Self-contemplating In-context Learning Enhances T cell Receptor Generation for Novel Epitopes

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Code

Paper

National Institute of General Medical Sciences

Background

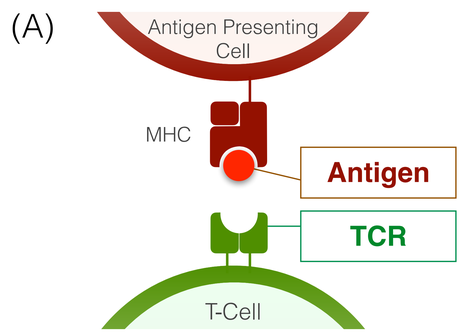
- **Role of TCRs in Immunity.** T cell receptors (TCRs) plays a critical role in adaptive immune systems as they enable T cells to recognize abnormal cells from healthy cells.

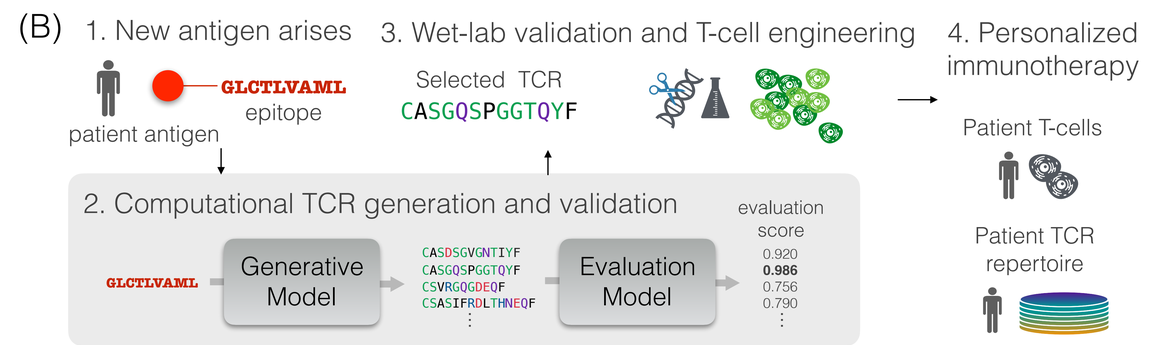
Motivations

- Designing TCRs for novel epitopes is essential for advancing engineering TCR therapy.
- Most novel epitopes lack known cognate TCRs, posing a challenge for generative models.

Contributions

- Expand context window with in-context training.
- Generate synthetic TRCs for novel epitopes.



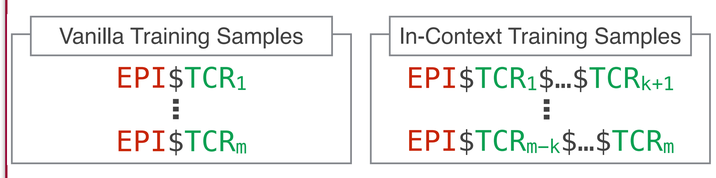


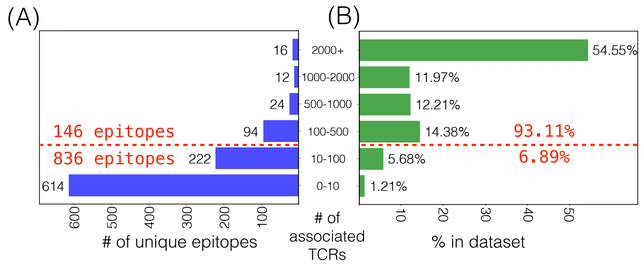
Prompting approches

- Designed for epitopes with no known binding TCRs.
- Step 1: **Generating candidate** TCRs using zero-shot inference.
- Step 2: **Scoring and ranking candidates** using: binding affinity predictor (e.g., BAP model) and sequence likelihood (e.g., GPT log-likelihood)
- Step 3: **Selecting the top-k filtered TCRs as in-context examples** for improved generation.

In-Context Training (ICT) with longer context windows

- Allows users to provide more context after training



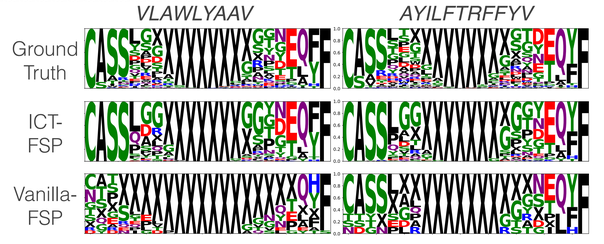


SCP enables effective TCR generation without access to real context data and matches or exceeds performance of few-shot prompting with real TCRs

	TCRMatch			GPT-LL			Bit Score			BLOSUM62 Score		
N. of Training Contexts	0	5	10	0	5	10	0	5	10	0	5	10
N. of Inference Contexts	0	5	10	0	5	10	0	5	10	0	5	10
Epitope-agnostic Generator (Baseline)	97.30 (1.14)	–	–	96.40 (2.01)	–	–	1.62 (0.16)	–	–	15.32 (1.97)	–	–
Vanilla-0-shot (Baseline)	93.13 (4.22)	–	–	92.46 (4.02)	–	–	70.22 (3.74)	–	–	74.80 (3.96)	–	–
ICT-FSP-Fake (Baseline)	–	90.43 (4.27)	96.63 (1.96)	–	91.15 (3.40)	95.93 (1.91)	–	69.23 (4.31)	74.86 (2.22)	–	72.93 (4.78)	78.30 (2.68)
ICT-FSP-Healthy (Baseline)	–	99.61 (0.10)	99.53 (0.14)	–	98.56 (0.16)	98.63 (0.11)	–	80.62 (1.20)	**76.91 (1.31)**	–	**84.53 (0.96)**	**80.89 (1.03)**
ICT-FSP (Oracle)	–	96.26 (3.36)	99.48 (0.12)	–	96.47 (2.22)	98.72 (0.21)	–	**77.71 (2.94)**	74.91 (1.49)	–	81.43 (3.05)	78.40 (1.19)
ICT-SCP-Random	–	99.70 (0.09)	99.71 (0.11)	–	98.63 (0.16)	99.14 (0.16)	–	75.34 (1.42)	62.31 (2.30)	–	78.55 (1.24)	65.59 (2.29)
ICT-SCP-Chain	–	99.07 (0.46)	98.39 (0.85)	–	98.45 (0.14)	**99.48 (0.07)**	–	77.44 (1.33)	63.33 (2.13)	–	81.23 (1.26)	66.00 (2.17)
ICT-SCP-Select	–	**99.75 (0.07)**	**99.77 (0.08)**	–	**98.99 (0.09)**	99.17 (0.21)	–	73.16 (1.51)	58.11 (2.49)	–	76.66 (1.30)	61.32 (2.47)

	BAP MLP			BAP LSTM			BAP CNN		
N. of Training Contexts	0	5	10	0	5	10	0	5	10
N. of Inference Contexts	0	5	10	0	5	10	0	5	10
Epitope-agnostic Generator (Baseline)	21.28 (1.54)	–	–	48.74 (0.67)	–	–	47.63 (0.80)	–	–
Vanilla-0-shot (Baseline)	88.14 (1.35)	–	–	78.66 (5.53)	–	–	70.41 (5.69)	–	–
ICT-FSP-Fake (Baseline)	–	78.15 (1.64)	79.67 (1.61)	–	73.18 (5.50)	72.66 (5.19)	–	60.71 (6.27)	64.67 (5.46)
ICT-FSP-Healthy (Baseline)	–	77.80 (1.31)	84.63 (0.92)	–	83.13 (3.82)	85.26 (3.76)	–	75.89 (4.23)	75.30 (4.56)
ICT-FSP (Oracle)	–	79.67 (1.47)	87.17 (1.01)	–	**85.20 (3.71)**	87.49 (3.03)	–	74.25 (4.92)	**77.54 (4.11)**
ICT-SCP-Random	–	80.54 (1.44)	89.61 (1.02)	–	84.25 (3.80)	86.29 (3.91)	–	75.77 (4.61)	75.94 (4.91)
ICT-SCP-Chain	–	80.00 (1.45)	90.86 (0.96)	–	84.30 (3.73)	**87.64 (3.72)**	–	75.49 (4.26)	77.41 (4.61)
ICT-SCP-Select	–	**82.70 (1.22)**	**91.91 (0.92)**	–	84.75 (3.75)	83.71 (5.38)	–	**76.62 (4.39)**	75.29 (5.88)

- Prompting strategies comparison table, shows that SCP achieved best performance across most of evaluation metrics.
- Training strategies comparison with Seqlogo.



Evaluation metrics