Machine learning in immunology

Prediction of binding affinity of peptide-MHC

Vadim Nazarov

Genomics of Adaptive Immunity Lab, IBCH RAS
National Research University Higher School of Economics

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Introduction to immunology

Immune system

- Recognizes foreign / dangerous substances from the environment (mainly microbes).
- Is involved in elimination of old and damaged cells of the body.
- Attacks tumor and virus-infected cells.

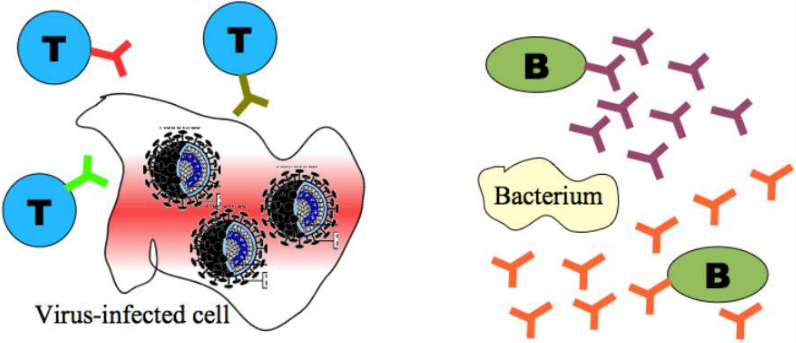
Two branches of immune system

- Innate, nonspecific – very quickly recognizes most foreign substances and eliminates them. No memory or learning.
- Adaptive, specific – high degree of specificity in distinction between self and non-self. The reaction takes several days to be effectively triggered. It learns and memorizes the pathogen landscape.

Adaptive immune system

T cells destroy infected cells to eradicate intracellular pathogens. (Some bacteria, all viruses)

B cells secrete antibodies to attack extracellular pathogens (Most bacteria)



The colors of the receptors indicate specificity: each can bind to one specific antigen. Adaptive immunity can only attack targets that it has prepared for.

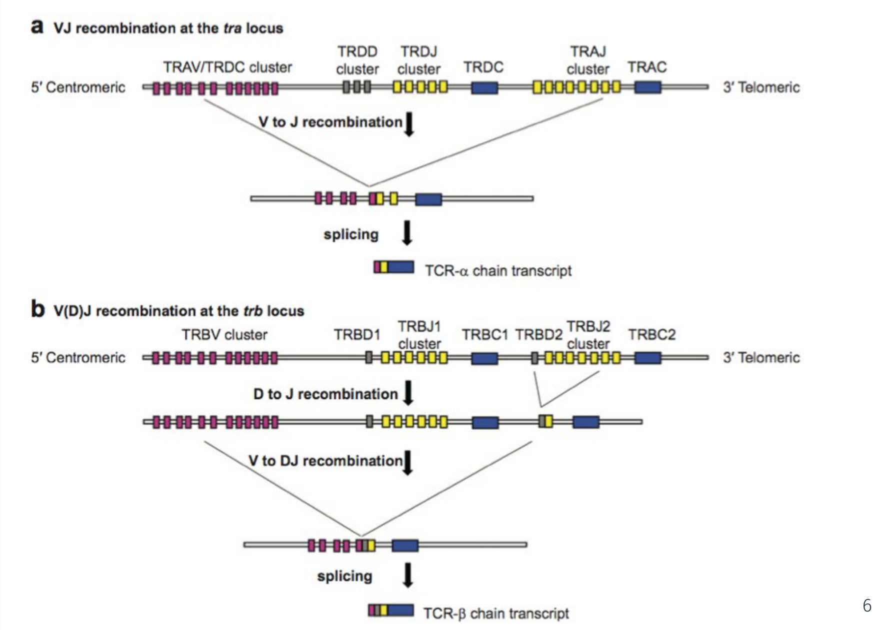
TCR chains

$\alpha\beta$ chain - ”classic” adaptive immunity (virus detection)

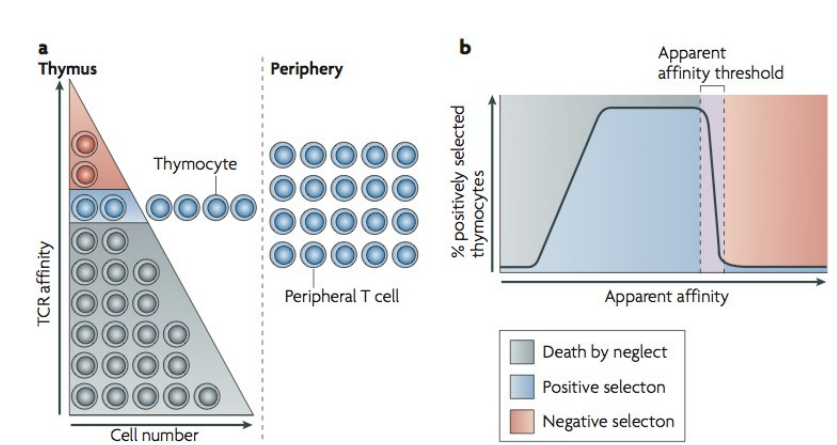
$\gamma\delta$ chain - terra incognita (phagocytosis, invariant cells)

Different generation processes!

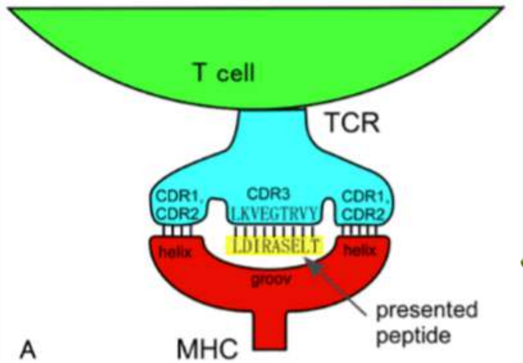
V(D)J recombination

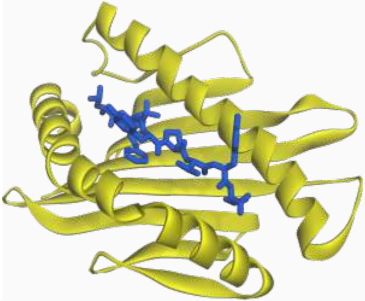


TCR selection

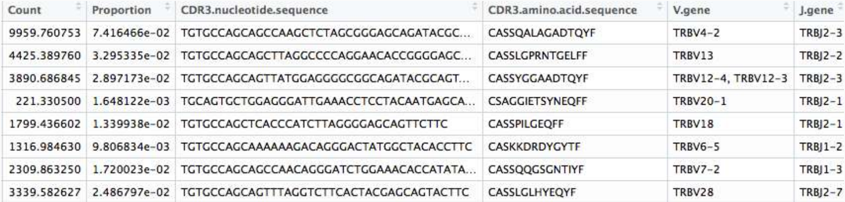


TCR:peptide:MHC interaction





TCR data example



Count	Proportion	CDR3.nucleotide.sequence	CDR3.amino.acid.sequence	V.gene	J.gene
9959.760753	7.416466e-02	TGTGCCAGCAGCCAAGCTCTAGCGGGAGCAGATACGC...	CASSQALAGADTQYF	TRBV4-2	TRBJ2-3
4425.389760	3.295335e-02	TGTGCCAGCAGCTTAGGCCCCAGGAACACCGGGGAGC...	CASSLGPRNTGELFF	TRBV13	TRBJ2-2
3890.686845	2.897173e-02	TGTGCCAGCAGTTATGGAGGGGCGGCAGATACGCAGT...	CASSYGGAADTQYF	TRBV12-4, TRBV12-3	TRBJ2-3
221.330500	1.648122e-03	TGCAGTGCTGGAGGGATTGAAACCTCCTACAATGAGCA...	CSAGGIETSYNEQFF	TRBV20-1	TRBJ2-1
1799.436602	1.339938e-02	TGTGCCAGCTCACCCATCTTAGGGGAGCAGTTCTTC	CASSPILGEQFF	TRBV18	TRBJ2-1
1316.984630	9.806834e-03	TGTGCCAGCAAAAAAGACAGGGACTATGGCTACACCTTC	CASKKDRDYGYTF	TRBV6-5	TRBJ1-2
2309.863250	1.720023e-02	TGTGCCAGCAGCCAACAGGGATCTGGAAACACCATATA...	CASSQQGSGNTIYF	TRBV7-2	TRBJ1-3
3339.582627	2.486797e-02	TGTGCCAGCAGTTTAGGTCTTCACTACGAGCAGTACTTC	CASSLGLHYEQYF	TRBV28	TRBJ2-7

Introduction to deep learning

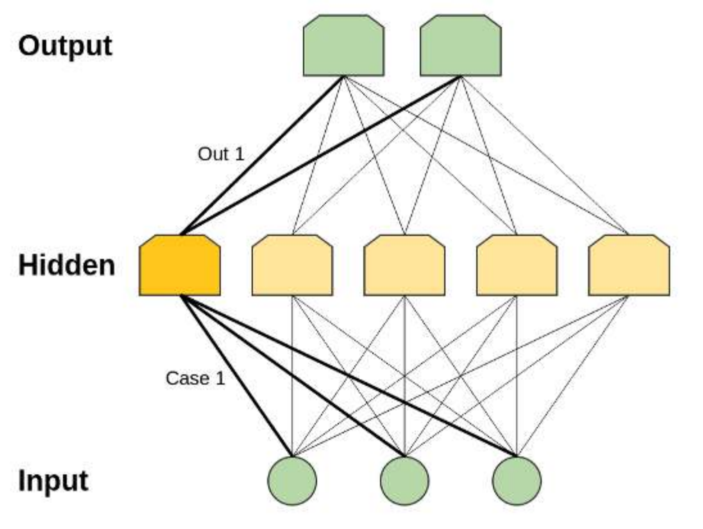
Deep network architecture ideas

Fully connected / dense networks (DNN)

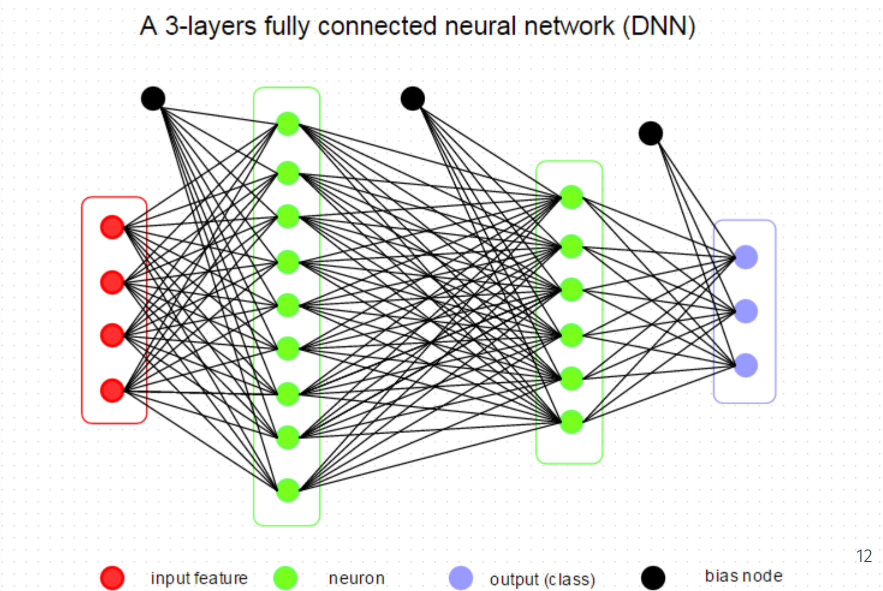
Convolutional neural networks (CNN)

Recurrent neural networks (RNN)

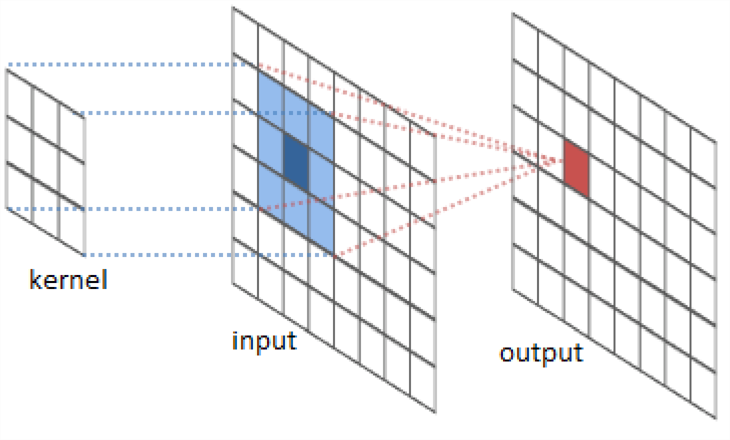
Fully connected networks 1



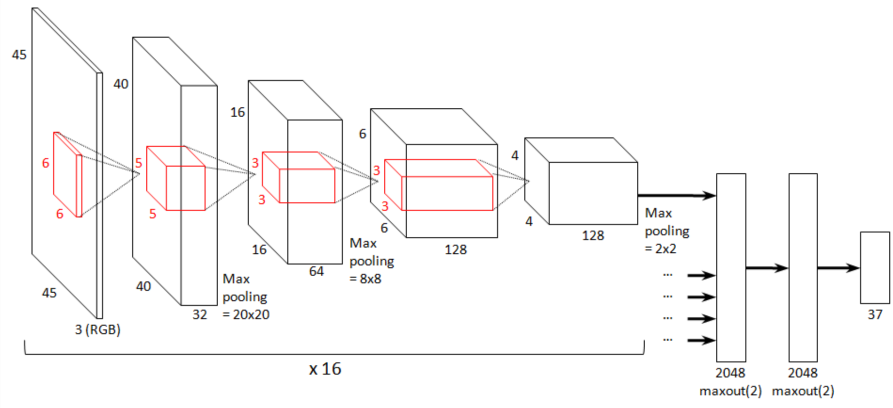
Fully connected networks 2



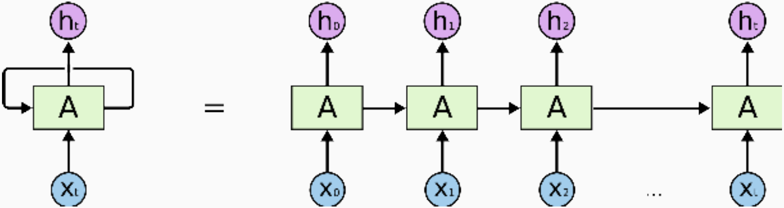
Convolutions



Convolutional neural networks



Recurrent neural networks



MHC:peptide binding affinity prediction

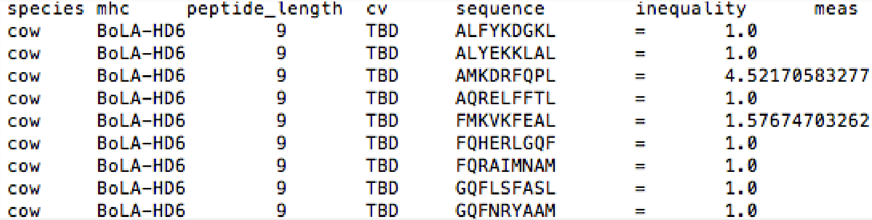
Problem

Prediction of strong / weak binders (immunotherapy, etc.)

Data

140,000 pairs of MHC-peptide for training

30,000 pairs of MHC-peptide for testing



species	mhc	peptide_length	cv	sequence	inequality	meas
cow	BoLA-HD6	9	TBD	ALFYKDGKL	=	1.0
cow	BoLA-HD6	9	TBD	ALYEKKLAL	=	1.0
cow	BoLA-HD6	9	TBD	AMKDRFQPL	=	4.52170583277
cow	BoLA-HD6	9	TBD	AQRELFFTL	=	1.0
cow	BoLA-HD6	9	TBD	FMKVKFEAL	=	1.57674703262
cow	BoLA-HD6	9	TBD	FQHERLGQF	=	1.0
cow	BoLA-HD6	9	TBD	FQRAIMNAM	=	1.0
cow	BoLA-HD6	9	TBD	GQFLSFASL	=	1.0
cow	BoLA-HD6	9	TBD	GQFNRYAAM	=	1.0

NetMHCpan

Paper: just google ”netMHCpan paper”

Features:

- Onehot encoding
- Blosum encoding
- Lengths
- Indels

Pseudo-sequences – pan-allele approach

Model: DNN with 60 hidden neurons

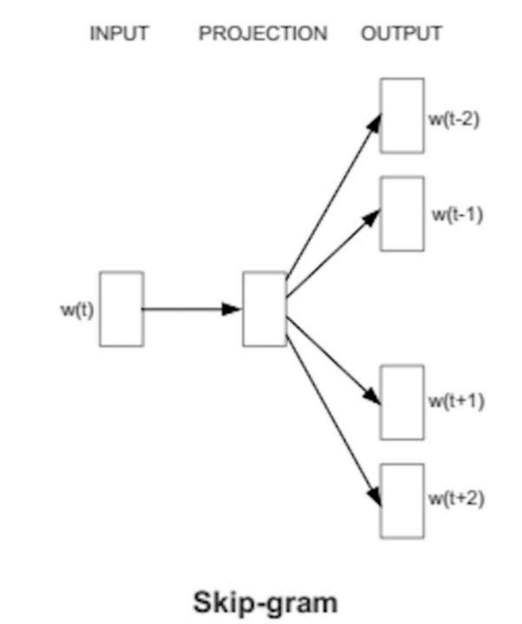
F1 score - 0.8

$$F1 = 2 * precision * recall/(precision + recall)$$

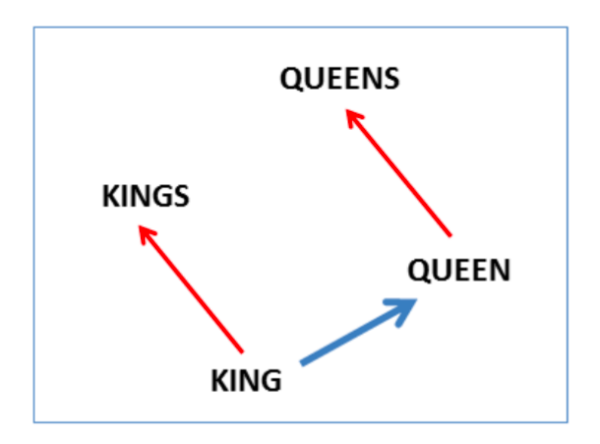
$$precision = TP/(TP + FP)$$

$$recall = TP/(TP + FN)$$

word2vec

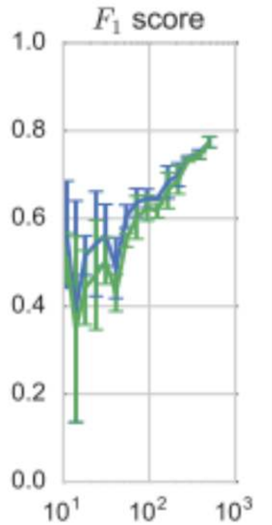


word2vec vectors



Imputation

MICE: average multiple imputations generated using Gibbs sampling from the joint distribution of columns.



mhcflurry

Paper: http://biorxiv.org/content/biorxiv/early/2016/05/22/054775.full.pdf

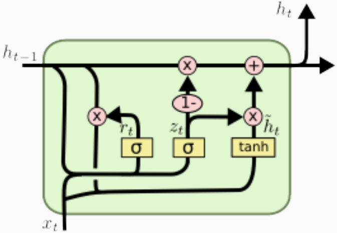
Features:

- Embeddings (per-pseudo-sequence!)

Model: DNN with 60 neurons

F1 score - 0.79

GRU



$$z_t = \sigma\left(W_z \cdot [h_{t-1}, x_t]\right)$$

$$r_t = \sigma\left(W_r \cdot [h_{t-1}, x_t]\right)$$

$$\tilde{h}_t = \tanh\left(W \cdot [r_t * h_{t-1}, x_t]\right)$$

$$h_t = (1 - z_t) * h_{t-1} + z_t * \tilde{h}_t$$

MHCnuggets

Paper:
http://www.biorxiv.org/content/biorxiv/early/2017/07/27/154757.full.pdf

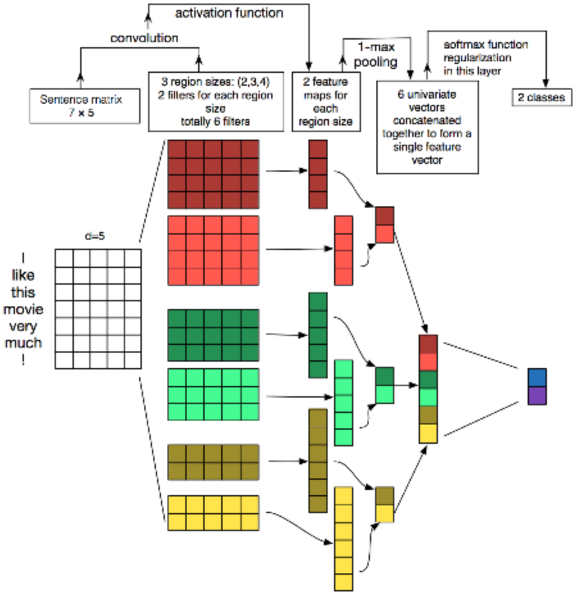
Features:

- One-hot
- Model per-pseudo-sequence (64 units + sigmoid)
- Not even multi-layer or bidirectional!

Model: simple GRU

F1 score - 0.81

CNN for NLP


activation function
convolution
1-max pooling
softmax function regularization in this layer
Sentence matrix 7 x 5
3 region sizes: (2,3,4) 2 filters for each region size totally 6 filters
2 feature maps for each region size
6 univariate vectors concatenated together to form a single feature vector
2 classes
d=5
I
like
this
movie
very
much
!

HLA-CNN

Paper:
http://www.biorxiv.org/content/biorxiv/early/2017/07/27/154757.full.pdf

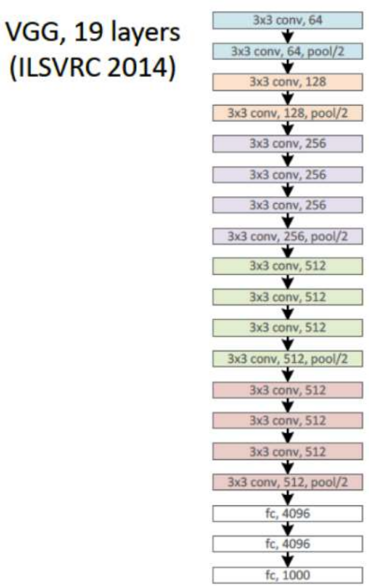
Features:

- Embeddings on the overall data
- Model per-pseudo-sequence (64 units + sigmoid)
- Large convolutions

Model: CNN

F1 score - 0.75

ResNet - old networks



VGG, 19 layers
(ILSVRC 2014)

3x3 conv, 64

3x3 conv, 64, pool/2

3x3 conv, 128

3x3 conv, 128, pool/2

3x3 conv, 256

3x3 conv, 256

3x3 conv, 256

3x3 conv, 256, pool/2

3x3 conv, 512

3x3 conv, 512

3x3 conv, 512

3x3 conv, 512, pool/2

3x3 conv, 512

3x3 conv, 512

3x3 conv, 512

3x3 conv, 512, pool/2

fc, 4096

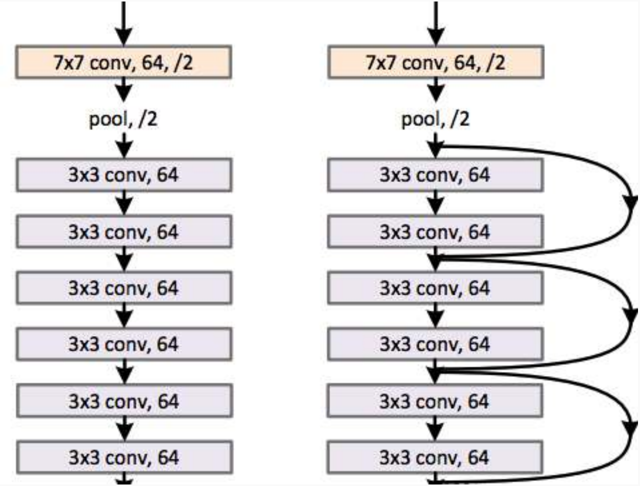
fc, 4096

fc, 1000

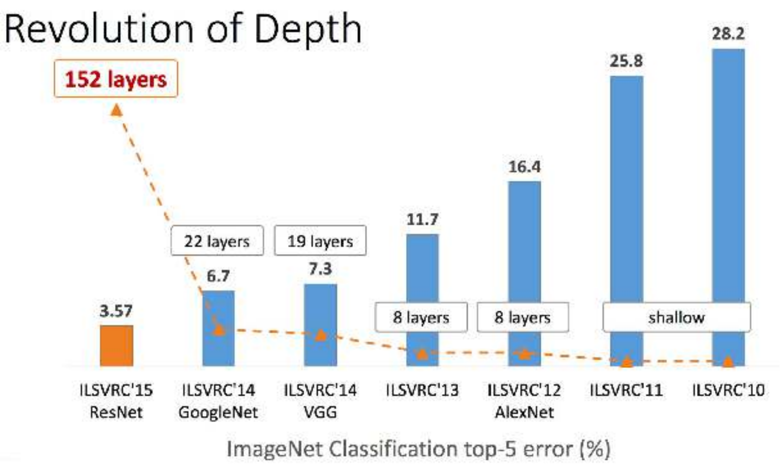
ResNet - old networks' problems

- Gradient vanishing
- Large number of parameters
- Shallowness

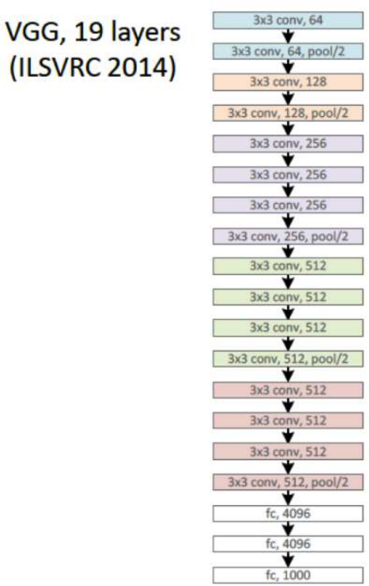
ResNet - proposed model



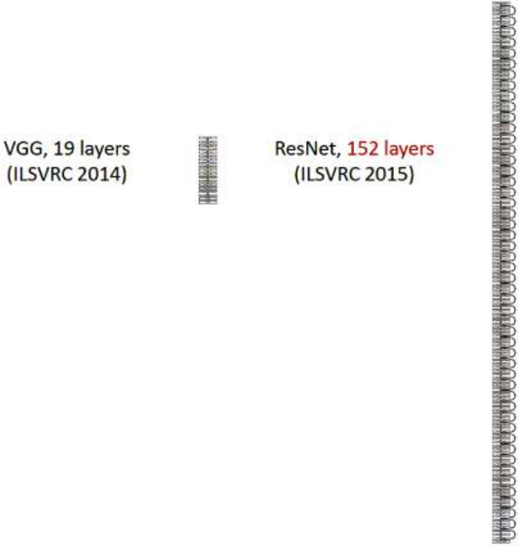
ResNet - results



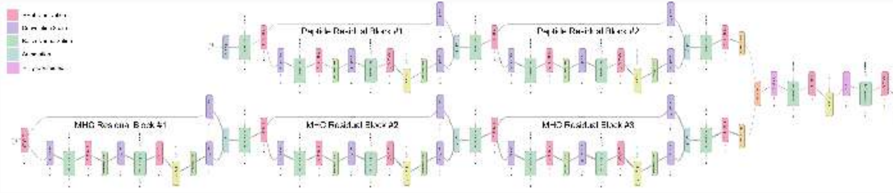
ResNet - old networks



ResNet - current deep networks



Our approach



Our approach - results

- F1 0.81
- Global models – prediction of binding affinities for unseen MHCs (mean F1 0.72)
- Better models for the per-pseudo-sequence approach.

Conclusion

Vadim I. Nazarov

Genomics of Adaptive Immunity Lab, IBCH RAS
National Research University Higher School of Economics

email: vdm.nazarov@gmail.com

telegram: @vadimnazarov