

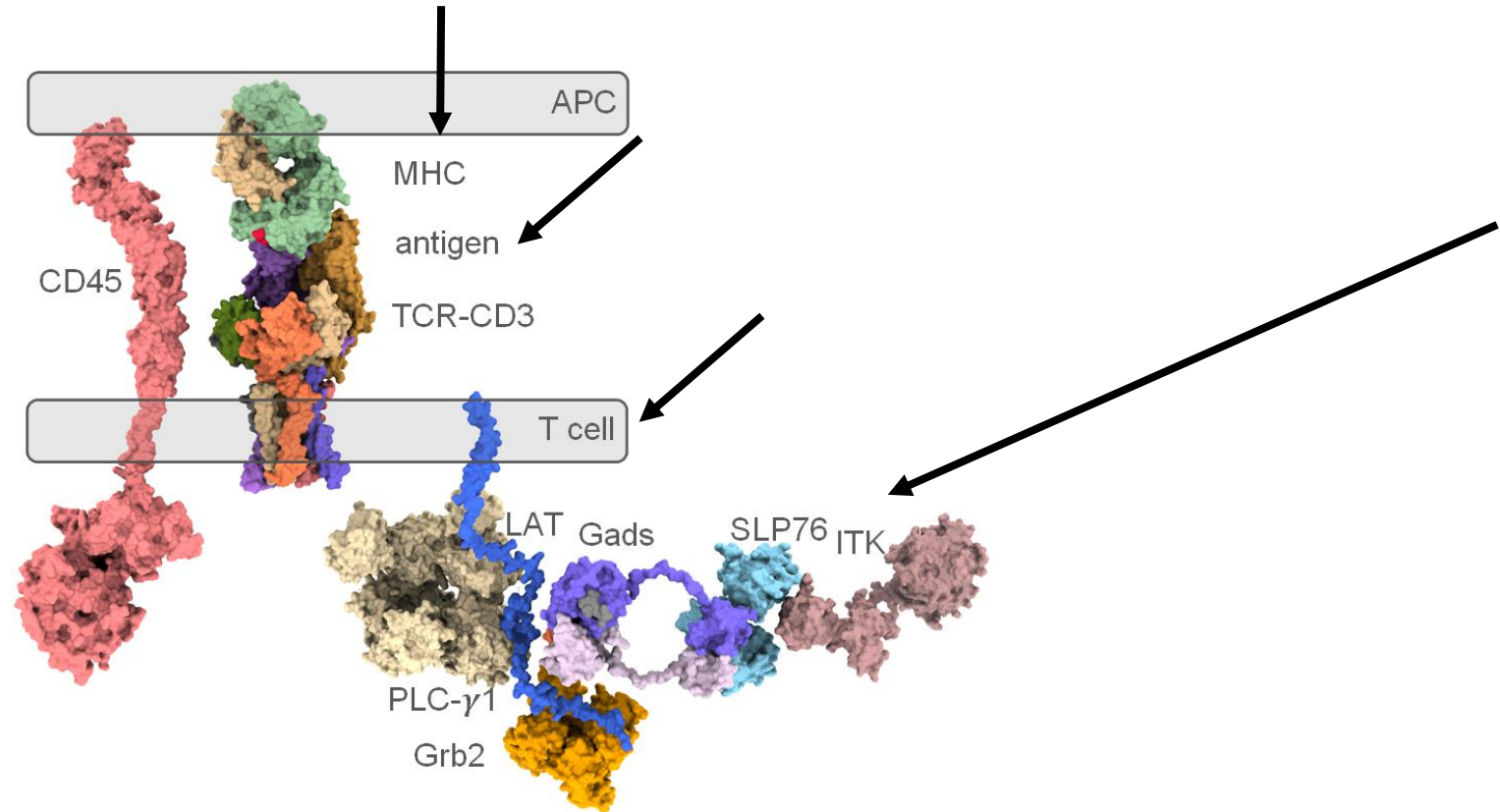
Extracting information for integrative modeling of T-cell activation using NLP approach

Ofer Feinstein

Dr. Barak Raveh & Dr. Gabi Stanovsky

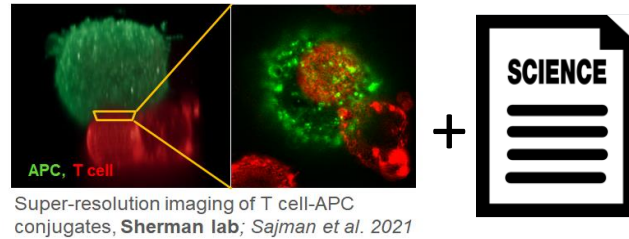
T-cell activation

❑ The immunological synapse by Dr. Dina Schneidman



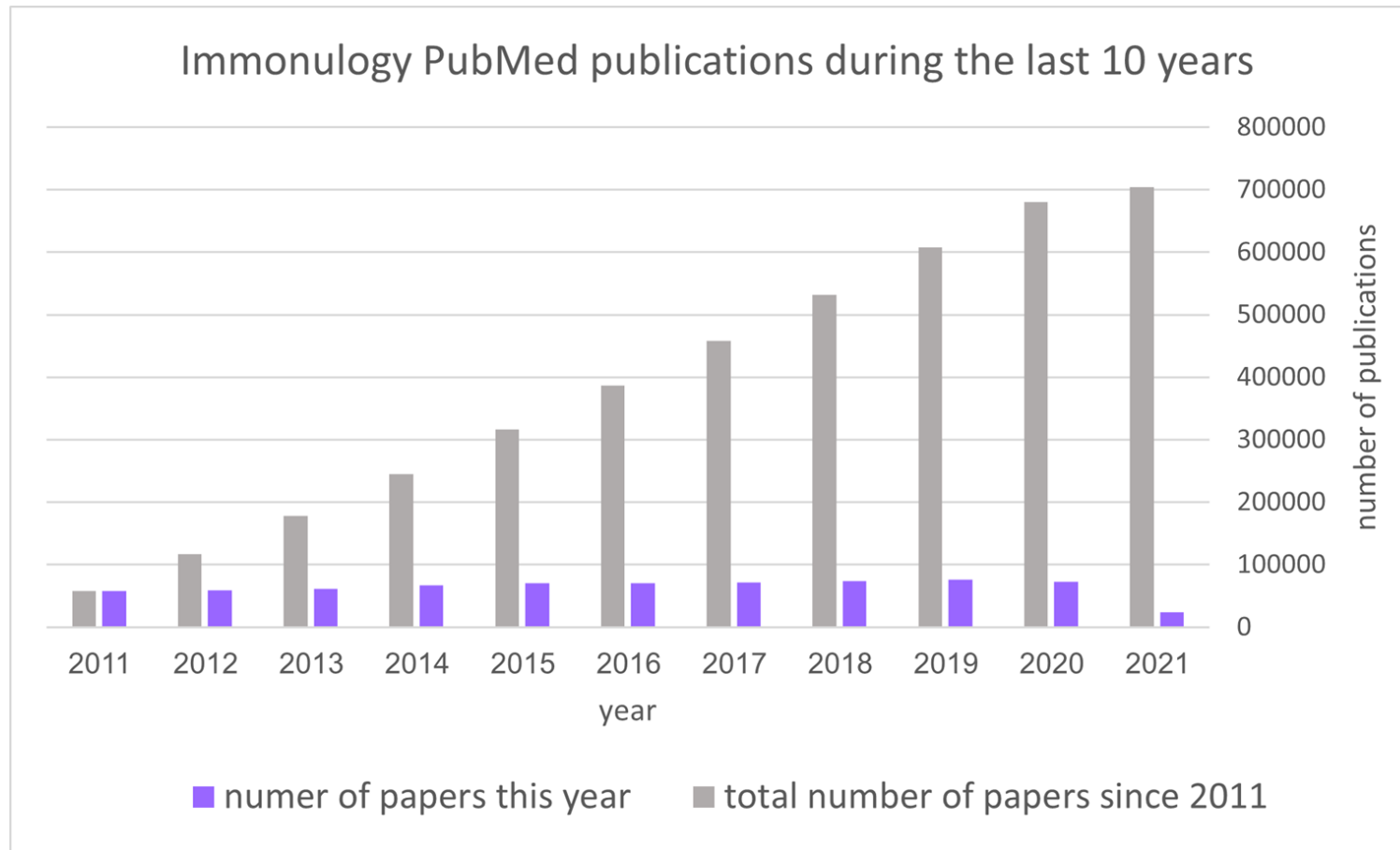
Motivation for integrative modeling

- ❑ Combining data from multiple sources of information (experimental & literature)



- ❑ Biology data is Noisy, Sparse, Ambiguous and inconsistently
- ❑ Combining all sources of information together **increases precision & accuracy**

Data challenge in integrative modeling



Motivation for using Natural Language Processing (NLP)

- ❑ Integrative modeling needs to take into account **millions of papers**
- ❑ This is far beyond what a single person or lab can read in a lifetime!
- ❑ NLP helps filter this data and **find relevant information**



Current status of NLP

- ❑ Highly-dependent on domain
- ❑ Uses deep learning to find patterns in the data
- ❑ Works at the sentence level

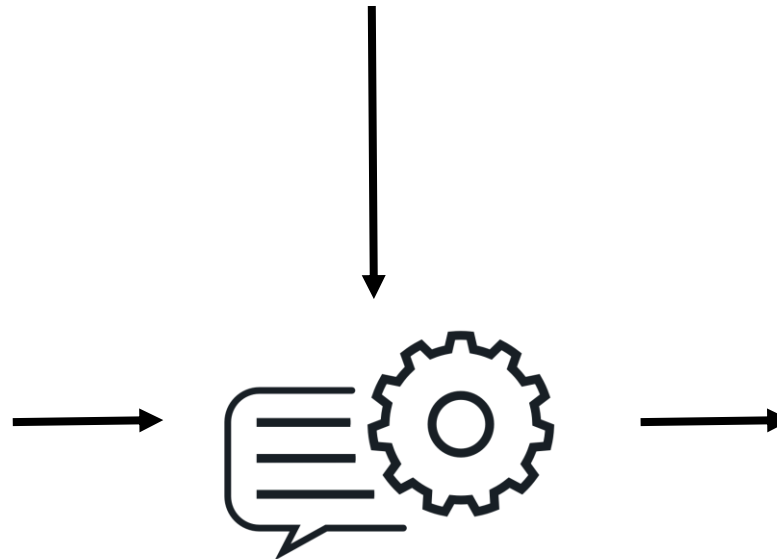


Current status of NLP

- ❑ What are the main molecules participate in the immunological synapse?
- ❑ What is known about their binding affinity?
- ❑ What is known about the association or dissociation constants between the molecules?
- ❑ What is known about their phosphorylation or dephosphorylation?

ABSTRACT

The essential function of the T cell receptor (TCR) is to translate the engagement of peptides on the major histocompatibility complex (pMHC) into appropriate intracellular signals through the associated cluster of differentiation 3 (CD3) complex. The spatial organization of the TCR–CD3 complex in the membrane is thought to be a key regulatory element of signal transduction, raising the question of how receptor clustering impacts on TCR triggering. How signal transduction at the TCR–CD3 complex encodes the quality and quantity of pMHC molecules is not fully understood. This question can be approached by reconstituting T cell signaling in model and cell membranes and addressed by single-molecule imaging of endogenous proteins in T cells. We highlight such methods and further discuss how TCR clustering could affect pMHC rebinding rates, the local balance between kinase and phosphatase activity and/or the lipid environment to regulate the signal efficiency of the TCR–CD3 complex. We also examine whether clustering could affect the conformation of cytoplasmic CD3 tails through a biophysical mechanism. Taken together, we highlight how the spatial organization of the TCR–CD3 complex – addressed by reconstitution approaches – has emerged as a key regulatory element in signal transduction of this archetypal immune receptor.



Why not use Google?

What is known about phosphorylation in the immunological synapse?

Google

phosphorylation in immunological synapse

Q All Images Videos News Shopping More Settings Tools

About 1,510,000 results (0.30 seconds)

Scholarly articles for phosphorylation in immunological synapse

... **synapse** is mediated by **phosphorylation**-regulated ... - Delon - Cited by 314
... **synapse** with sustained tyrosine **phosphorylation** - Hailman - Cited by 162
... **phosphorylation** during early **immunological synapse** ... - Yu - Cited by 79

<https://www.frontiersin.org> > fimmu.2012.00167 > full ▾
How does the kinase Lck phosphorylate the T cell ... - Frontiers
by J Rossy · 2012 · Cited by 45 — In this model, ITAM phosphorylation is ... cell activation sites and immunological synapses and ...
[Abstract](#) · [Introduction](#) · [Spatial Patterning of the...](#) · [Interactions Governing Lck...](#)

<https://www.frontiersin.org> > fimmu.2019.01447 > full ▾
Frontiers | Immunology
by P Castro-Sánchez · 2019 · Cited by 2 — This molecular dynamics is tightly regulated by **phosphorylation** ... Regulation of CD4⁺ T Cell Signaling and Immunological Synapse by Protein ...

<https://www.ncbi.nlm.nih.gov> > articles > PMC2826677
Immunological synapse: a multi-protein signalling cellular ...
by K Padhan · 2010 · Cited by 37 — Current model of signalling in T cells states that stimulation of T-cell receptor (TCR) with specific major histocompatibility complex–peptide complexes (MHC–p) leads to **phosphorylation** of tyrosine residues within the immune receptor tyrosine-based activation motifs (ITAMs) of the invariant CD3 chains by Src family ...

<https://pubmed.ncbi.nlm.nih.gov> > ...
Mechanism of recruitment of WASP to the immunological ...
by Y Sasahara · 2002 · Cited by 285 — Mechanism of recruitment of WASP to the **immunological synapse** and of its ... TCR engagement also causes PKC θ -dependent **phosphorylation** of WIP; ...

<https://journals.plos.org> > plosone > article > journal.po... ▾
Myosin IIA Modulates T Cell Receptor Transport and CasL ...
by Y Yu · 2012 · Cited by 79 — In the **immunological synapse**, the role of non-muscle myosin IIA, the myosin II isoform ... Inhibition of myosin IIA reduces CasL **phosphorylation**.

People also ask

What is the function of the immunological synapse? ^

The **immunological synapse** (IS) is an excellent example of cell–cell communication, where signals are exchanged between two cells, resulting in a well-structured line of defense during adaptive **immune** response.

<https://www.sciencedirect.com/topics/immunological-synapse>

[Immunological Synapse - an overview | ScienceDirect Topics](#)

Search for: [What is the function of the immunological synapse?](#)

How does the kinase LCK phosphorylate the T cell receptor? ▾

What is LCK in immunology? ▾

What is the function of LCK? ▾

Why is the immunological synapse crucial for T cell activation? ▾

Where does immunological synapse occur? ▾

What activates LCK? ▾

How many domains are found in the LCK protein? ▾

Is LCK membrane bound? ▾

What does CTLA 4 bind to? ▾

What is the role of LCK in the TCR signaling cascade? ▾

What potential mechanisms may be contributing to the immune dysregulation seen in patients with ZAP70 deficiency? ▾

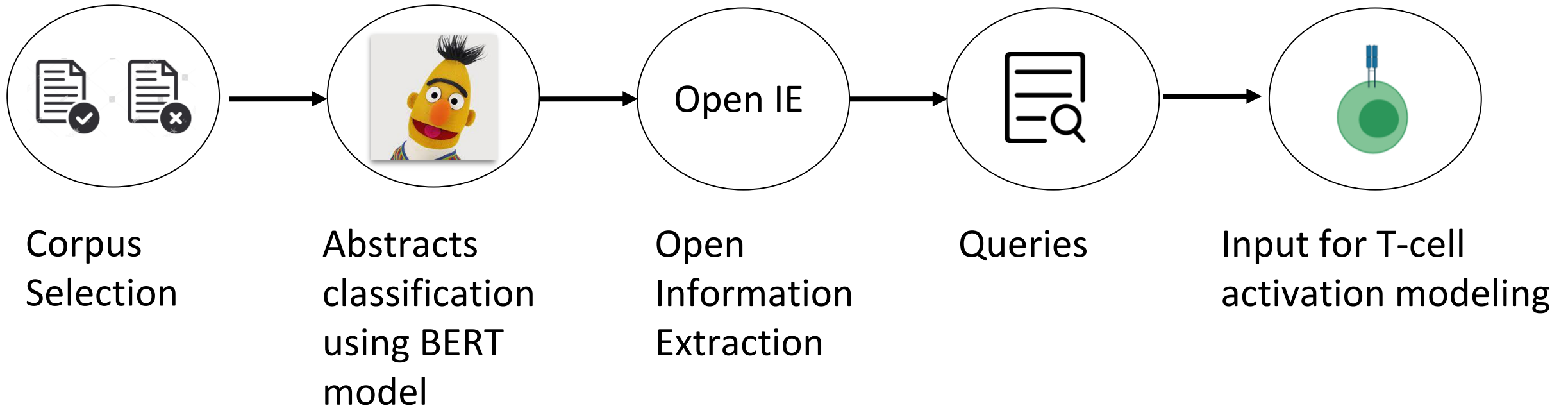
Queries in numbers

- ❑ Database contains **~16M** statements from ~500K papers

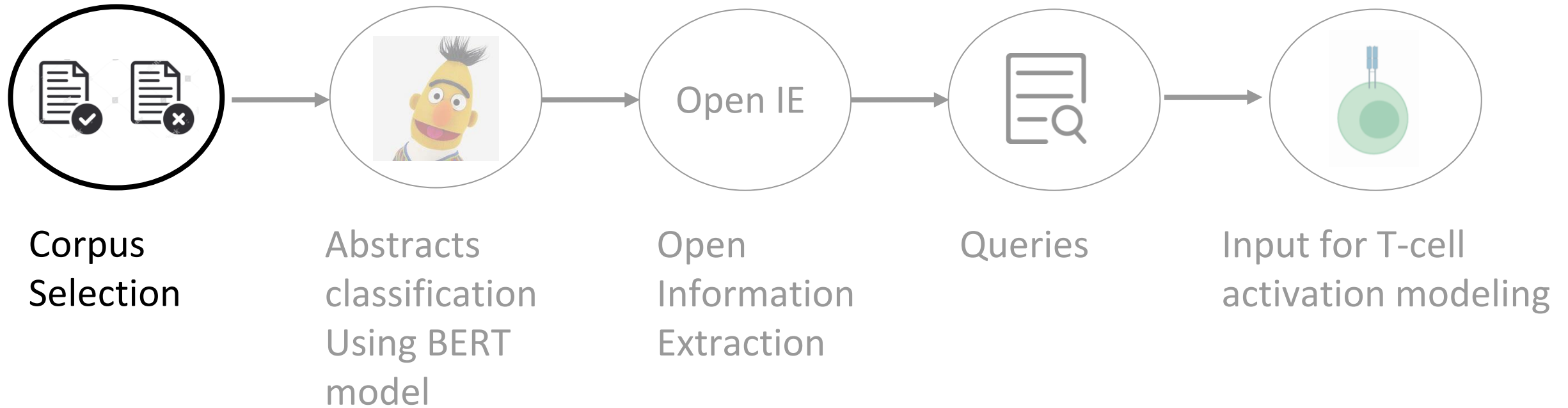
*“**LAT and Lck tyrosine phosphorylated** exclusively following **CD38** engagement.”*

- ❑ **~5000** statements from “**phosphorylation**” query
- ❑ **~180** statements from “**immunological synapse**” query
- ❑ **~1000** statements from “**dissociation**” query

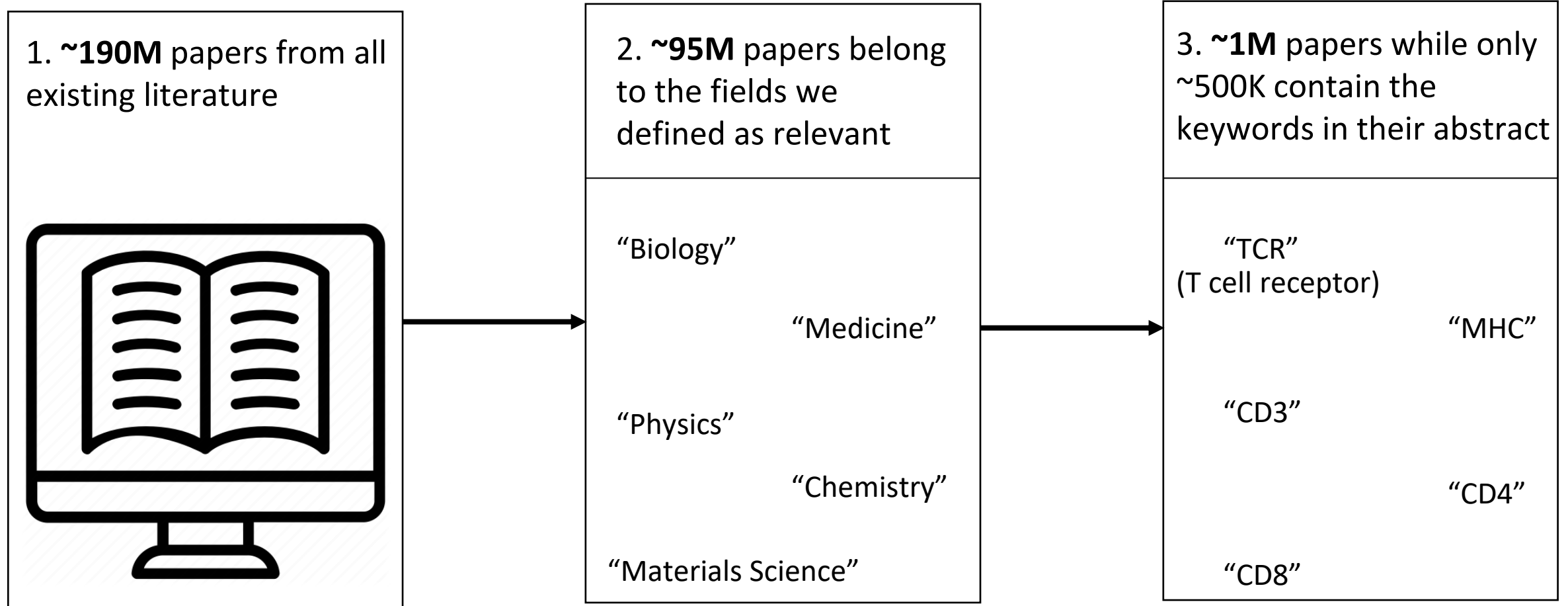
Workflow



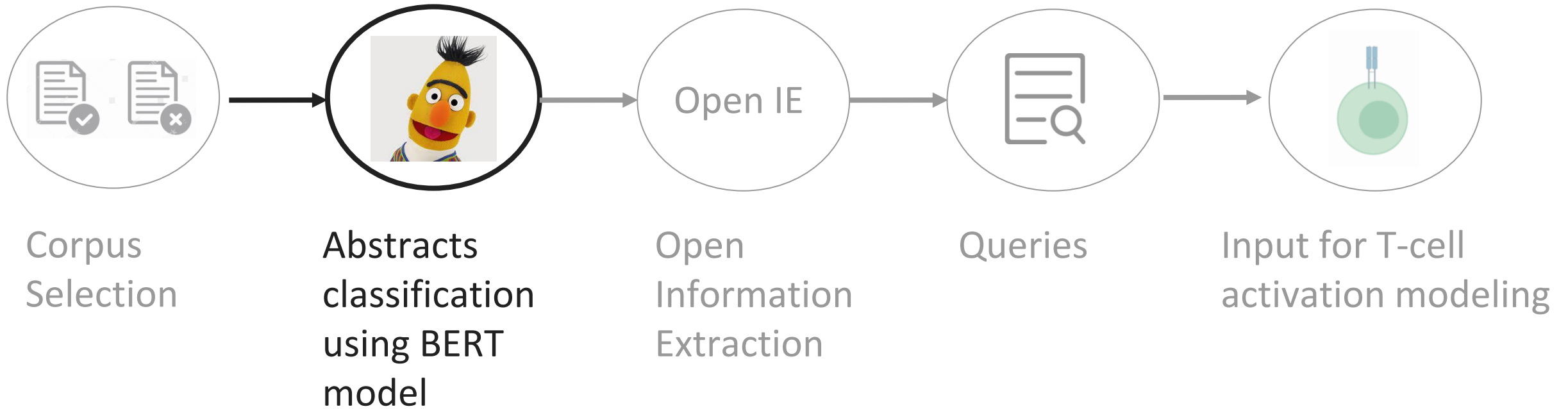
Workflow



Corpus Selection



Workflow



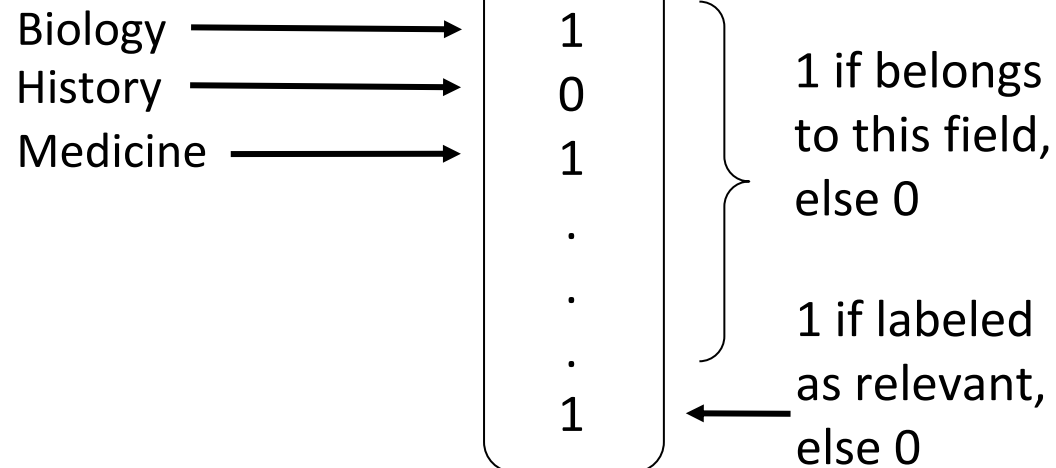
Abstracts classification

ABSTRACT

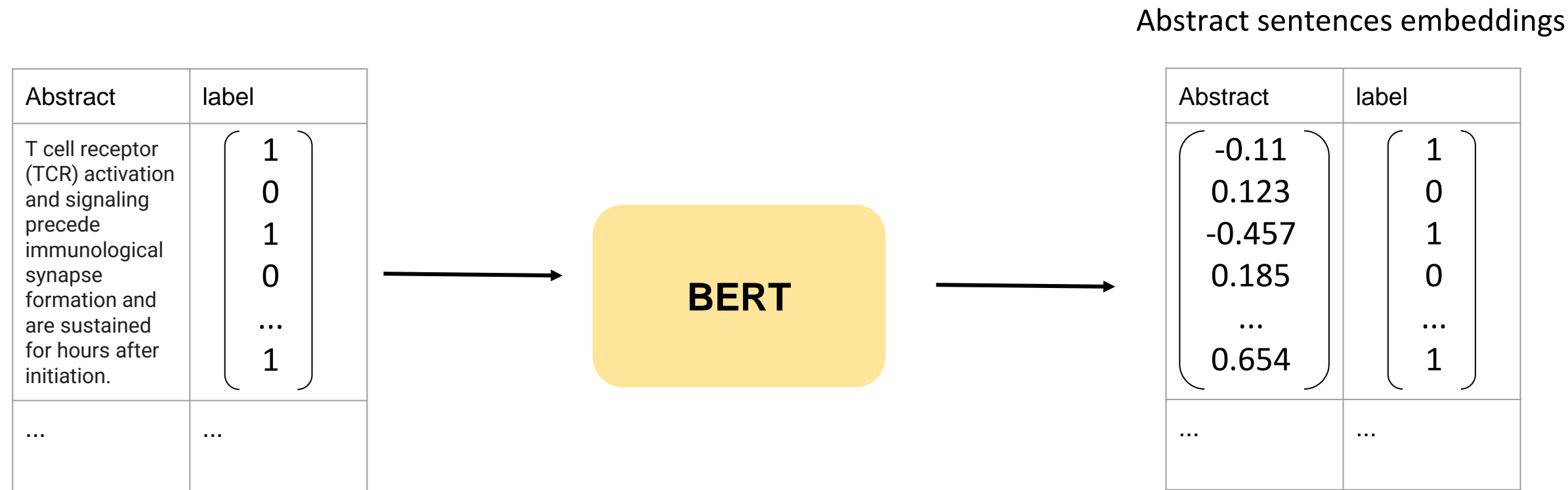
The essential function of the T cell receptor (TCR) is to translate the engagement of peptides on the major histocompatibility complex (pMHC) into appropriate intracellular signals through the associated cluster of differentiation 3 (CD3) complex. The spatial organization of the TCR-CD3 complex in the membrane is thought to be a key regulatory element of signal transduction, raising the question of how receptor clustering impacts on TCR triggering. How signal transduction at the TCR-CD3 complex encodes the quality and quantity of pMHC molecules is not fully understood. This question can be approached by reconstituting T cell signaling in model and

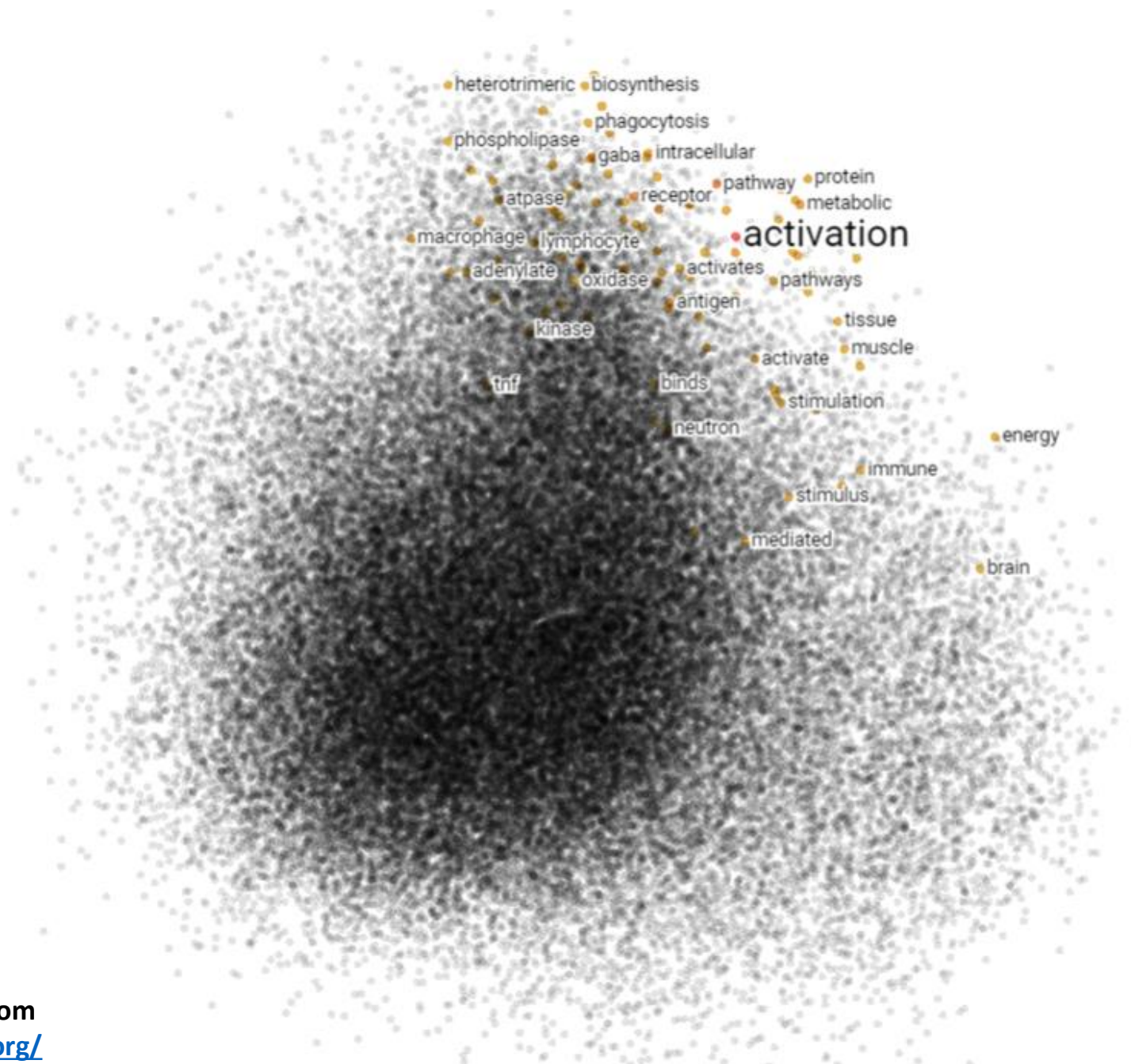
labeled by

Fields Of Study

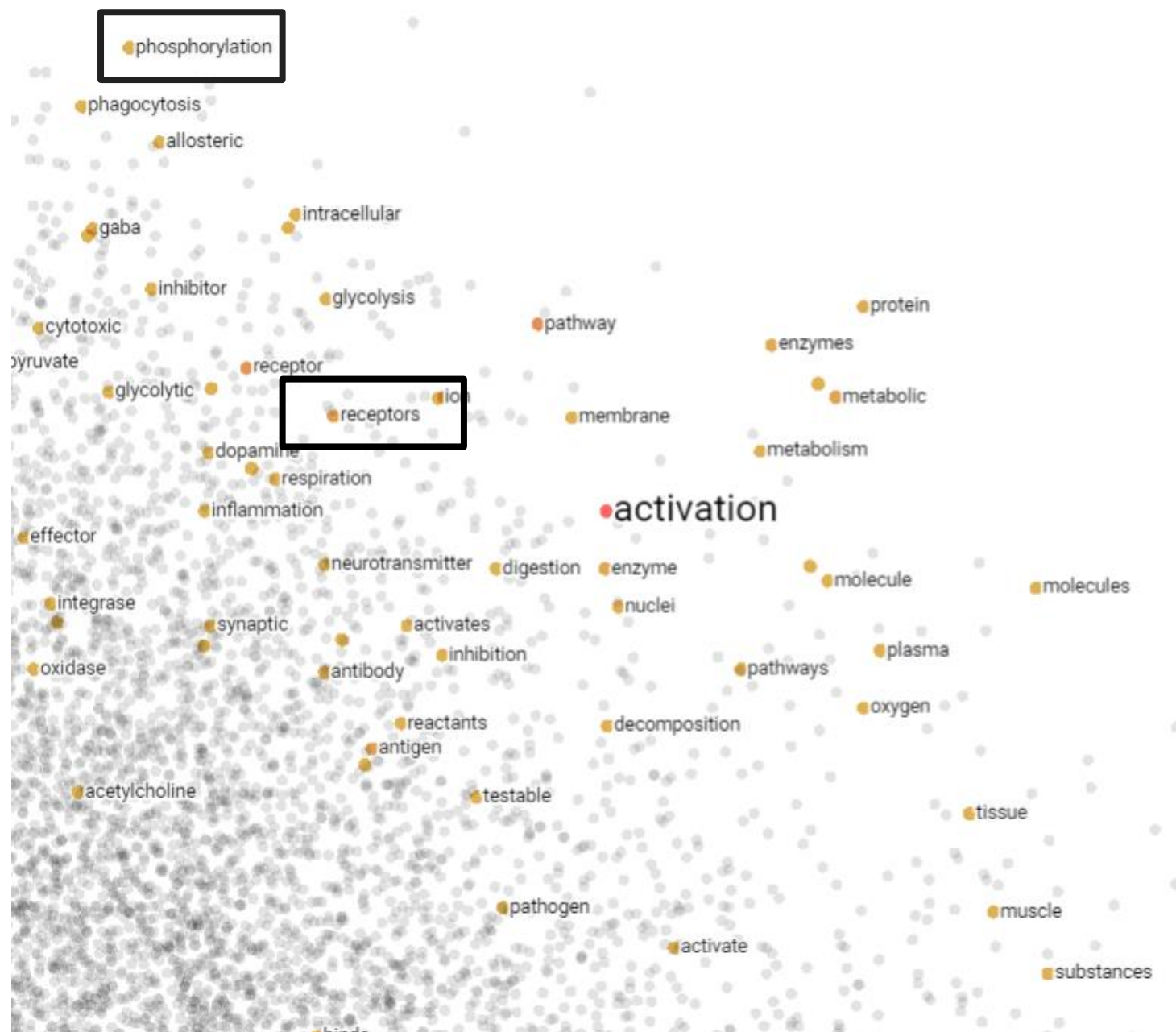


Feature extraction using BERT



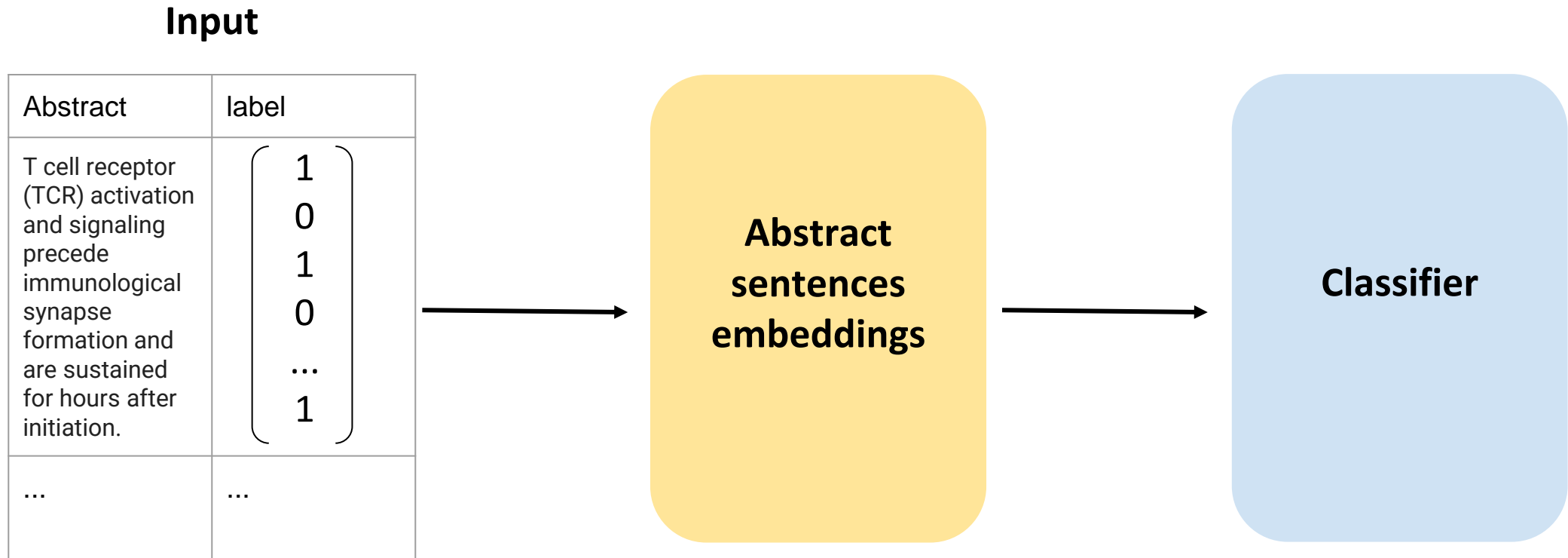


This visualization was taken from
<https://projector.tensorflow.org/>

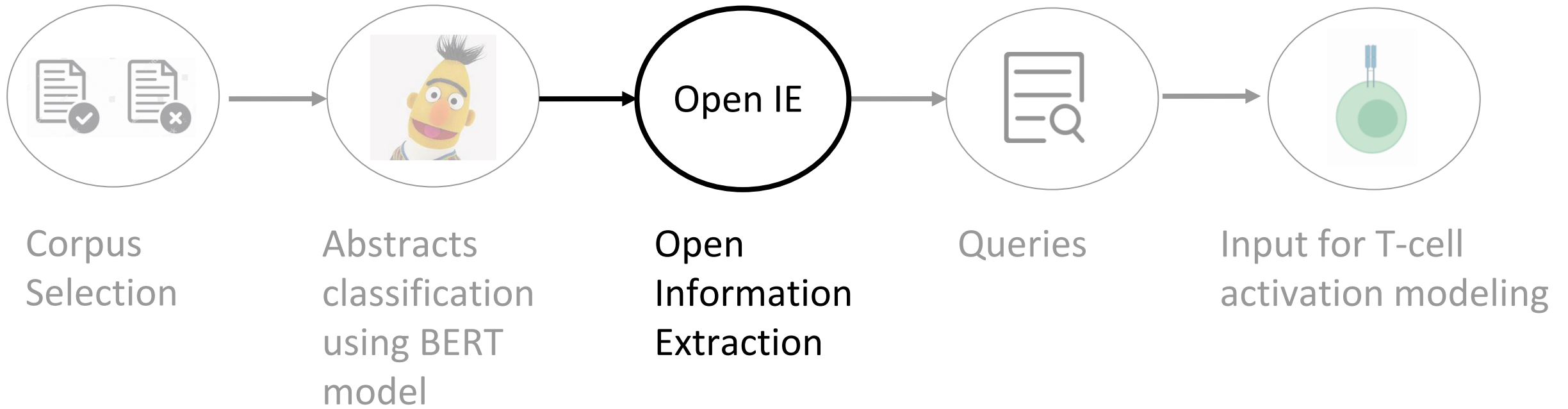


This visualization was taken from
<https://projector.tensorflow.org/>

BERT Fine-tuning on classification



Workflow



Open Information Extraction (Open IE)

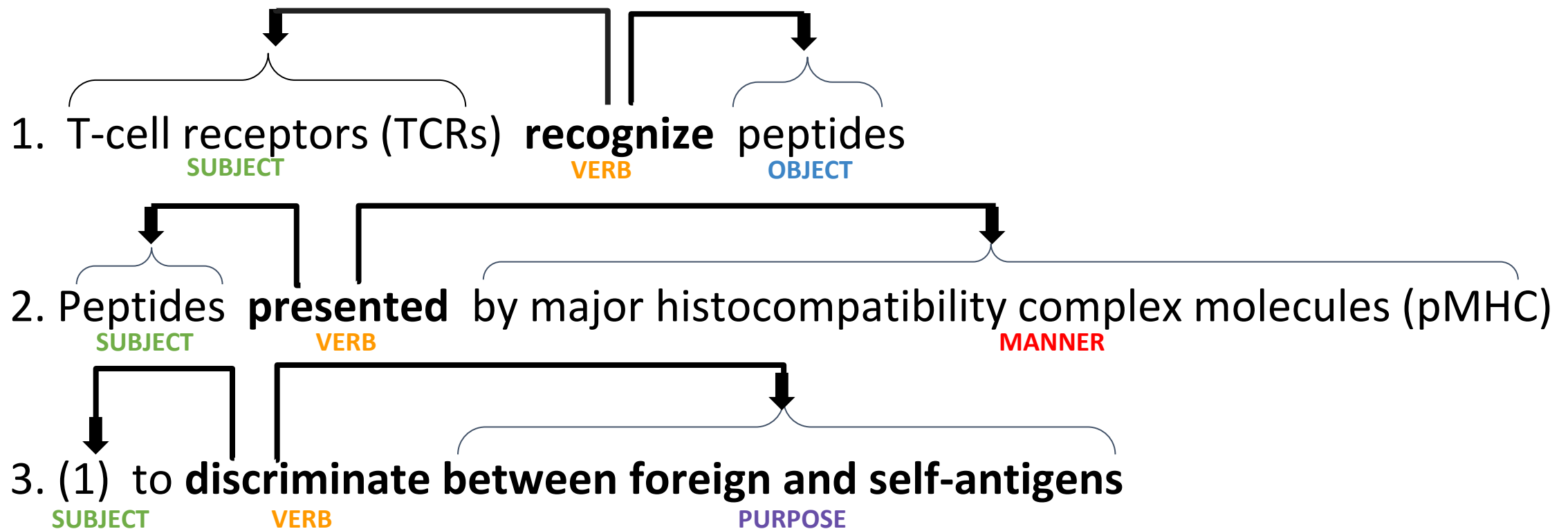
- ❑ **Input:** sentences of abstracts labeled as relevant
- ❑ **Output:** a set of statements mentioned in the abstract



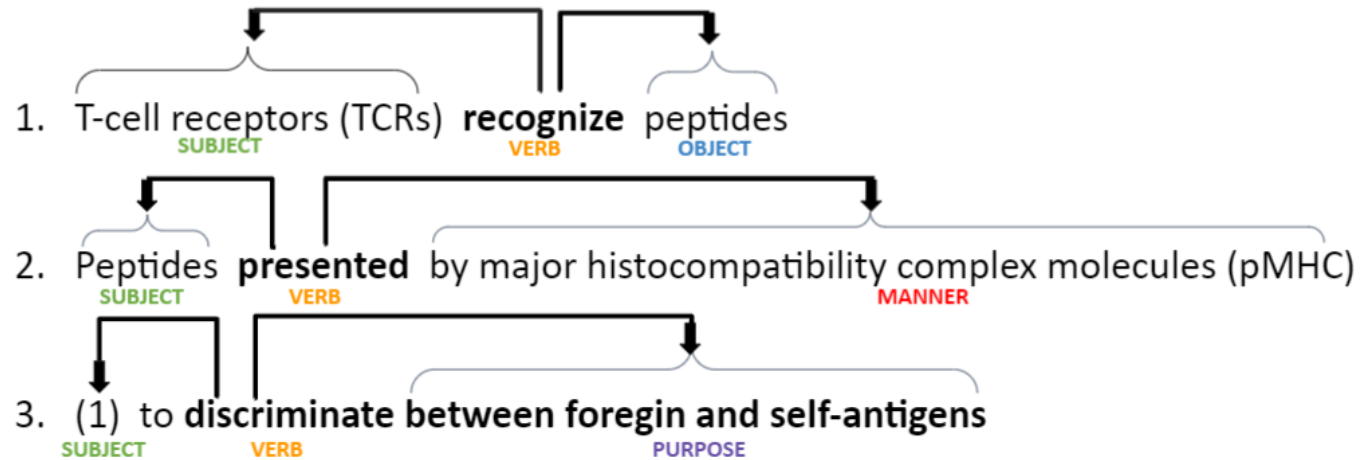
Stanovsky et. al., 2018

Open Information Extraction (Open IE)

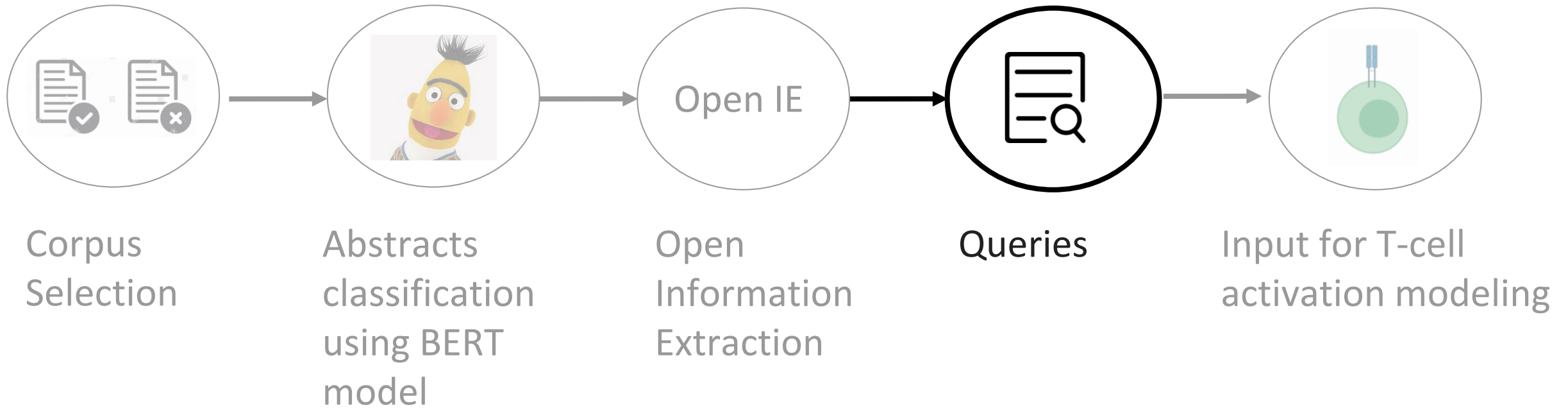
“T-cell receptors (TCRs) recognize peptides presented by major histocompatibility complex molecules (pMHC) to discriminate between foreign and self-antigens.”



From statements to database

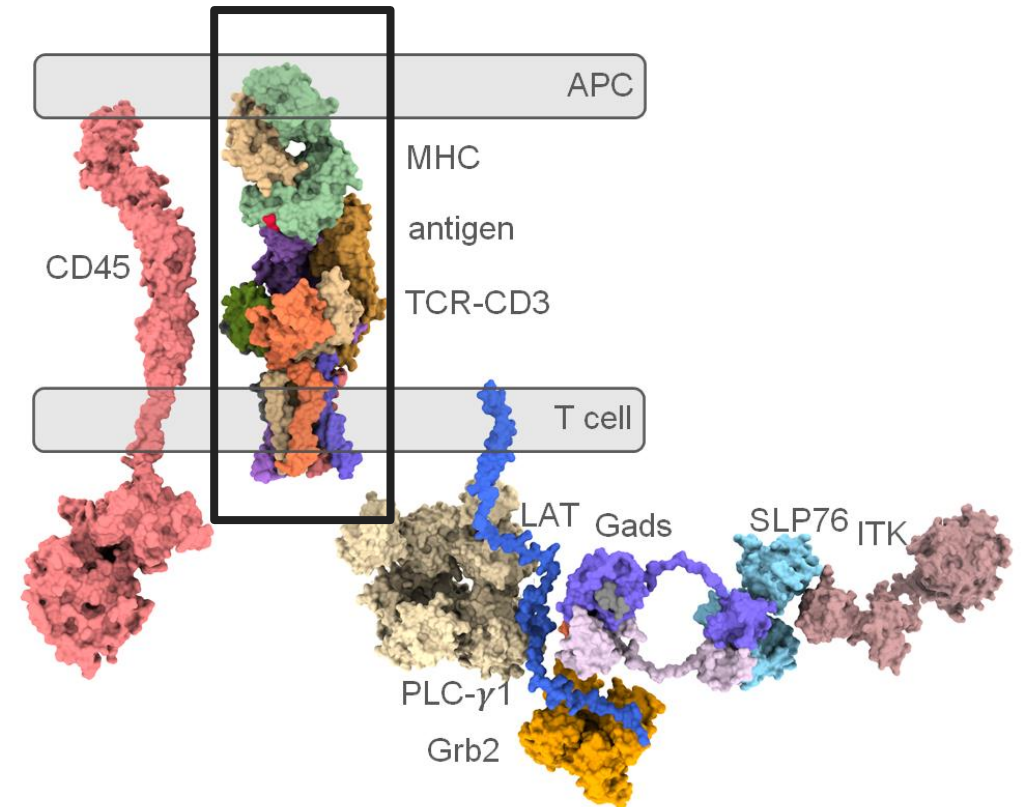


Workflow



T-cell activation

- ❑ Triggers to T-cell Activation
- ❑ TCR-MHC interaction



T-cell activation

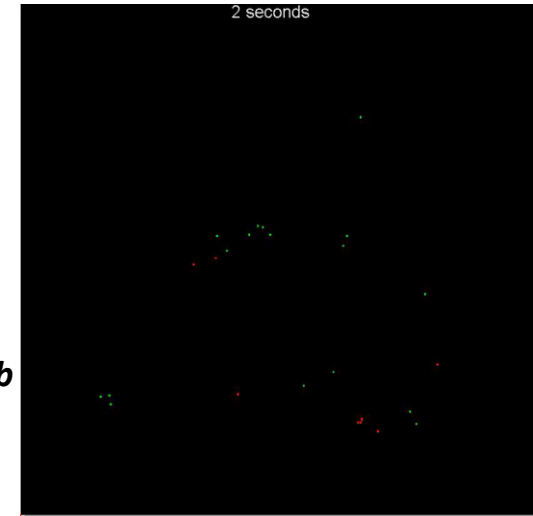
- ❑ Triggers to T-cell Activation
- ❑ TCR-MHC interaction
- ❑ Binding affinity

TCR-MHC interaction

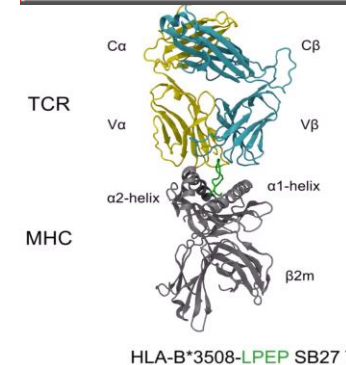
Cellular
scale



Molecule
scale



Atoms
scale



T-cell activation

- ❑ Triggers to T-cell Activation
- ❑ TCR-MHC interaction
- ❑ Binding affinity
- ❑ K_D value: low value \rightarrow high-affinity

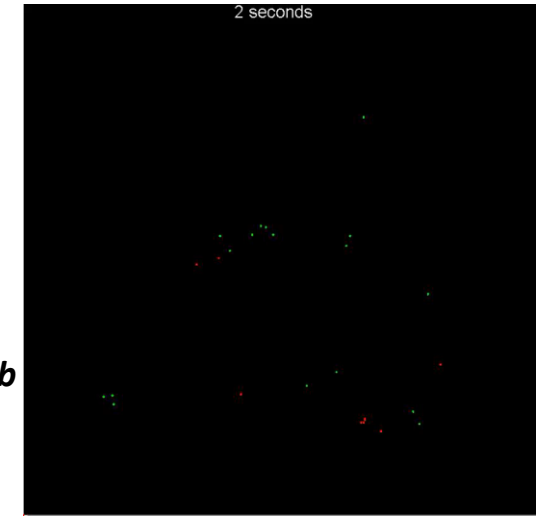
TCR-MHC interaction

Cellular
scale

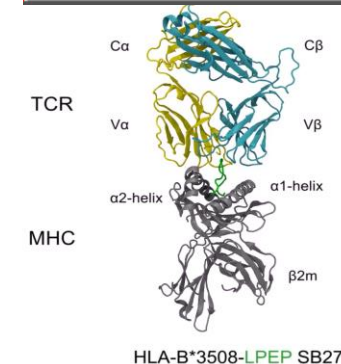


Molecule
scale

Sherman lab



Atoms
scale



T-cell activation

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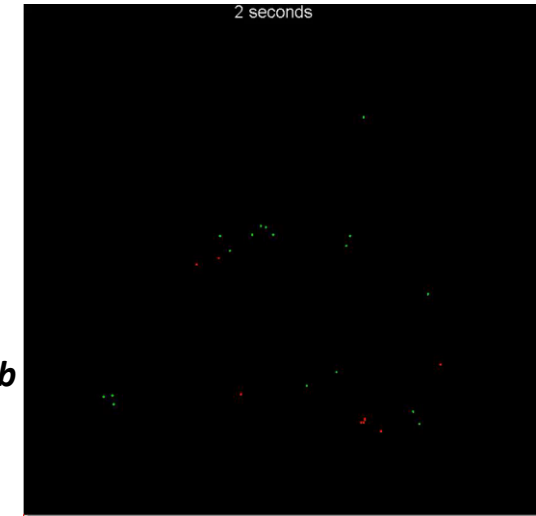
TCR-MHC interaction

Cellular
scale

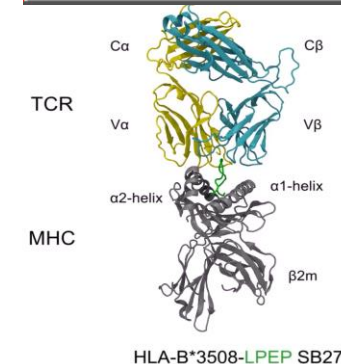


Molecule
scale

Sherman lab

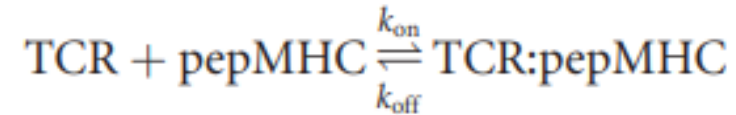


Atoms
scale



Query & answers: example

- ❑ Query: dissociation constant (K_D) values



1. T-cell receptors (TCRs) recognize peptides
SUBJECT VERB OBJECT

```
SELECT * FROM Database_Table
WHERE SUBJECT = 'T-cell receptor'
AND OBJECT = 'pepMHC';
```

Query & answers: example

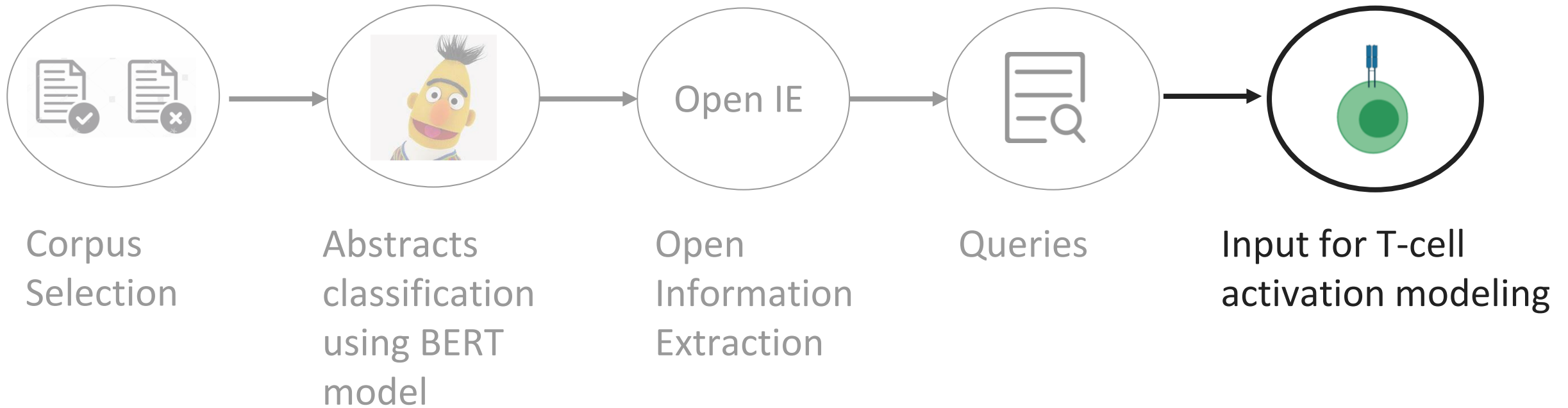
```
SELECT * FROM Database_Table
      WHERE SUBJECT = 'T-cell receptor'
      AND OBJECT = 'pepMHC';
```

□ Answers examples:


"wild-type TCR affinities (K_D values) with pepMHC have been shown to be in the **range of 1–100 μM** "
SUBJECT OBJECT


"The affinities of these high-affinity TCR with pepMHC ranged from 30 nM to 26pM"
SUBJECT OBJECT

Workflow



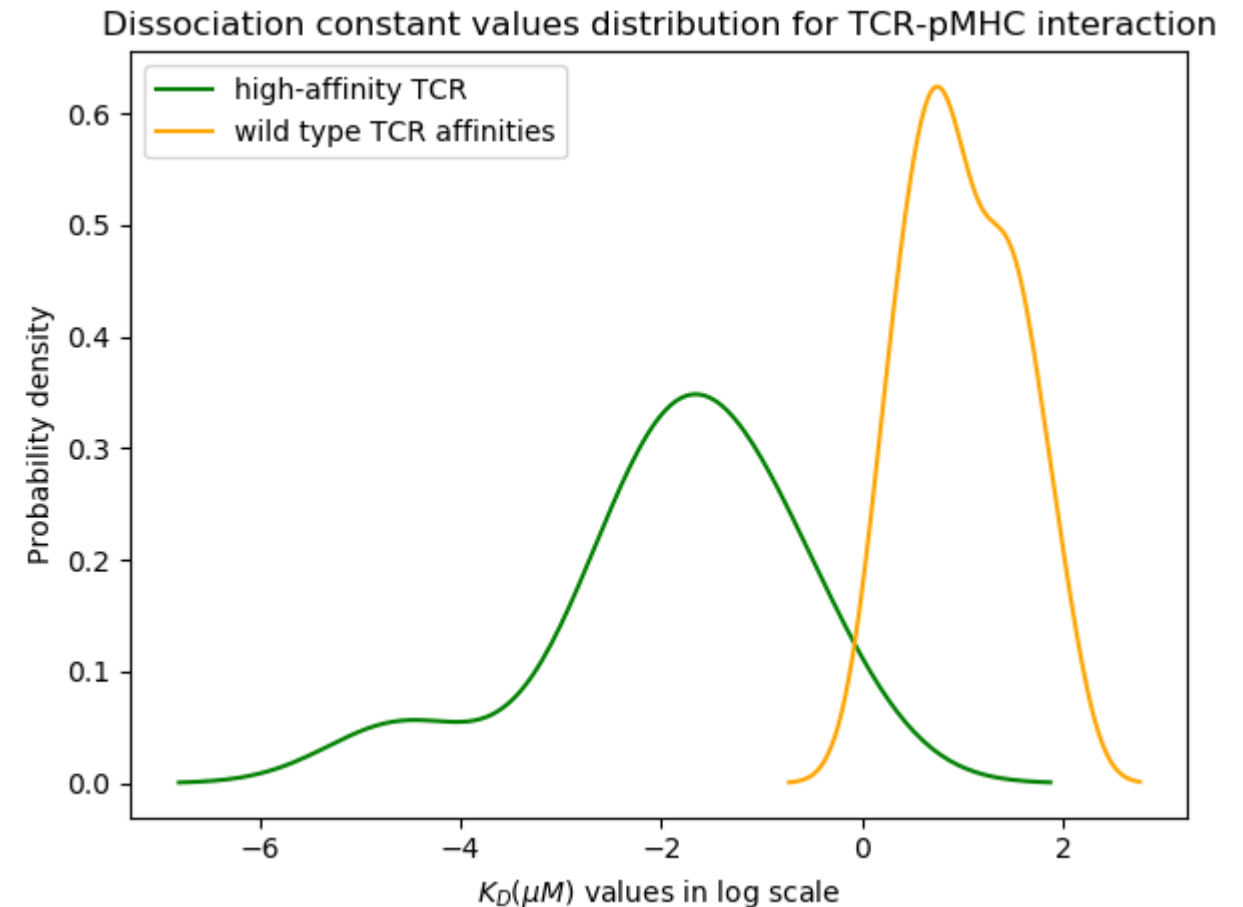
From queries output to T-cell activation modeling

"wild-type TCR affinities (K_D values) with pepMHC have been shown to be in the range of 1–100 μM "

SUBJECT OBJECT

"The affinities of these high-affinity TCR with pepMHC ranged from 30 nM to 26pM"

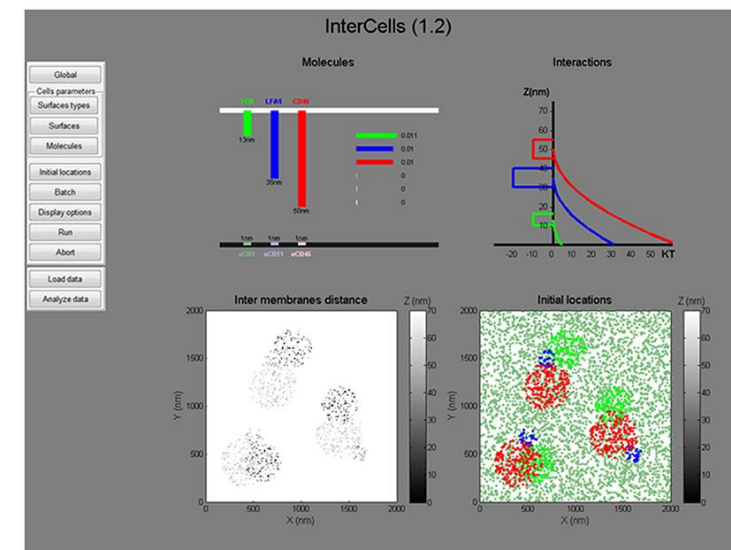
SUBJECT OBJECT



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November 2008; accepted 7 November 2008.
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review.
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Senior author: David M. Kranz

The interaction between the T-cell receptor (TCR) and its peptide-major histocompatibility complex (pMHC) ligand plays a critical role in determining the activity and specificity of the T cell. The binding properties associated with these interactions have now been studied in many systems, providing a framework for a mechanistic understanding of the initial events that govern T-cell function. There have been various other reviews that have described the structural and biochemical features of TCR : pMHC interactions. Here we provide an overview of four areas that directly impact our understanding of T-cell function, as viewed from the perspective of the TCR : pMHC interaction: (1) relationships between T-cell activity and TCR : pMHC binding parameters, (2) TCR affinity, avidity and clustering, (3) influence of coreceptors on pMHC binding by TCRs and T-cell activity, and (4) impact of TCR binding affinity on antigenic peptide specificity.

Keywords: agonists; antagonists; binding affinity; coreceptors; dissociation rate; major histocompatibility complex; peptide specificity; peptide-major histocompatibility complex; serial triggering; T-cell receptor; T-cell receptor clustering



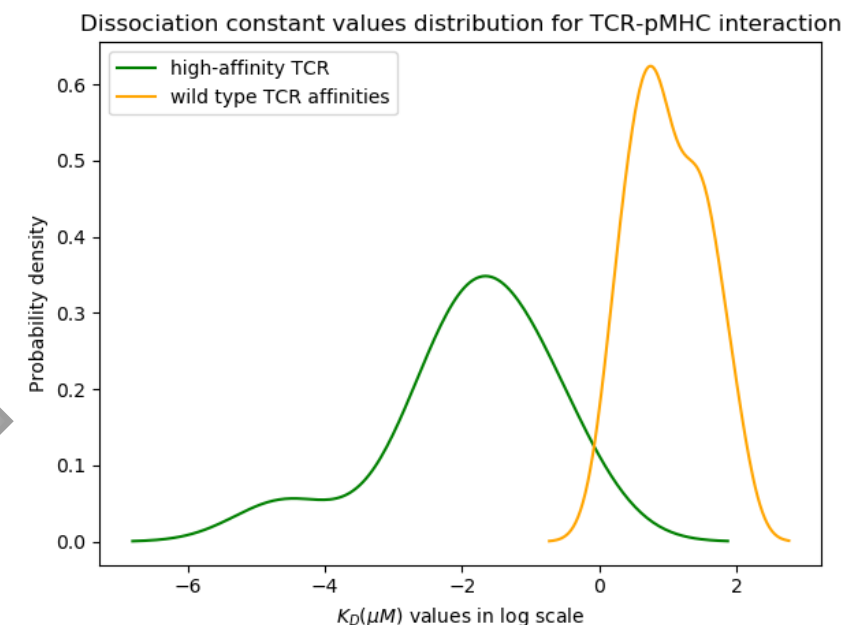
Neve-Oz et. al., 2018

SUBJECT

OBJECT

SUBJECT

OBJECT



Summary



Classification model for relevant papers



Database contains statements from relevant abstracts



Asking questions in large scale



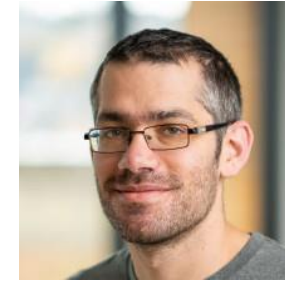
Answers to part of the asked questions

Future work

- ➔ Extracting information from the paper content
- ➔ Context between abstract sentences to the content
- ➔ Using the found parameters as input to the T-cell activation model

Thank you!

□ Barak & Gabi



□ Amir Bar



□ For your listening

Questions?

