Universidad Nacional de San Agustín

Detección de neo antígenos utilizando *deep learning* en el marco del desarrollo de vacunas personalizadas en la inmunoterapia del Cáncer

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DNA
Localización

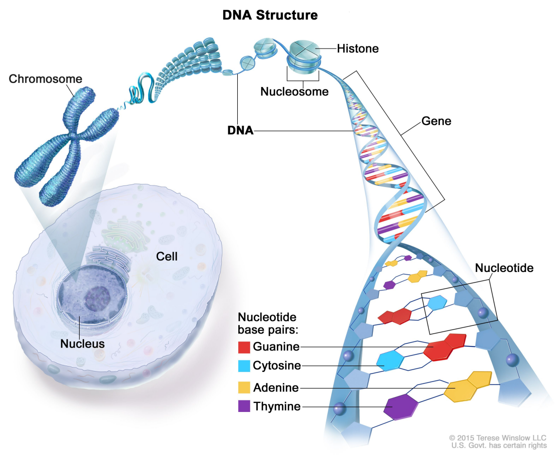

Figure: Where DNA is located [1].

DNA

De DNA a proteínas

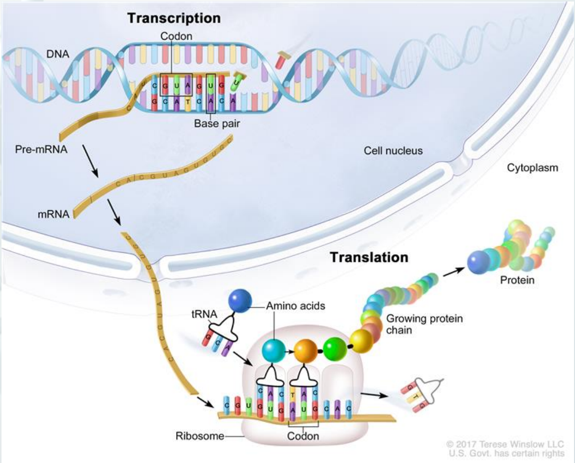

Figure: Transcription and translation [2].

Variantes y Mutaciones

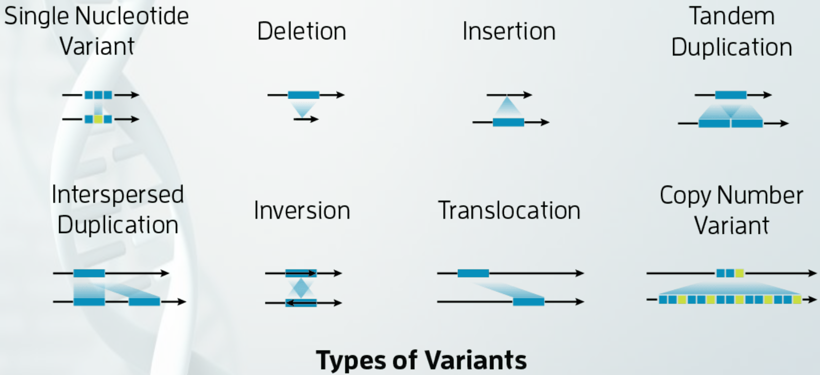

Figure: Example of structural variants. Source: [3]

Variantes y Mutaciones

Frameshift

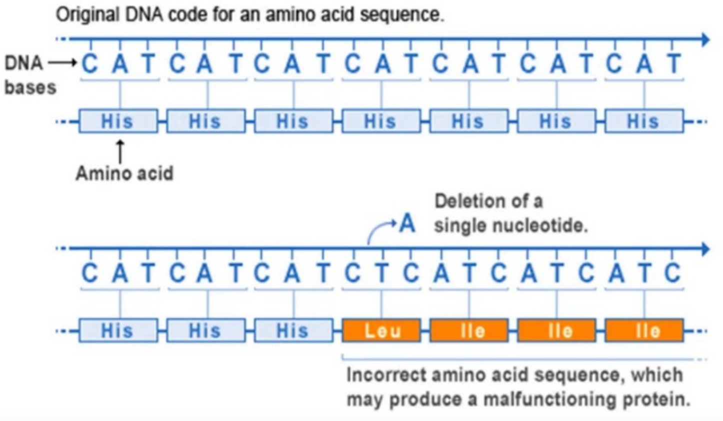
Original DNA code for an amino acid sequence.
DNA bases
C A T C A T C A T C A T C A T C A T C A T
His His His His His His His
Amino acid
Deletion of a single nucleotide.
A
C A T C A T C A T C T C A T C A T C A T C
His His His Leu Ile Ile Ile
Incorrect amino acid sequence, which may produce a malfunctioning protein.

Figure: Ejemplo de una mutación INDELS causante de un *frameshift*.

Fusión de genes

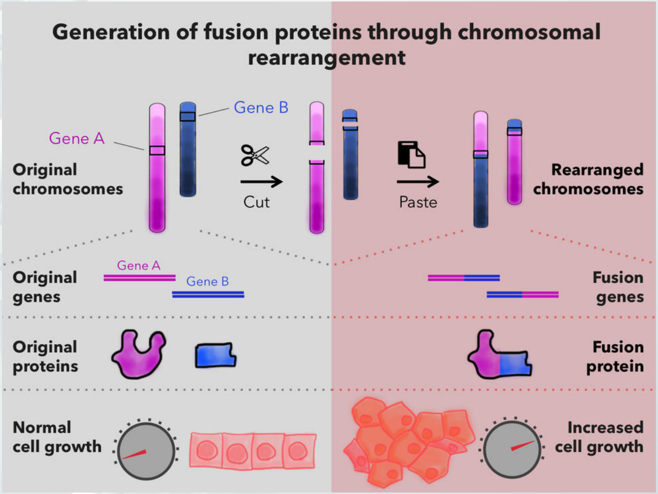

Figure: Ejemplo de una fución de genes.

Inmunoterapia del Cáncer

Es un tipo de tratamiento contra el Cáncer que estimula las defensas naturales del cuerpo para combatir el Cáncer [4].

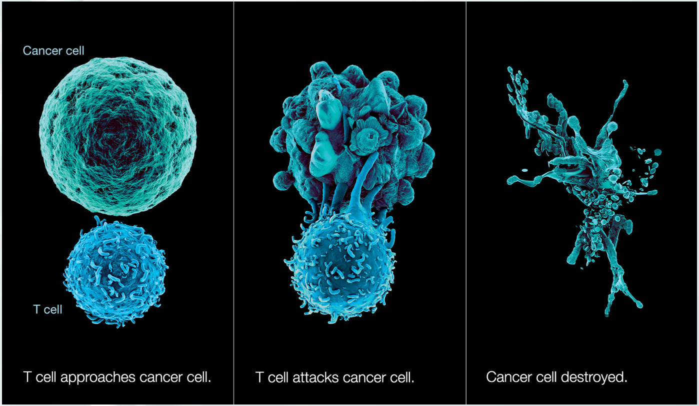

Figure: Ejemplo de como una célula T destruye células del cancer [5].

Inmunoterapia del Cáncer

Neo antígenos

Es una **proteína** que se forma en las células de Cáncer cuando ocurre mutaciones en el DNA, cumplen un rol importante al **estimular una respuesta inmune** [1, 6].

En la actualidad hay varios métodos para detectar a predecir neo antígenos, pero **solo una pequeña cantidad de ellos** logran estimular al sistema inmune [7, 8].

MHC-I

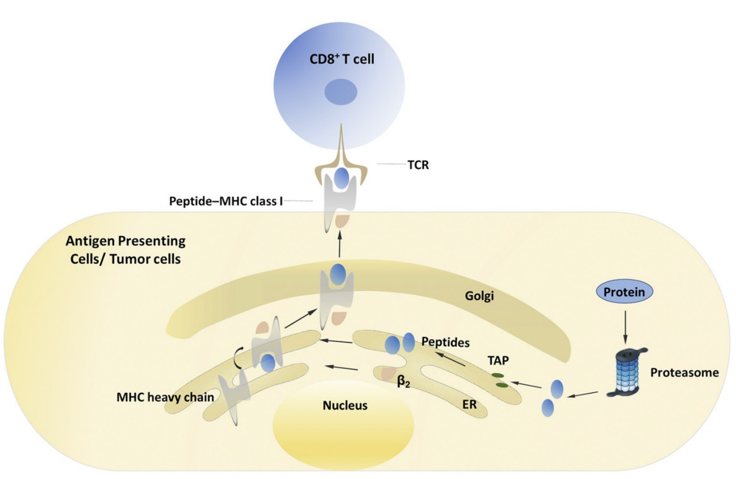

Figure: Presentación de antígenos por MHC-I. Fuente: [9]

MHC-II

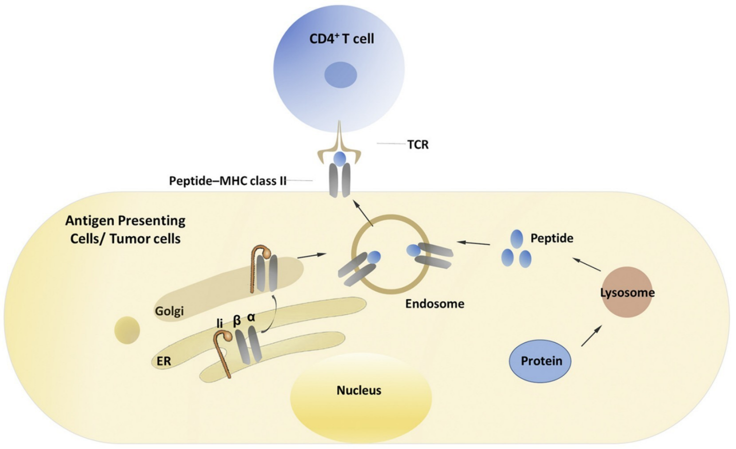

Figure: Presentación de antígenos por MHC-II. Fuente: [9]

Inmunoterapia del Cáncer

Generación de vacunas

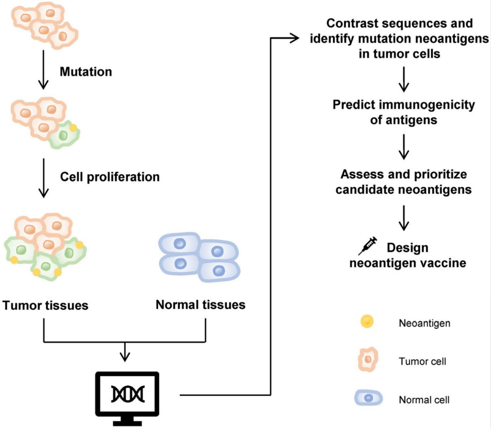
Mutation
Cell proliferation
Tumor tissues
Normal tissues
Contrast sequences and identify mutation neoantigens in tumor cells
Predict immunogenicity of antigens
Assess and prioritize candidate neoantigens
Design neoantigen vaccine
Neoantigen
Tumor cell
Normal cell

Figure: Proceso para la generación de vacunas personalizadas [10].

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Motivación

El cáncer representa el mayor problema de salud mundial, pero lamentablemente los métodos basados en cirugías, radioterapias, quimioterapias tienen baja efectividad [10].

La inmunoterapia del cáncer es una alternativa para el desarrollo de vacunas personalizadas, pero este proceso depende de una correcta detección de neo antígenos [11, 10].

Problema

Menos del **5% de péptidos** detectados en *pMHC binding*, llegan a la membrana de la células. Para *peptide-MHC presentation*, propuestas recientes solo llegan a **0.6 de *presicion* y 0.4 de *recall*** [12].

En este contexto, la tesis se enfoca en el problema de *pMHC presentation*, considerándolo como un problema de clasificación binaria, y tomando como entrada la secuencia de aminoácidos del péptido y la secuencia de aminoácidos de la proteína MHC.

Objetivo general

Proponer un método basado en *deep learning* para la detección de neo antígenos, enfocados en el problema de *peptide-MHC presentation*.

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Table: Cadenas de busqueda utilizadas en la RSL.

Cadena de busqueda
neoantigen AND (detection OR pipeline) AND deep learning
(MHC OR HLA) AND binding AND deep learning
(MHC-I OR MHC-II OR MHC OR HLA) AND (peptide OR epitope) AND (binding OR affinity OR prediction OR detection OR presentation)
TCR interaction prediction

Table: Bases de datos utilizadas en la RSL.

Bases de datos
IEEE Xplore
Science Direct
Springer
ACM Digital Library
PubMed
BioRxiv

Table: Criterios de inclusión y exclusión de artículos utilizados en la RSL.

Criterios de inclusión	**Criterios de exclusión**
Artículos con categoría ERA (A, B o C) si son conferencias y Journals Q1, Q2 o Q3.	Trabajos de baja calidad, que no esten rankeados.
Sobre *deep learning*	
La metodología es detallada.	
Tiene repositorio de código fuente y base de datos (deseable).	

RSL

Metodología

Table: Cantidad de artículos encontrados y seleccionados según los criterios de inclusión y exclusión en la RSL.

Año	Artículos encontrados	Artículos seleccionados
2018	57	21
2019	72	31
2020	86	29
2021	61	34
2022	58	19
Total	**334**	**134**

Table: List of research since 2018 that uses CNNs for peptide-MHC binding and presentation.

Year	Ref.	Approach	Name	MHC	Encoding
2022	[13]	pMHC(b)	DeepMHCII	II	PFR
2021	[14]	pMHC(b)	DeepImmuno	I	AAindex1
2021	[15]	pMHC(p)	APPM	I	One-hot
2021	[16]	pMHC(p)	MHCfovea	I	One-hot
2021	[17]	pMHC(b)	CNN-PepPred	II	BLOSUM
2020	[18]	pMHC(b)	IConMHC	I	PCA and AAindex3
2020	[19]	pMHC(b)	OnionMHC	I	BLOSUM and structural features
2020	[20]	pMHC(p)	MINERVA	I	Physicochemical properties
2019	[21]	pMHC(b)	CNN-NF	I	Sequence, Hydropathy, Polarity, Length
2019	[22]	pMHC(b)	DeepSeqPan	I	One-hot
2018	[23]	pMHC(b)	ConvMHC	I	Contact side HLA.peptide

Table: List of research since 2018 that uses CNNs s with RNN or attention mechanisms for peptide-MHC binding and presentation. MHCherryPan uses CNN with RNN, the other uses CNN witn Attention mechanims.

Year	Ref.	Approach	Name	MHC	Encoding
2021	[24]	pMHC(b)	DeepNetBim	I	BLOSUM
2021	[25]	pMHC(b)	Deep Attention Pan	I	BLOSUM
2019	[26]	pMHC(b)	ACME	I	BLOSUM
2020	[27]	pMHC(b)	MHCherryPan	I	BLOSUM

Table: List of research since 2018 that uses RNNs for peptide-MHC binding and presentation. MATHLA, DeepSeqPanII and DeepHLApan uses RNN with attention mechanims, meanwhile the other focus on GRU and LSTM.

Year	**Ref.**	**Approach**	**Name**	**MHC**	**Encoding**
2021	[28]	pMHC(b)	MATHLA	I	BLOSUM
2021	[29]	pMHC(b)	DeepSeqPanII	II	One-hot and BLOSUM
2021	[30]	pMHC(b)	GRU-based RNN	II	Embeding layer
2021	[31]	pMHC(b)	BVLSTM-MHC	I	One-hot and BLOSUM
2020	[32]	pMHC(b)	MHCnuggets	I, II	One-hot
2019	[33]	pMHC(b)	DeepHLApan	I	One-hot

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Transformers

Table: List of research since 2018 that uses Transformers (self-attention) for peptide-MHC binding and presentation.

Year	Ref.	Approach	Name	MHC	Encoding
2022	[34]	pMHC(b)	MHCRoBERTa	I	Tokenized from a pre-trained model
2022	[35]	pMHC(b)	TransPHLA	I	Character embedding model
2021	[36]	pMHC(b)	BERTMHC	II	Embeding layer
2021	[37]	pMHC(p)	ImmunoBERT	I	Embeding layer

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Bases de datos

Table: Public databases of *pMHC binding*, *pMHC presentation*, pMHC-TCR interaction, and 3D structures of proteins.

Name	Year ref.	Description
VDJdb	2018 [38]	TCR binding to pMHC, contains 5491 samples.
IEDB	2018 [39]	The bigger database, contains information *T-cell epitopes*
TSNAdb	2018 [40]	It contains 7748 samples of mutations and HLA of 16 types of cancer.
NeoPeptide	2019 [41]	It contains samples of neoantigens resulting from somatic mutations and related items. 1818137 epitopes of more than 36000 neoantigens.
pHLA3D	2019 [42]	Presents 106 3D structures of the alpha, *beta*2*M* chains, and peptides of HLA-I molecules
dbPepNeo	2020 [43]	It has validated samples of the *peptide-MHC* bond, from MS. It contains 407794 low-quality samples, 247 medium-quality, and 295 high-quality samples.
dbPepNeo2.0	2022 [44]	It gathers a list of neoantigens and HLA molecules. It presents 801 high-quality and 842,289 poor-quality HLAs. Also, 55 class II neoantigens and 630 TCR-bound neo antigens.
IntroSpect	2022 [45]	Tool for building databases on *peptide-MHC binding*. It uses data from *Mass Spectrometry*.
IPD-IMGT/HLA	2022 [46]	With 25000 MHC molecules and 45 alleles.

Table: List of *pipelines* since 2018 for the detection of neoantigens.

Name	Year ref.	Input	Output
Neopepsee	2018 [47]	RNA-seq, somatic mutations (VCF), HLA type (optional)	Neoantigens and gene expression levels
PGV Pipeline	2018 [48]	DNA-seq	Neoantigens
ScanNeo	2019 [49]	RNA-seq	Neoantigens
NeoPredPipe	2019 [50]	Mutations (VCF) y HLA type	Neoantigens and variant annotation
pVACtools	2020 [51]	Mutations (VCF)	Neoantigens
ProGeo-neo	2020 [52]	RNA-seq y somatic mutations (VCF)	Neoantigens
Neoepiscope	2020 [53]	Somatic mutations (VCF) and BAM files	Neoantigens and mutations
NeoANT-HILL	2020 [54]	RNA-seq y somatic mutations (VCF)	Neoantigens and gene expression levels
NAP-CNB	2021 [55]	RNA-seq	Neoantigens
PEPPRMINT	2021 [56]	DNA-seq	Neoantigens
Valid-NEO	2022 [57]	Somatic mutations (VCF), HLA type (optional)	Neoantigens

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Propuesta

La propuesta se basa el los modelos BERTMHC [36] y APPM [8]. Tambien, se utilizará *transfer learning* de ESM-1b [58], esta red neuronal fue entrenada con 250 millones de proteínas a diferencia de TAPE (utilizada por BERTMHC), que fue entrenada con 30 milllones de proteínas.

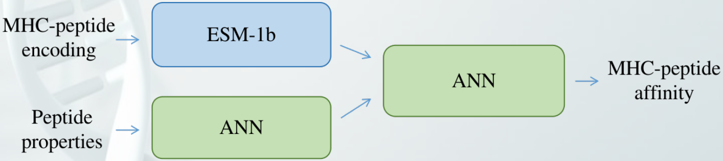


Figure: Proceso general utilizado para la detección de neo antígenos a partir de secuencias de DNA. Fuente: [59].

Propuesta

BERTMHC

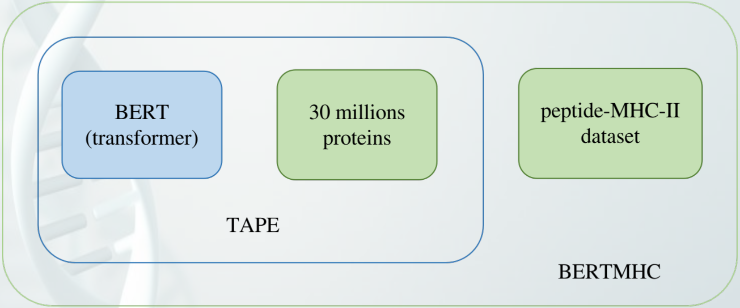
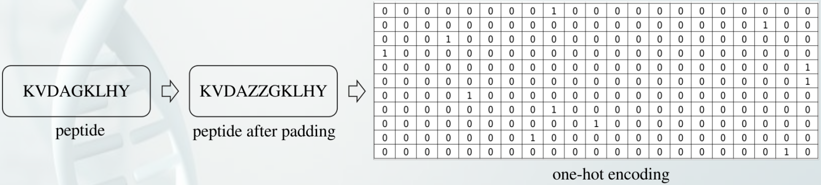


Figure: BERTMHC.

Propuesta

APPM



0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0

one-hot encoding

Figure: Proceso para obtener una matriz (imagen) a partir de un péptido (APPM).

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MHC alleles utilizados

Table: Cantidad de muestras por tipo de *allele*.

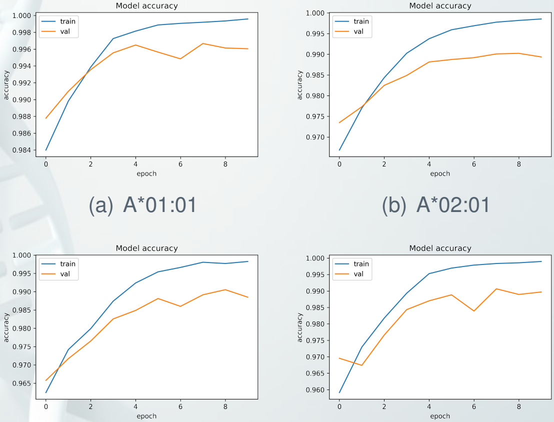
Alleles	**Label = 1**	**Label = 0**	**Train**	**Test**
A*01:01	3398	48700	45498	6600
A*02:01	6779	165342	160921	11200
A*02:03	1780	116299	107879	10200
A*31:01	1879	45918	41597	6200
B*44:02	1525	44760	40085	6200
B*44:03	1487	39482	34769	6200
MHC-II alleles	1917	496	1533	384

Resultados

Table: Resultados obtenidos en cada base de datos.

Allele	*Accuracy*	*F1 score*	*Precision*	*Recall*
A*01:01	0.978	0.917	0.982	0.887
A*0201	0.962	0.956	0.965	0.948
A*02:03	0.992	0.979	0.994	0.969
A*31:01	0.980	0.968	0.989	0.951
B*44:02	0.991	0.981	0.968	0.997
B*44:03	0.992	0.987	0.995	0.980

Resultados



(a) A*01:01

(b) A*02:01

(c) A*02:03

(d) A*31:01

Figure: *Accuracy* durante cada *epoch*, para cada base de datos. Las bases de datos representan las células HLA A*01:01, A*02:01, A*02:03, A*31:01.

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Conclusiones

Se ha desarrollado una RSL, sobre los métodos de detección de neoantígenos utilizando *deep learning*. Esto ha logrado identificar las tendencias, retos y problemas del tema de interes.

Se ha realizado experimentos preliminares, sobre el uso de CNNs para el problema de peptide-MHC presentation. Se ha utilizado muestras de MS con un enfoque *single allele* (se entrena varios modelos para cada tipo de MHC).

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Trabajos futuros

Recientemente un trabajo [60] tambien propone el uso de *transfer learning* pero de un modelo pre-entrenado con 250 millones de proteínas. Entonces, se plantea utilizar la misma red, aumentar la cantidad de muestras y evaluar los resultados.

Actualmente se cuenta con una base de datos de proteínas MHC [42], entonces utilizando AlphaFold de Google, se plantea predecir la estructura de varios péptidos y analizar el enlace péptido-MHC desde un punto de vista de la computación gráfica.

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