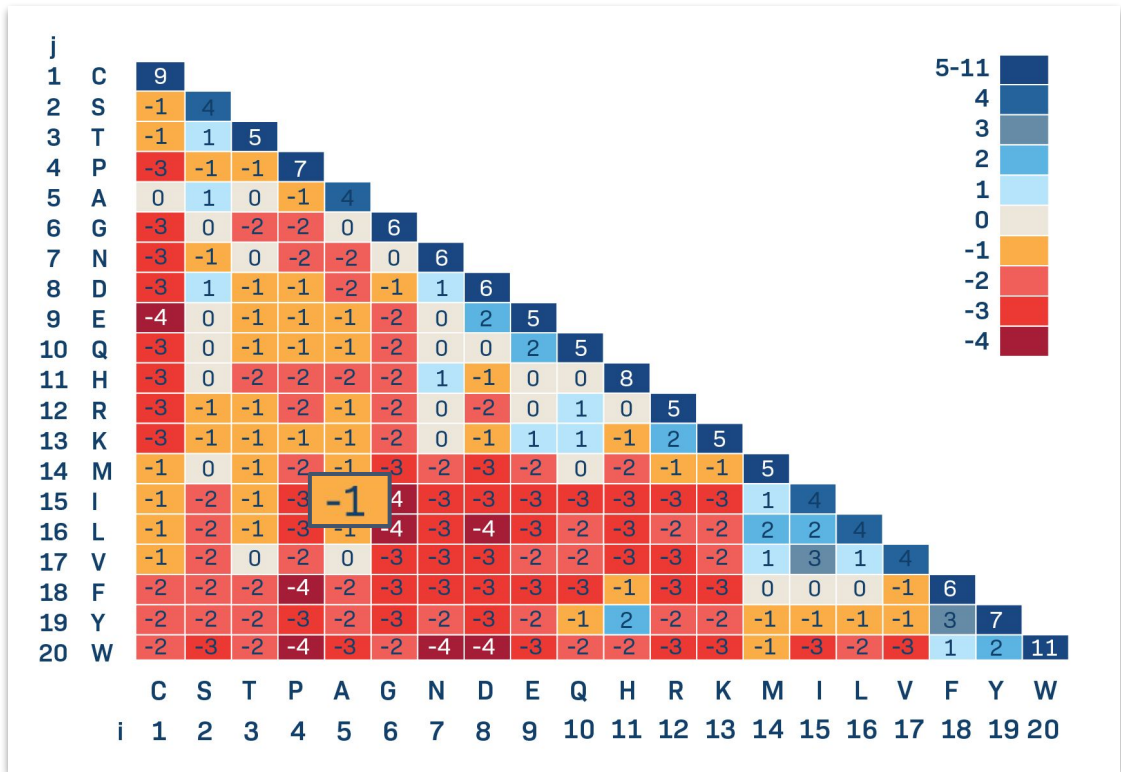
ASSSANYGYT
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TCRmatch

$$k = 2$$

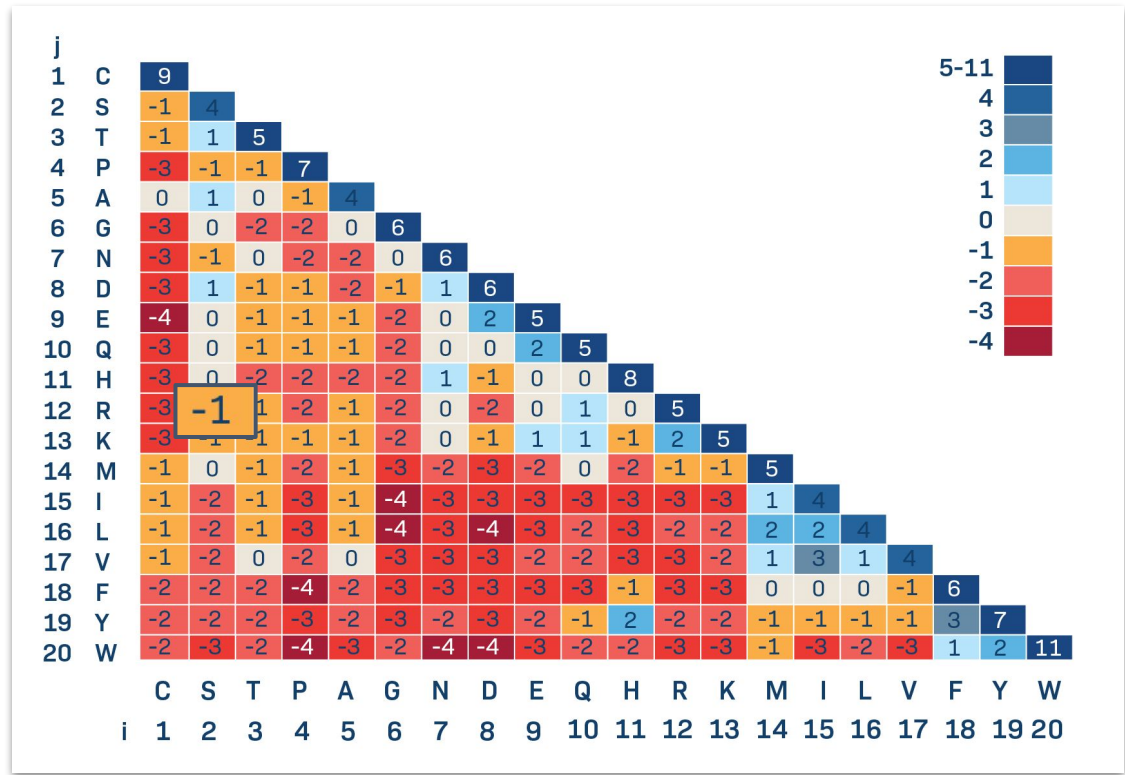
ASSSANYGYT
ASSIRAAETQY



TCRmatch

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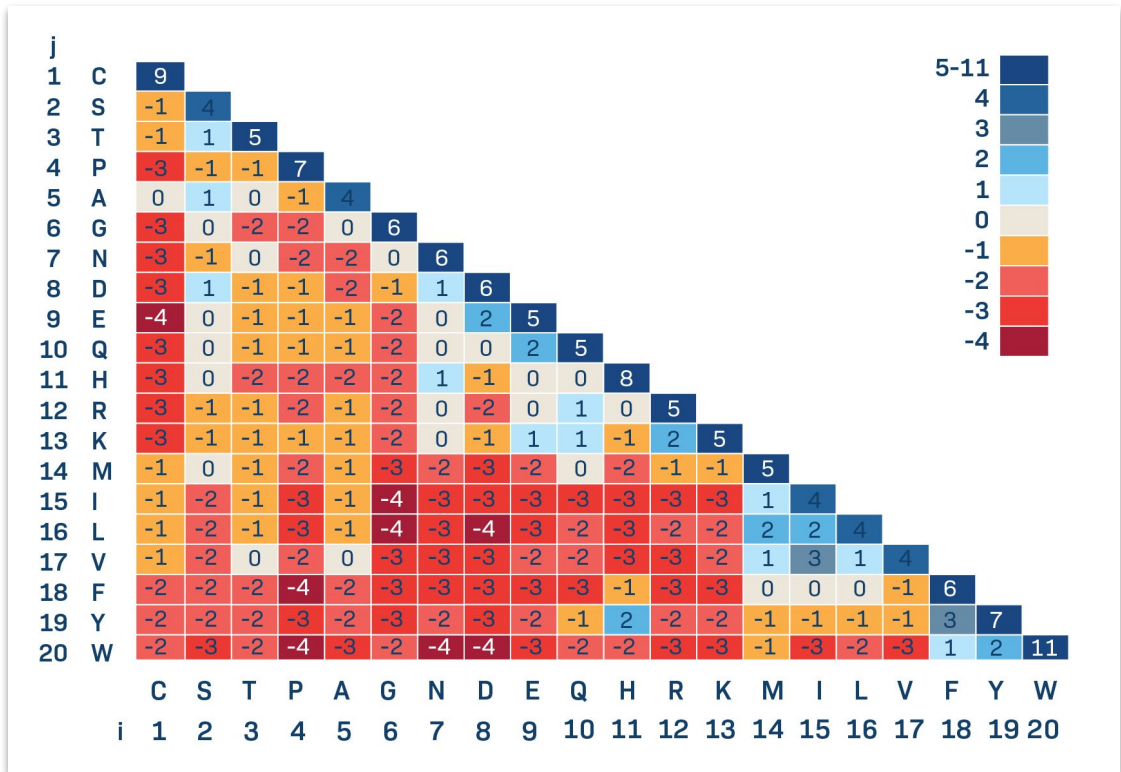
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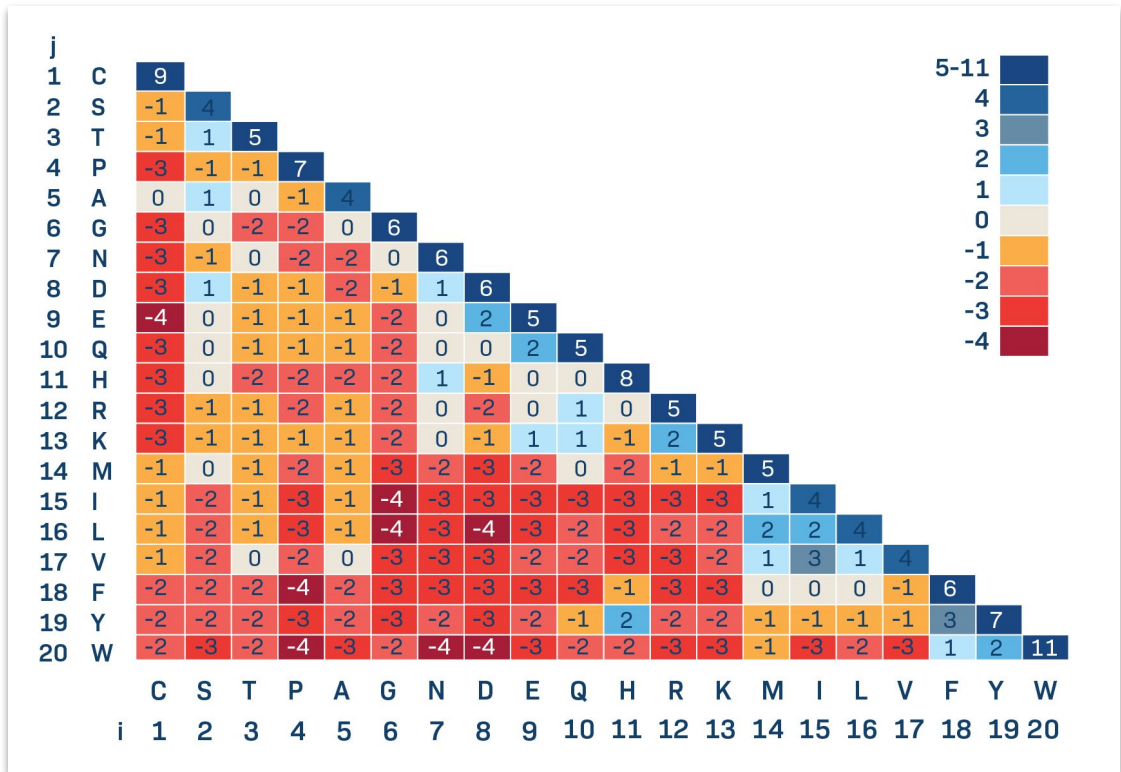
ASSSANYGYT
ASSIRAAETQY
(...)



TCRmatch

$$k = 2$$

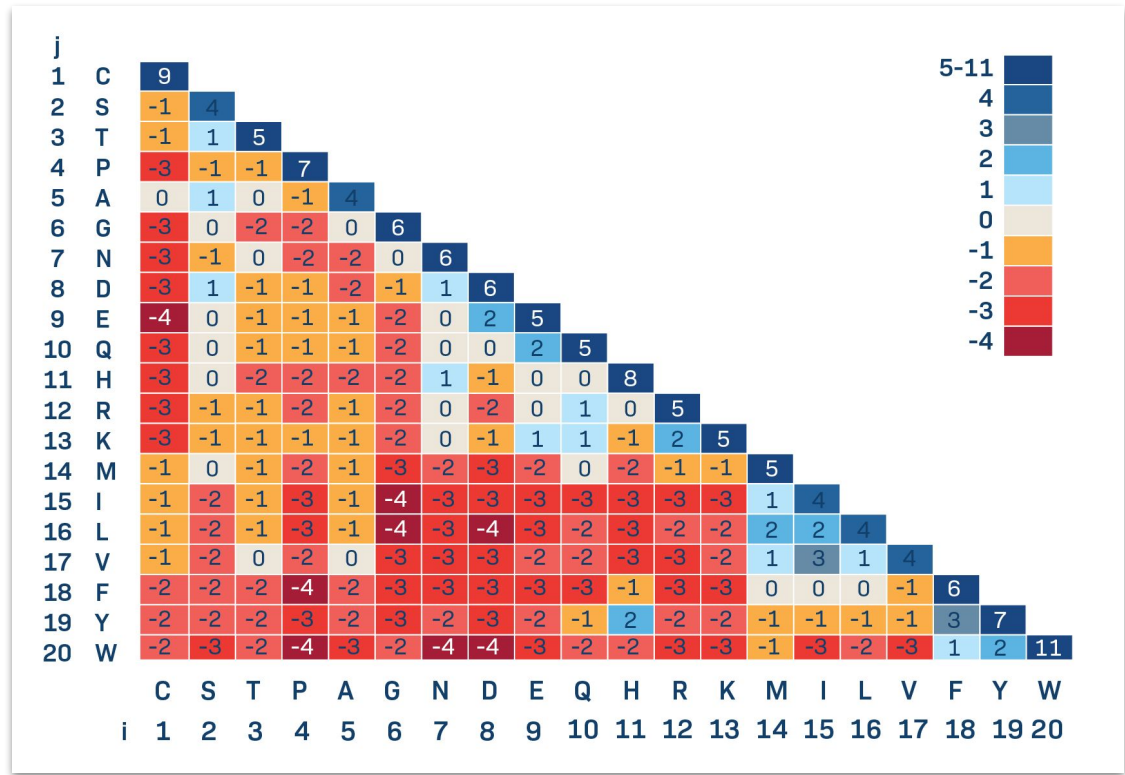
ASSSANYGYT
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(...)



TCRmatch

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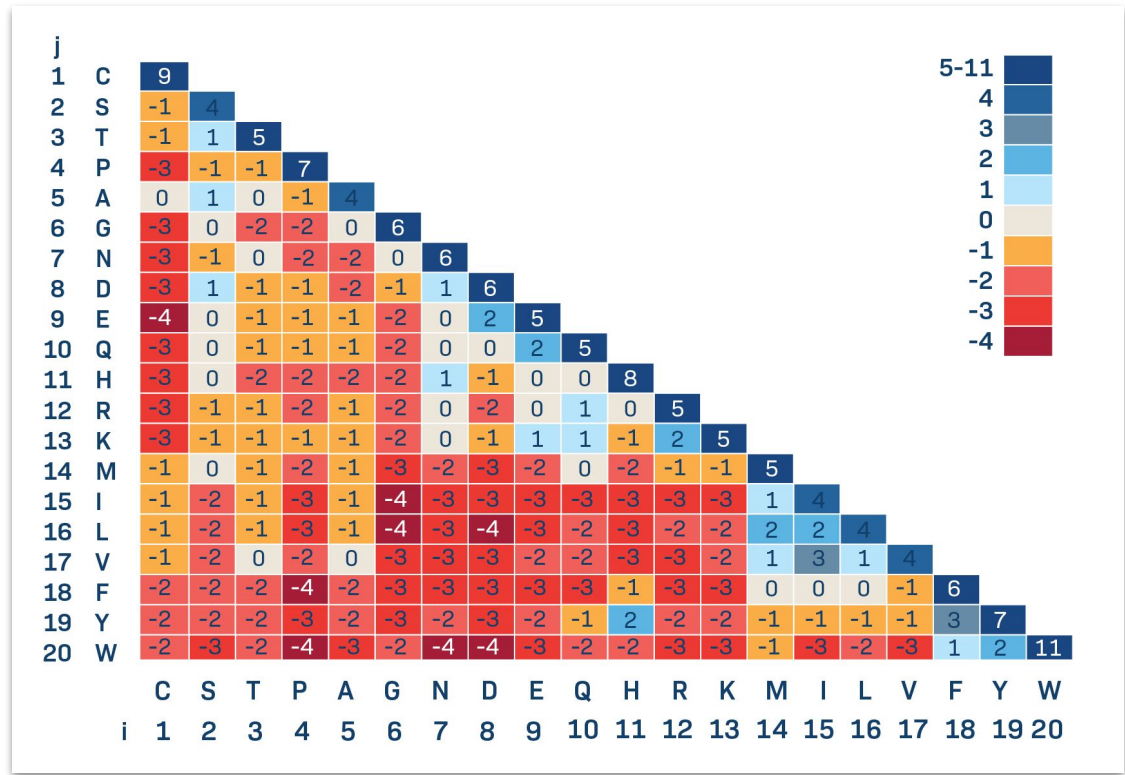
ASSSANYGYT
ASSIRAAETQY
(...)



TCRmatch

$$k = 2$$

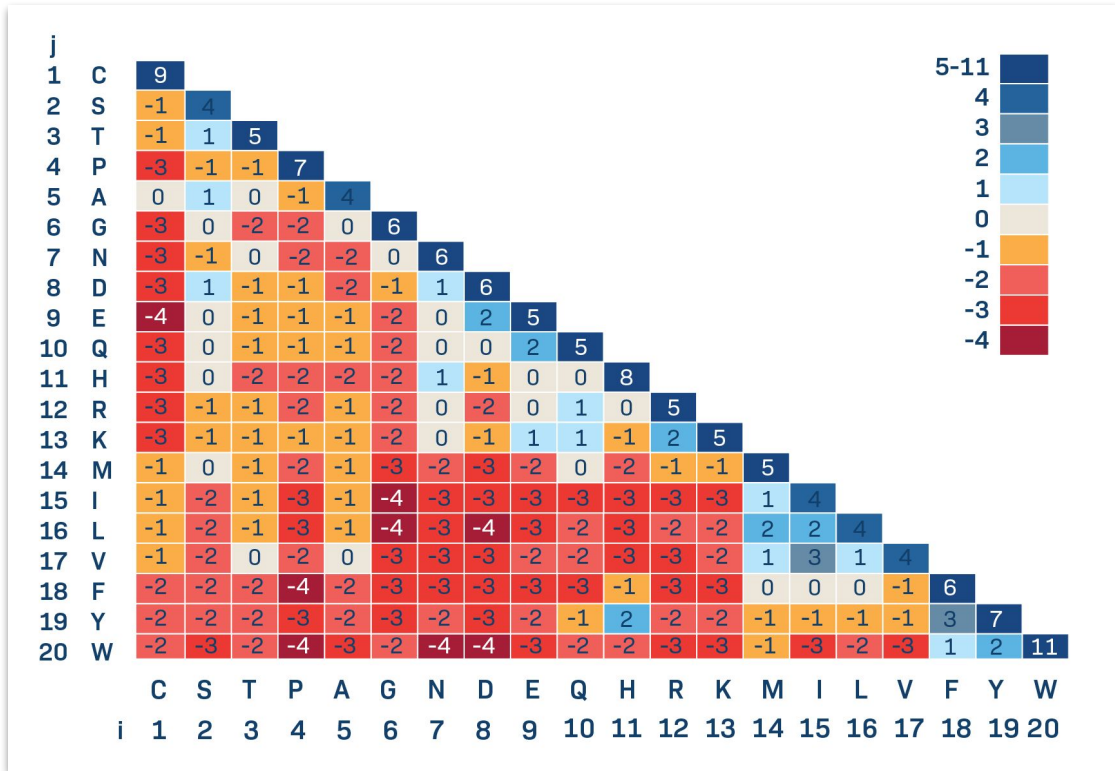
ASSSANYGYT
ASSIRAAETQY
(...)



TCRmatch

$k = 10$

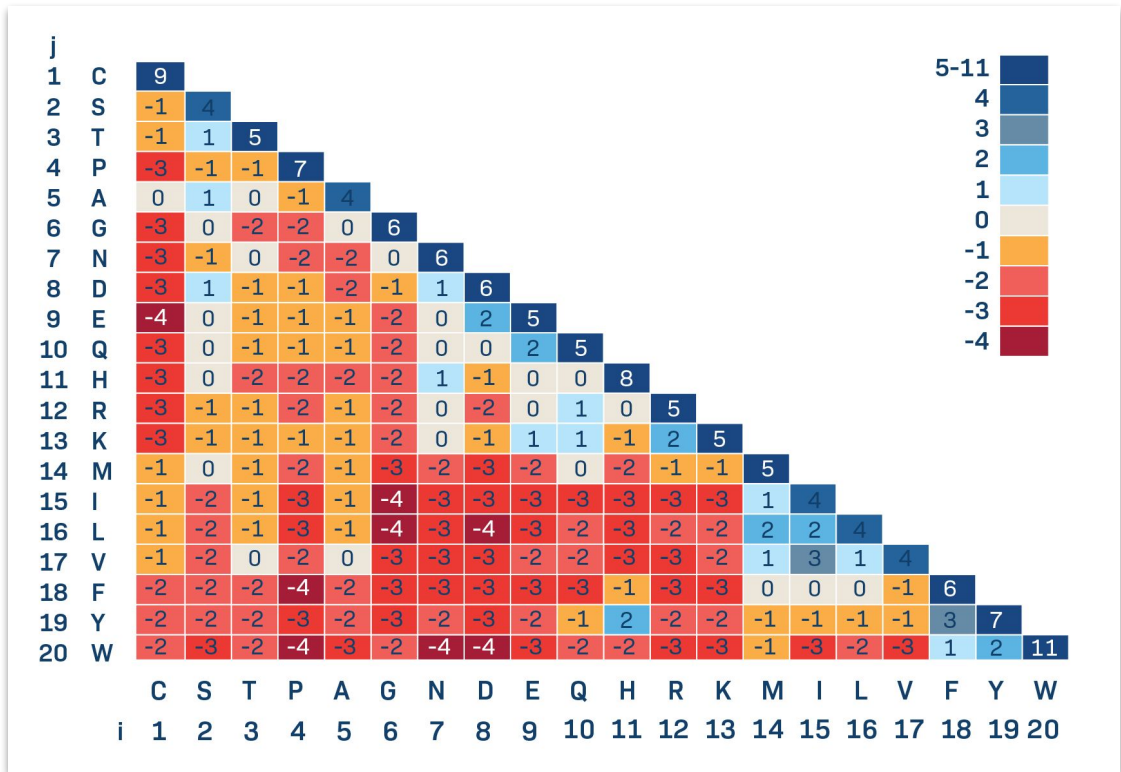
ASSSANYGYT
ASSIRAAETQY



TCRmatch

$k = 10$

ASSSANYGYT
ASSIRAAETQY

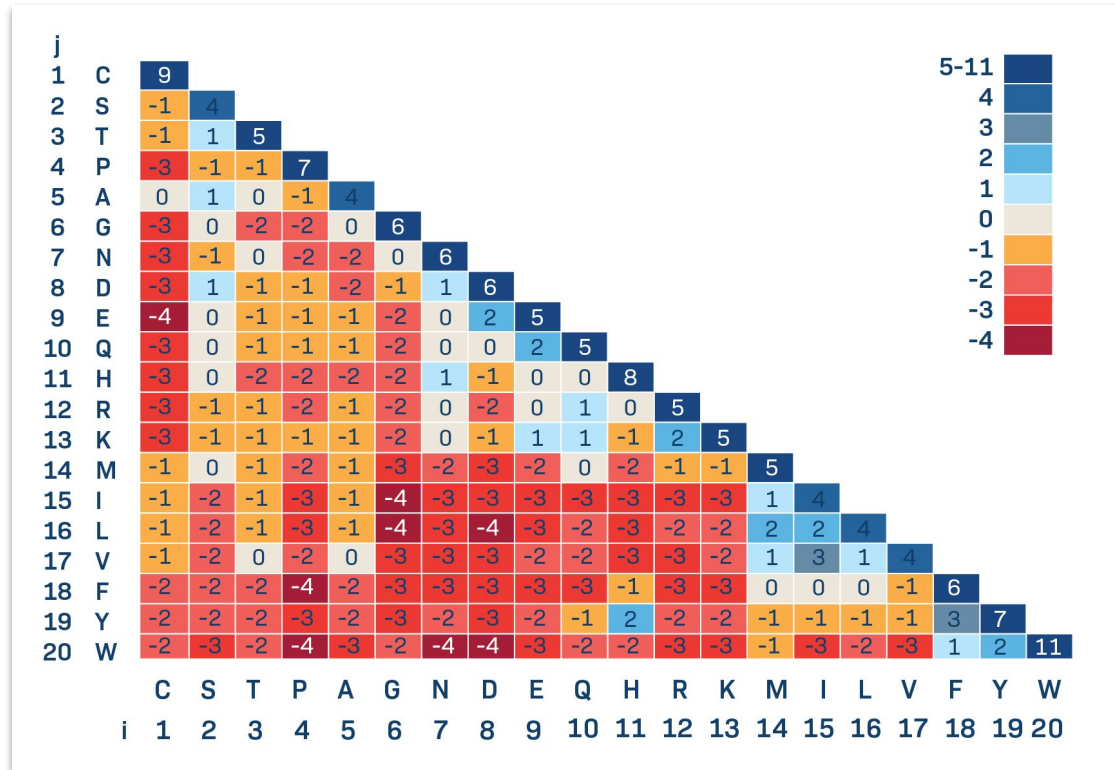


TCRmatch

$k = 10$

ASSSANYGYT
ASSIRAAETQY

Final score:
0 - 1
(1: perfect match)



Acknowledgments

Bjoern Peters
Alessandro Sette
Nina Blazeska
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Lindsay Cowell (UTSW)



TCRMatch: Predicting T-Cell Receptor Specificity Based on Sequence Similarity to Previously Characterized Receptors

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The adaptive immune system in vertebrates has evolved to recognize non-self antigens, such as proteins expressed by infectious agents and mutated cancer cells. T cells play an important role in antigen recognition by expressing a diverse repertoire of antigen-specific receptors, which bind epitopes to mount targeted immune responses. Recent advances in high-throughput sequencing have enabled the routine generation of T-cell receptor (TCR) repertoire data. Identifying the specific epitopes targeted by different TCRs in these data would be valuable. To accomplish that, we took advantage of the ever-increasing number of TCRs with known epitope specificity curated in the Immune Epitope Database (IEDB) since 2004. We compared seven metrics of sequence similarity to determine their power to predict if two TCRs have the same epitope specificity. We found that a comprehensive *k*-mer matching approach produced the best results, which we have implemented into TCRMatch, an openly accessible tool (<http://tools.iedb.org/tcrmatch/>) that takes TCR β -chain CDR3 sequences as an input, identifies TCRs with a match in the IEDB, and reports the specificity of each match. We anticipate that this tool will provide new insights into T cell responses captured in receptor repertoire and single cell sequencing experiments and will facilitate the development of new strategies for

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