AI-driven prediction of protein-protein binding trends from atomistic simulation data

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CENTER FOR CELLULAR CONSTRUCTION

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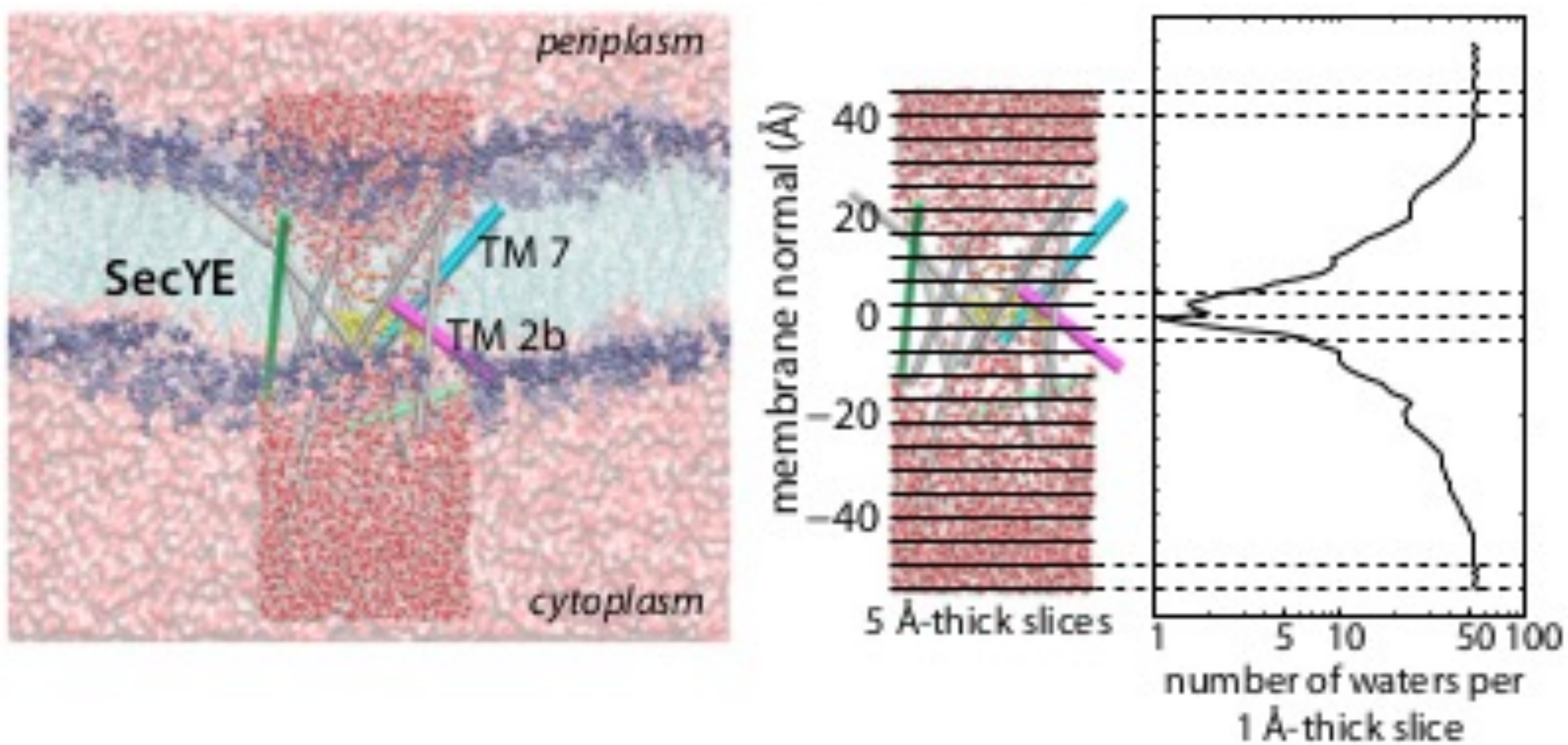
BACKGROUND in COMPUTATIONAL BIOPHYSICS

Molecular Dynamics (MD) Atomistic Simulations → simulate biological processes at atomic resolution (limitations in simulation length)

…unless you can access IBM supercomputers…



Capponi et al., *PNAS* 2015

@ UCI

BACKGROUND in COMPUTATIONAL BIOPHYSICS

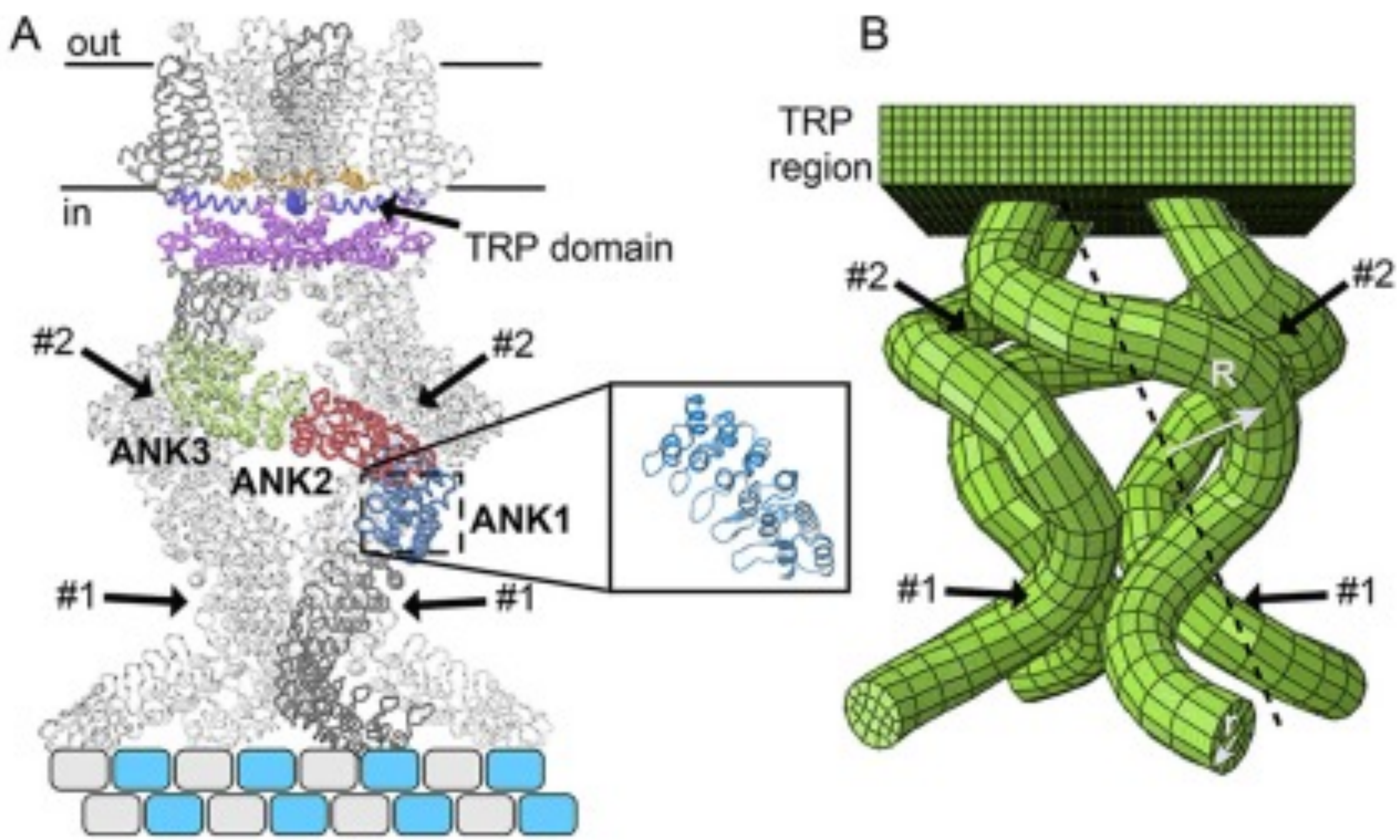
Molecular Dynamics (MD)
Atomistic Simulations
+
Finite Element Model

→

MD to extract mechanical properties
to describe the motion
of the ankyrin chains of
mechanotransduction channel

MD

Finite Element Model



Argudo et al., *J. Gen Phys.* 2019

@ UCSF

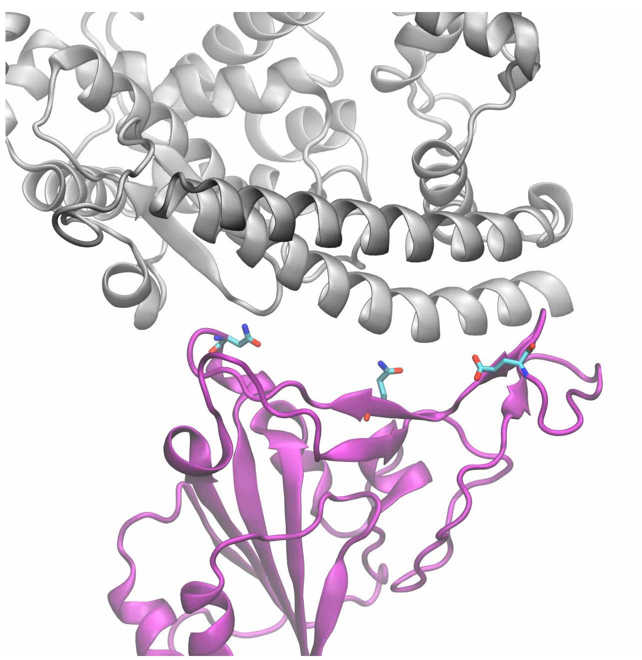
BACKGROUND in COMPUTATIONAL BIOPHYSICS

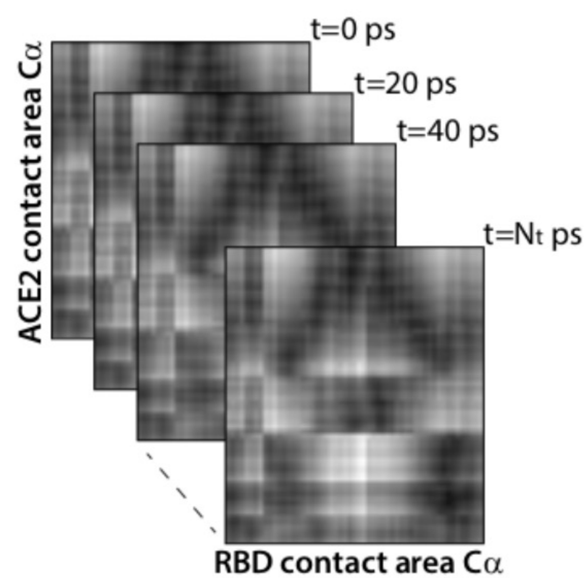
Molecular Dynamics (MD)
Atomistic Simulations
+
Artificial Intelligence

→

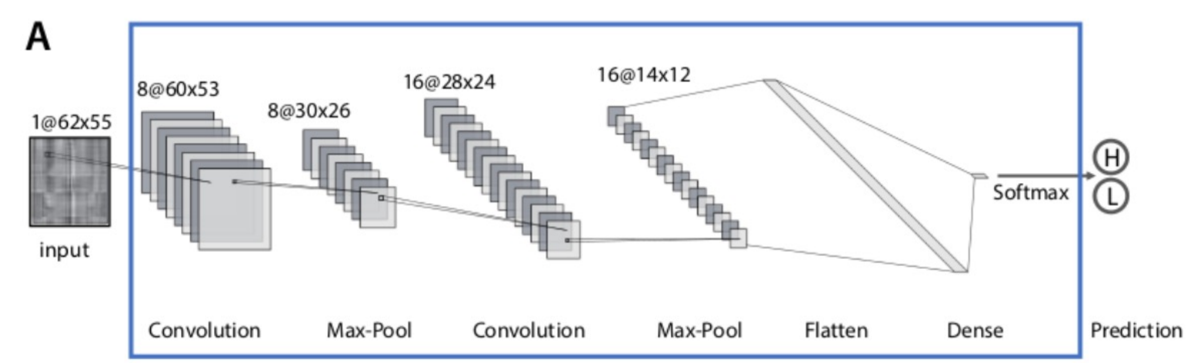
MD to extract dynamical information
to feed AI algorithms and make predictions

MD





AI



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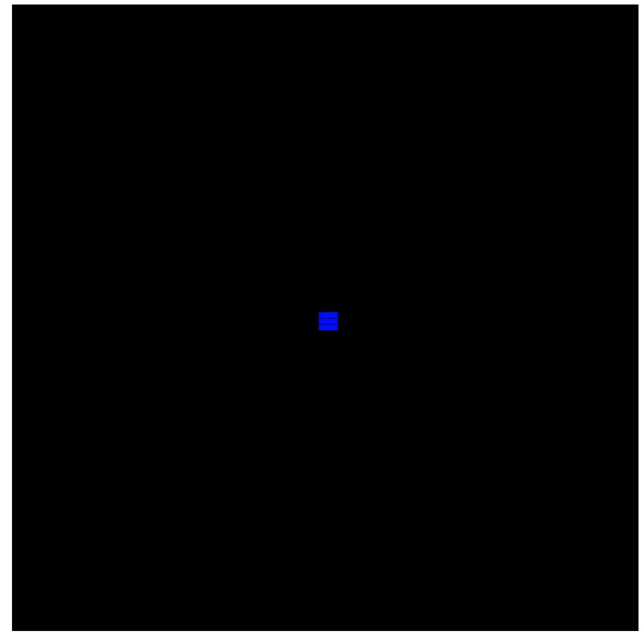
BACKGROUND in COMPUTATIONAL BIOPHYSICS

Agent Based Model (ABM)

to study **viral infection**
in presence of DIPs and IFN

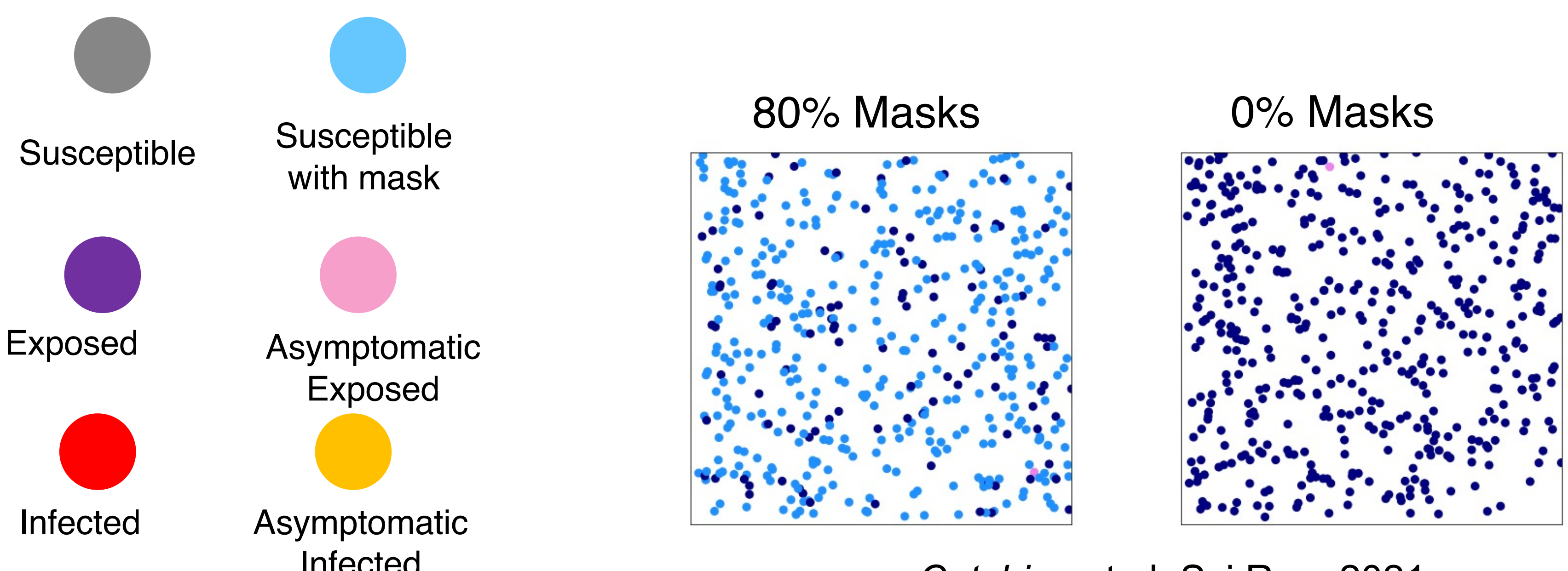


agents = viral particles
cells = lattice squares

DARPA grant @ IBM, S Bianco

to probe **mask effectiveness** for
reducing COVID-19 transmission

IBM COVID-19 Task Force, S Bianco



agents = individuals

Catching et al. Sci Rep, 2021

@ IBM

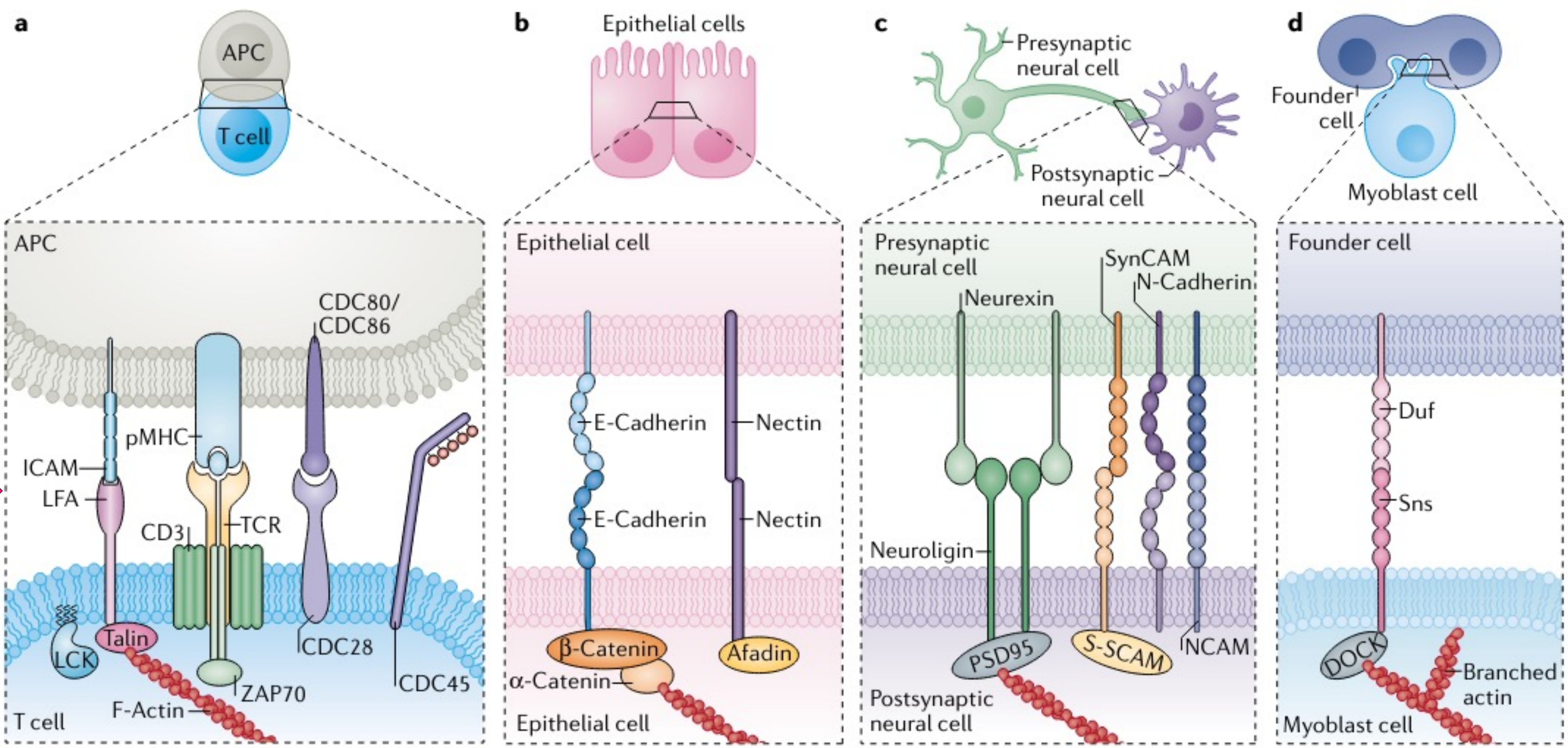
AI-driven prediction of protein-protein binding trends from atomistic simulation data

Motivations

Why do we care about binding affinity?

cell binding → protein-protein binding

between cells



inside cells

Dan Fletcher, *Nature Rev* 2020

Motivations

Can we *efficiently* measure and predict binding affinity?

Experiments and biased atomistic simulations are expensive (money and time)

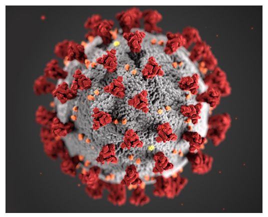
Build a **CNN framework** to:

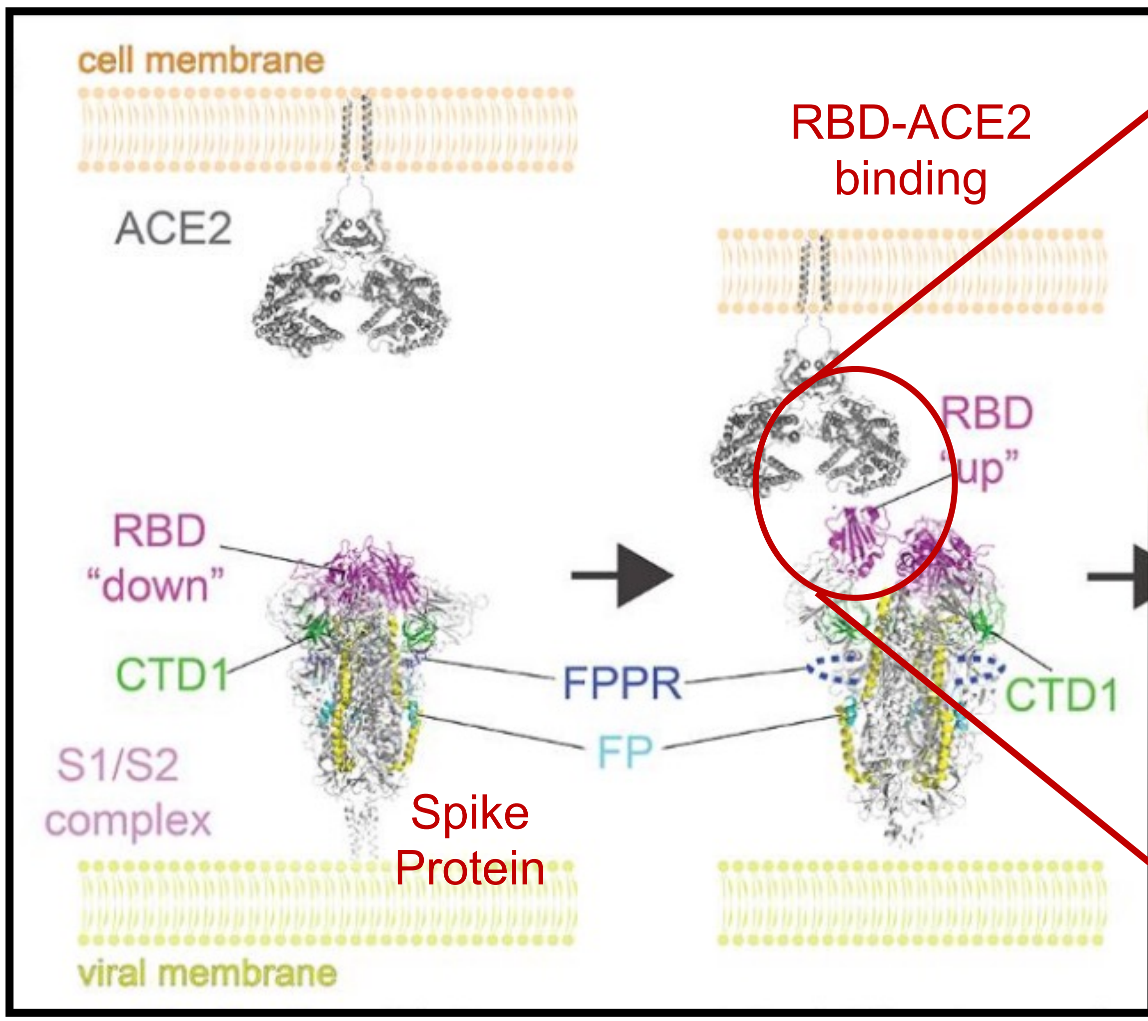
- predict **efficiently protein-protein binding affinity** trend from unbiased atomistic simulation data
- **shortening** the length of **unbiased atomistic simulation** data used for binding affinity estimation

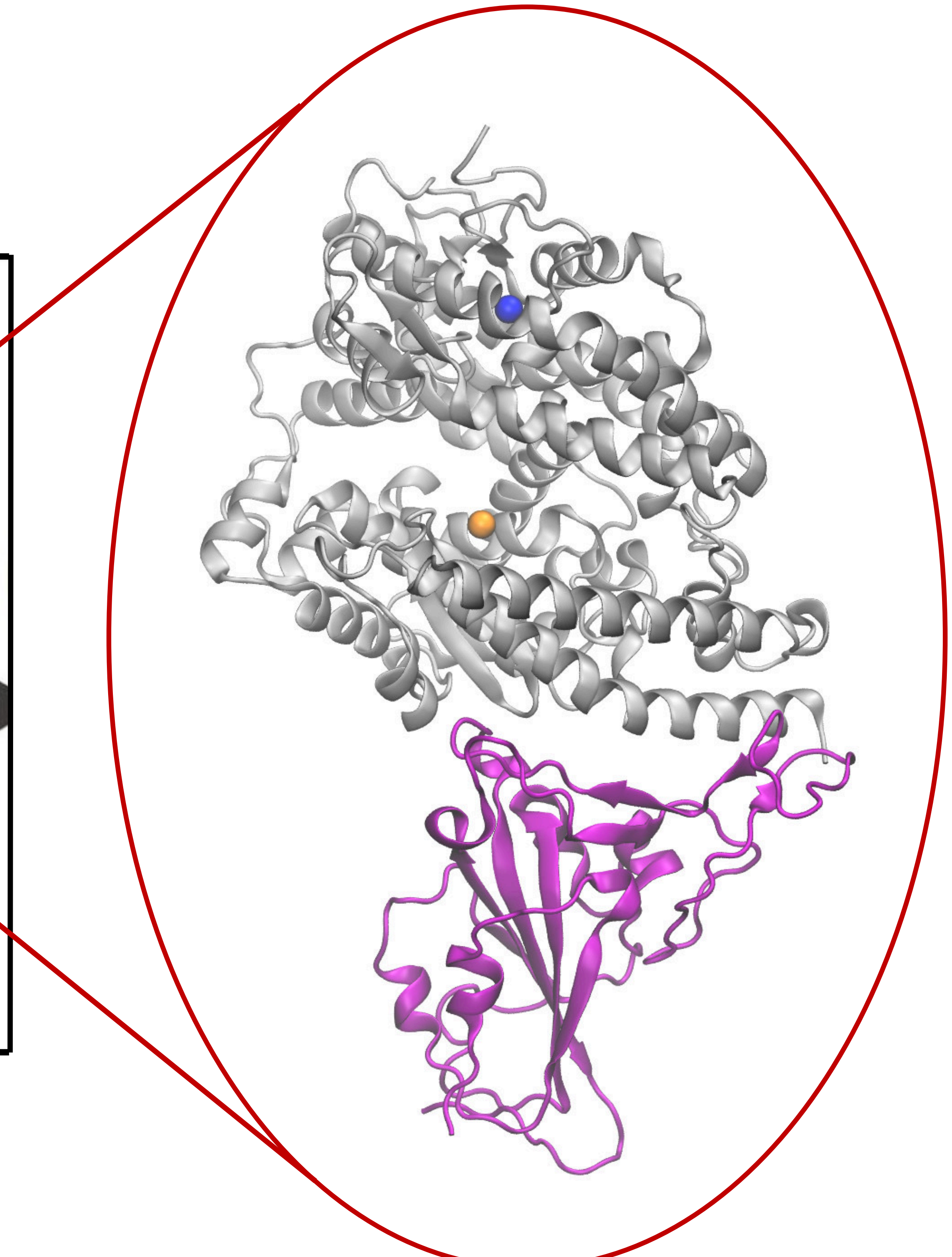
Spike protein S test case:

S responsible for **binding & membrane fusion**

SARS-CoV-2 cell entry mechanism: ACE2-RBD complex







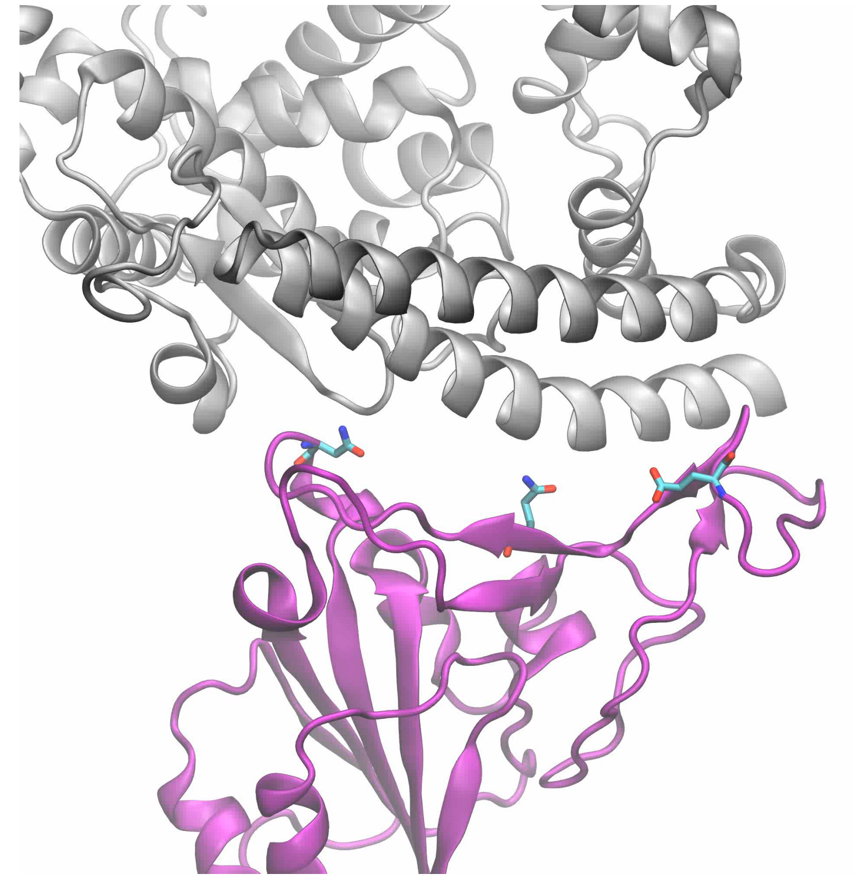
ACE2-RBD binding affinity estimation

Reference data

RBD-ACE2 $\Delta\log_{10}(K_{D,app}) = 0$ (reference)

Mutation	Origin	$\Delta \log_{10}(K_{D,app})$
N501Y	English variant	0.24
Q498Y	SARS-CoV	0.16
N501V	-	0.15
Q493Y	Bat RaTG13	0.12
N501T	SARS-CoV	0.1
E484K	Brazilian variant	0.06
N501S	-	-0.13
Q493N	SARS-CoV	-0.21
Q498N	-	-0.5
Q498K	-	-2.26
N501D	Bat RaTG13	-2.42
G502P	-	-4.55

simulation	lenght (ns)
cRBD-ACE2	270
N501Y-ACE2	187
Q498Y-ACE2	206.84
N501V-ACE2	204.86
Q493Y-ACE2	197.28
N501T-ACE2	186.58
E484K-ACE2	204.56
N501S-ACE2	205.2
Q493N-ACE2	197.18
Q498N-ACE2	198.84
Q498K-ACE2	204.46
N501D-ACE2	210.44
G502P-ACE2	160.58



T Starr et al, *Cell* 2020

Hydrophobic RBD mutations

Mutation	Origin	$\Delta \log_{10}(K_{D,app})$	Length (ns)
V503I	SARS-CoV	0.05	187.8
L492I	–	0.03	261.24
L455I	–	−0.01	272.24
V503A	—	−0.06	188.18
A475V	SARS-CoV	−0.14	226.6
L455A	–	−0.43	280.72
L455V	–	−0.73	280.98
A475L	–	−1.27	279.28
A475P	SARS-CoV	−1.62	281.02

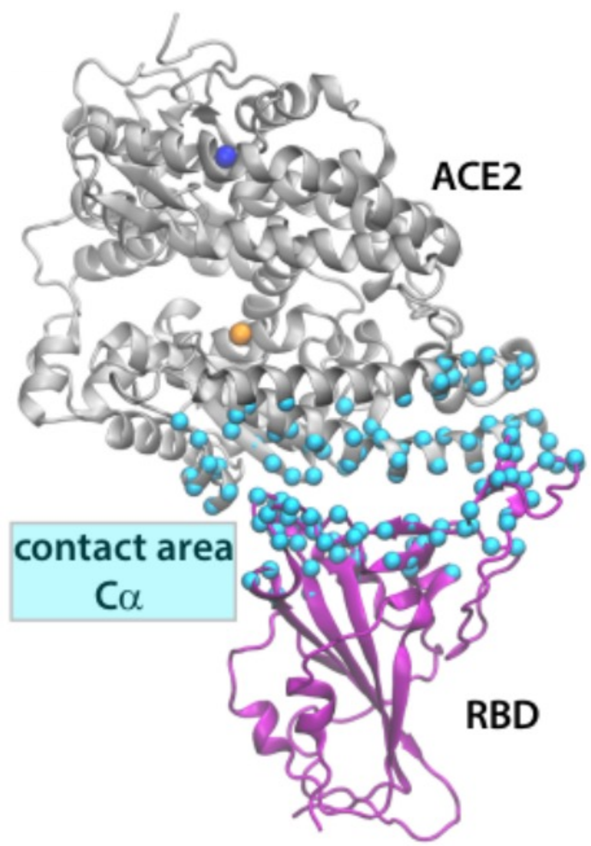
160 ns → ~ 5 days IBM supercomputer
~ 23 days lab server

… if not in parallel
→ 5 days x 22 simulations ~ 4 months

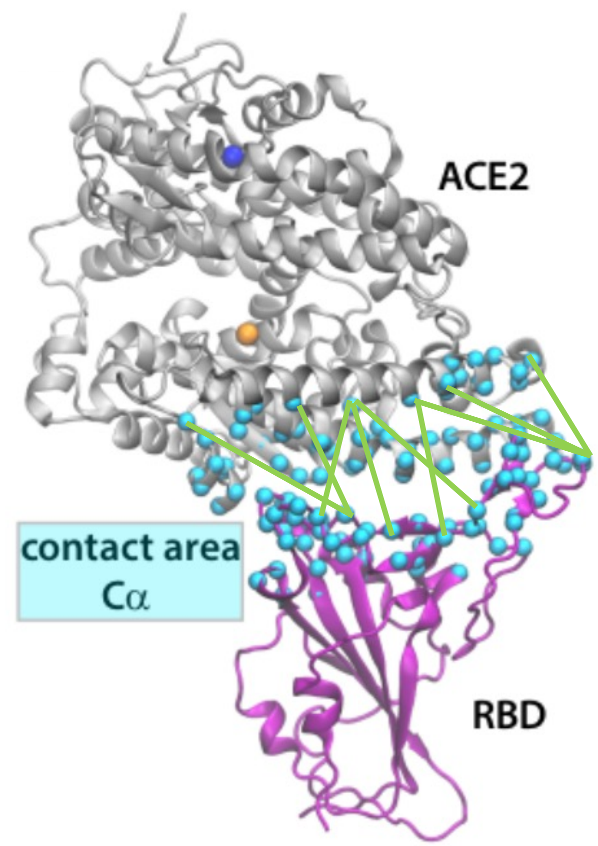
ACE2-RBD binding affinity estimation

training set preparation

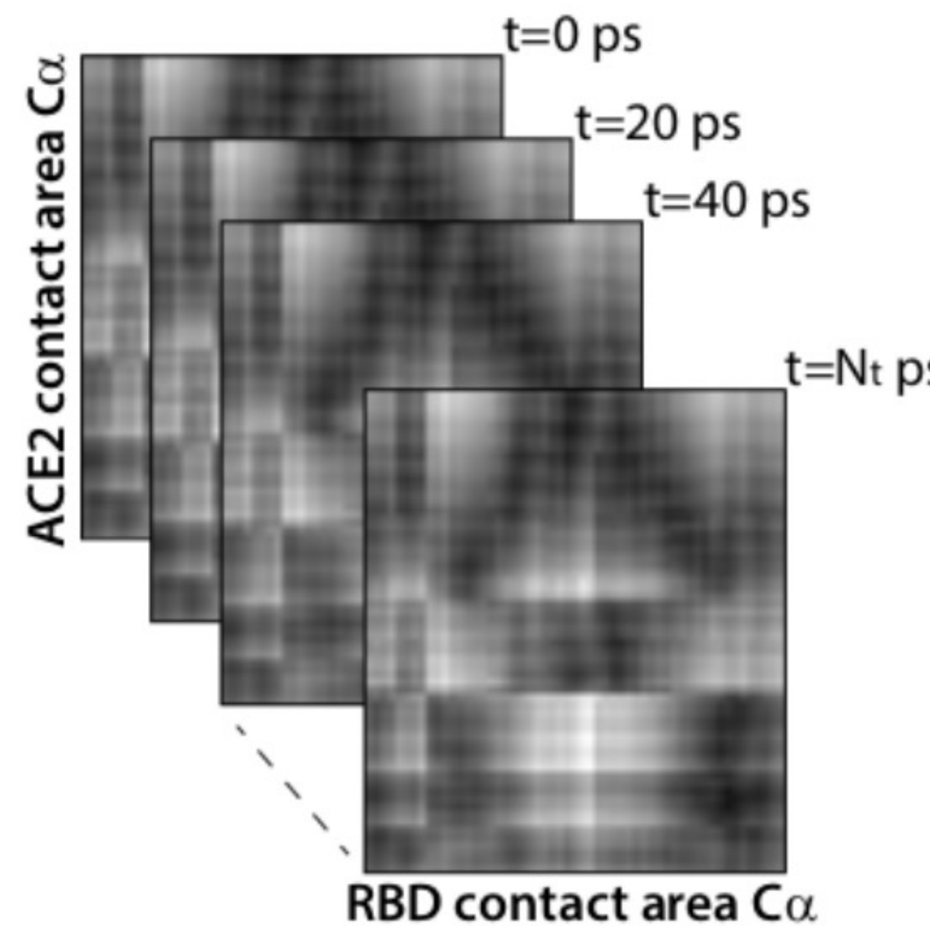
Conversion of MD data to inputs for machine learning algorithm



contact area



calculation all distances
between all Ca atoms
belonging to the *contact area*
(62 ACE x 55 RBD contact matrix)



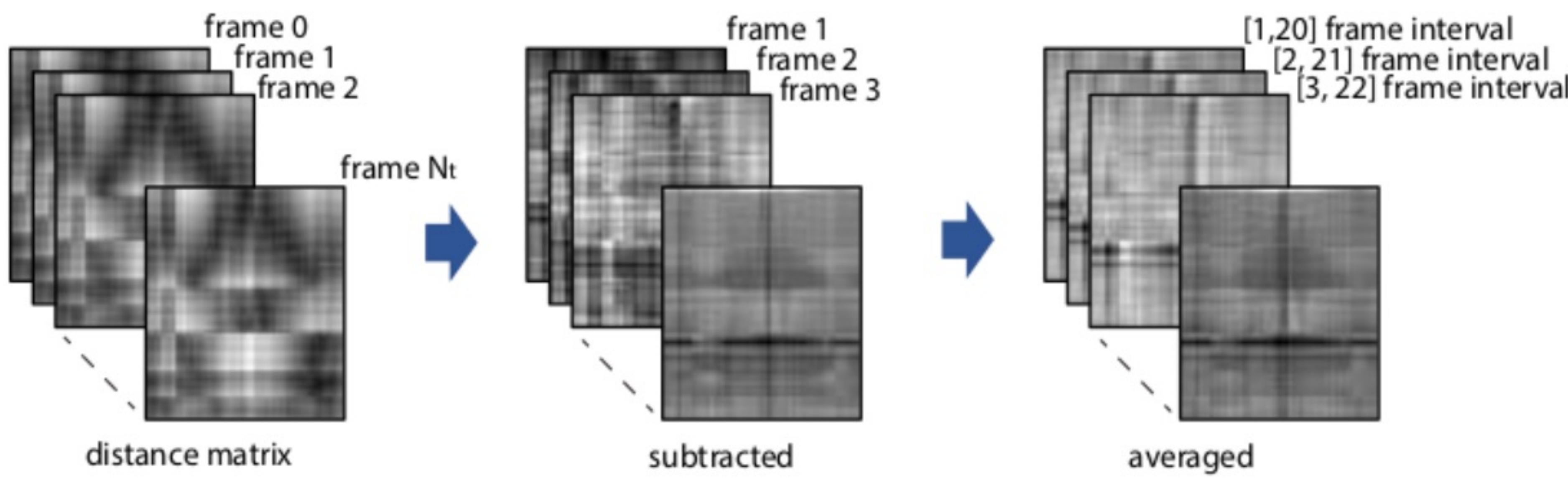
contact matrices
=
gray-scale images

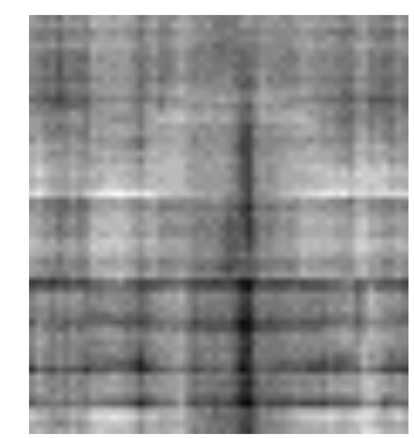
Capponi, et al, *EPJE* 2021

ACE2-RBD binding affinity estimation

training set preparation

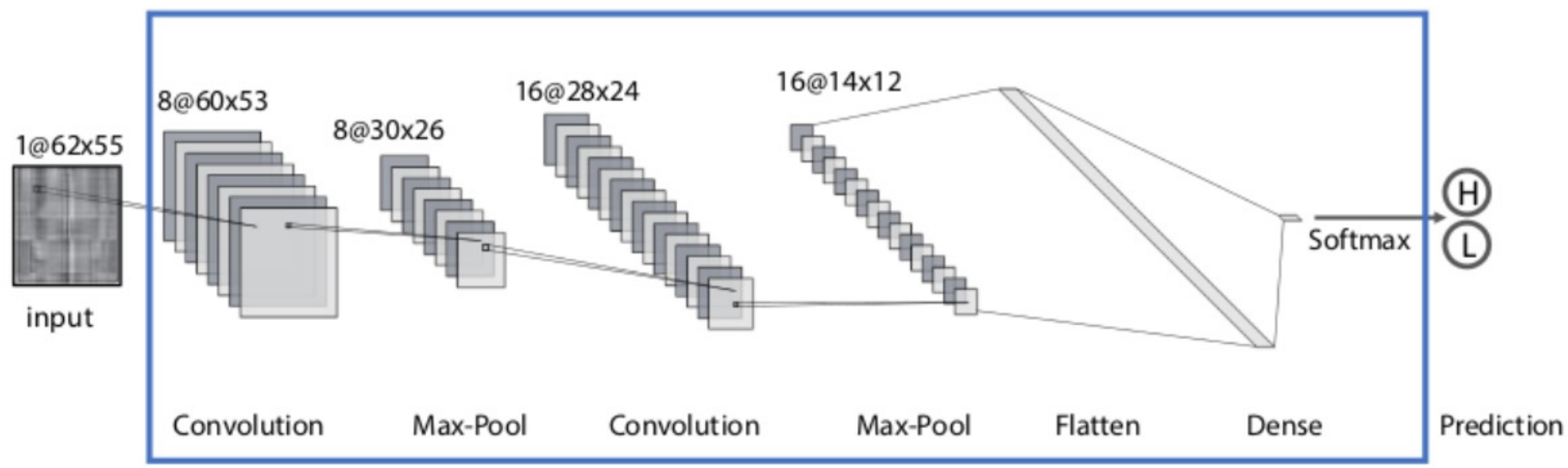
Data processing

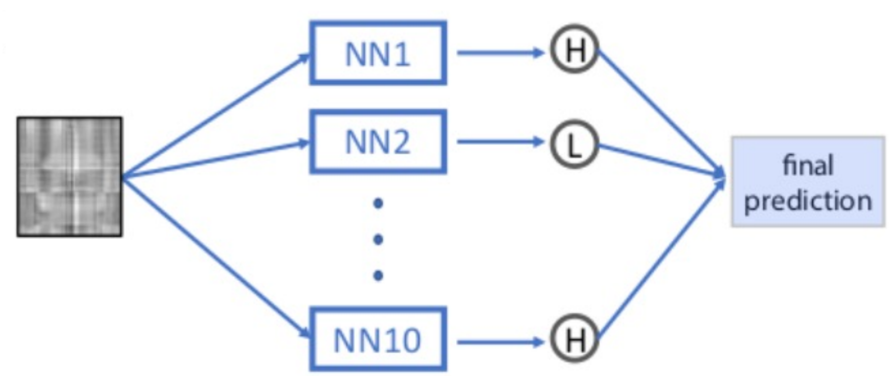




ACE2-RBD binding affinity estimation

Convolutional Neural Network Framework





ensemble prediction strategy (10 NNs)

S. Wang et al, *Nat Comm* (2019)

ACE2-RBD binding affinity estimation

Training and Validation Data Set

prediction on whole simulation length (160 ns)

Mutation	Origin	$\Delta \log_{10}(K_{D,app})$
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N501V	-	0.15
Q493Y	Bat RaTG13	0.12
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G502P	-	-4.55

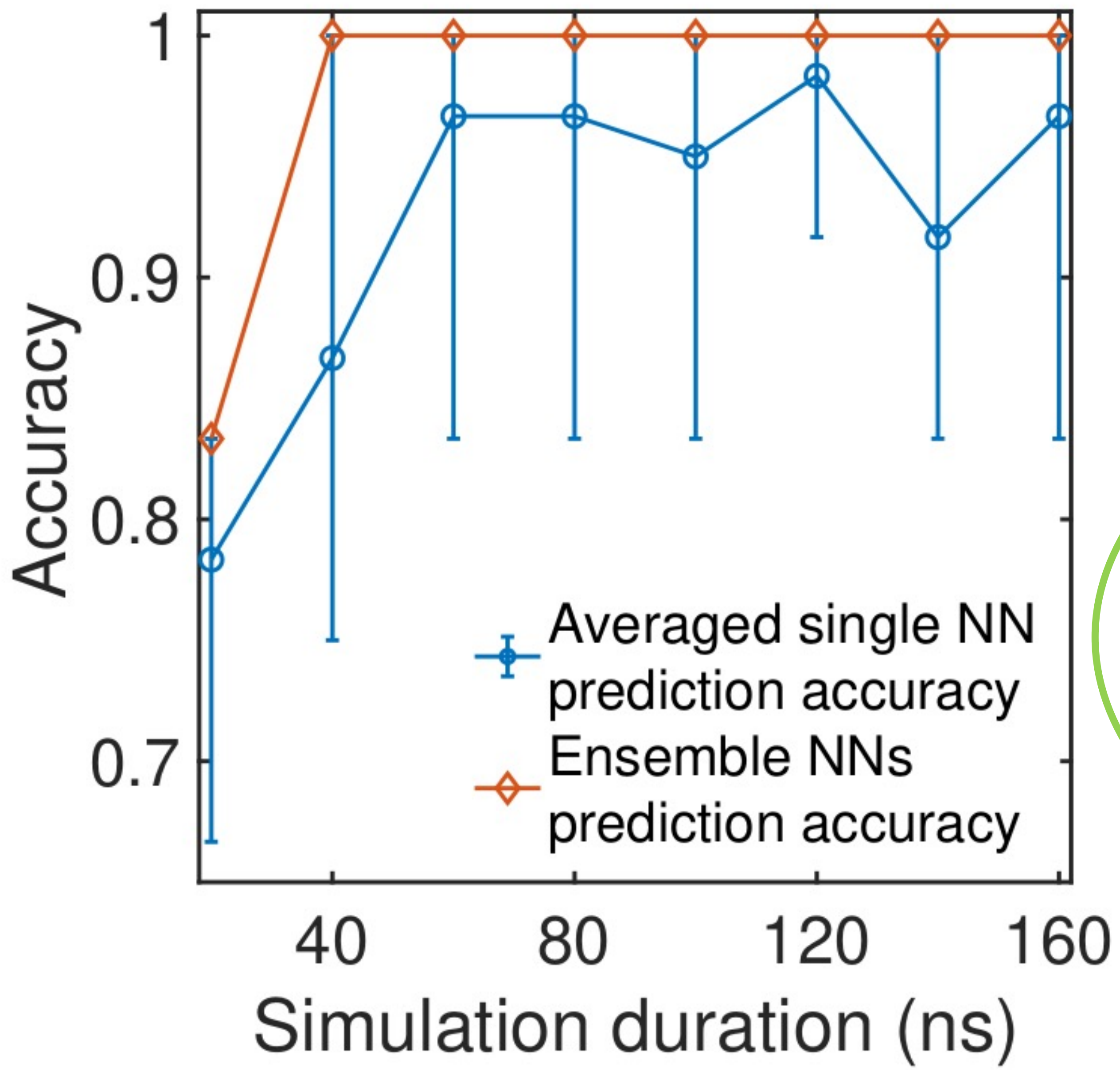
- 100 % NN ensemble accuracy
- 96.67 % averaged accuracy on single NN of the ensemble

CNN ensemble predicts accurately binding affinity trend

ACE2-RBD binding affinity estimation

Predictions on shorter simulated time

prediction on **increasing time window (20ns to 160ns, step 20ns)**



100 % NN ensemble accuracy using 40ns unbiased simulation data

CNN ensemble predicts accurately binding affinity trend using unbiased short atomistic data (40 ns)

Conclusions

- **Ensemble of CNNs** trained on distance matrices predicts with **high accuracy** the binding affinity trend

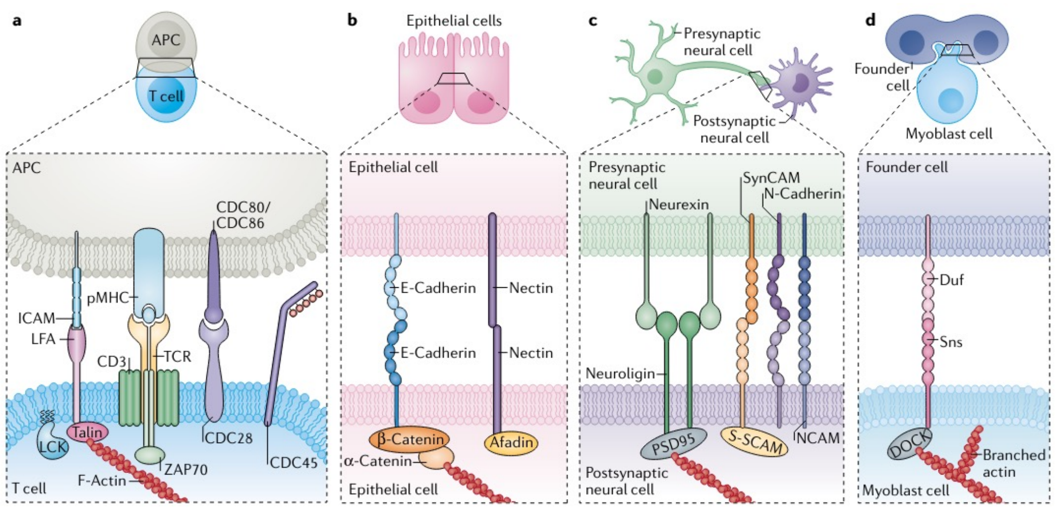
- We proved our AI method predicts binding affinity trends using **short, unbiased atomistic simulations**

  (40ns *vs* 160ns simulations → 1 day *vs* 5 days on a HPC cluster)

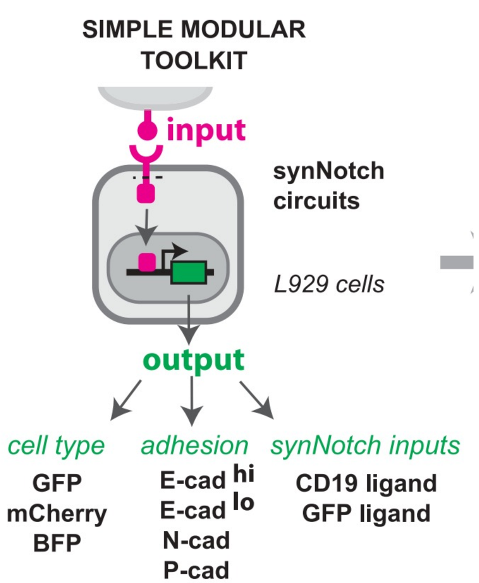
Contribution to CCC: MD-AI

IBM supercomputers

Cell-cell interactions

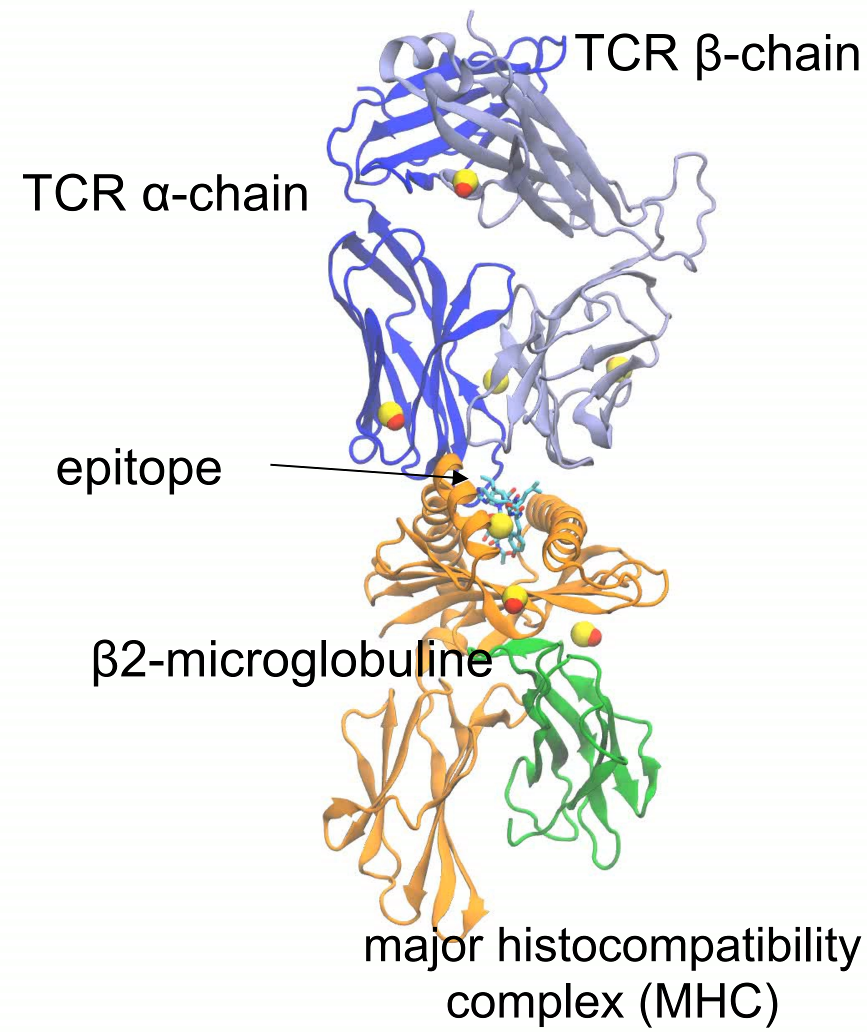


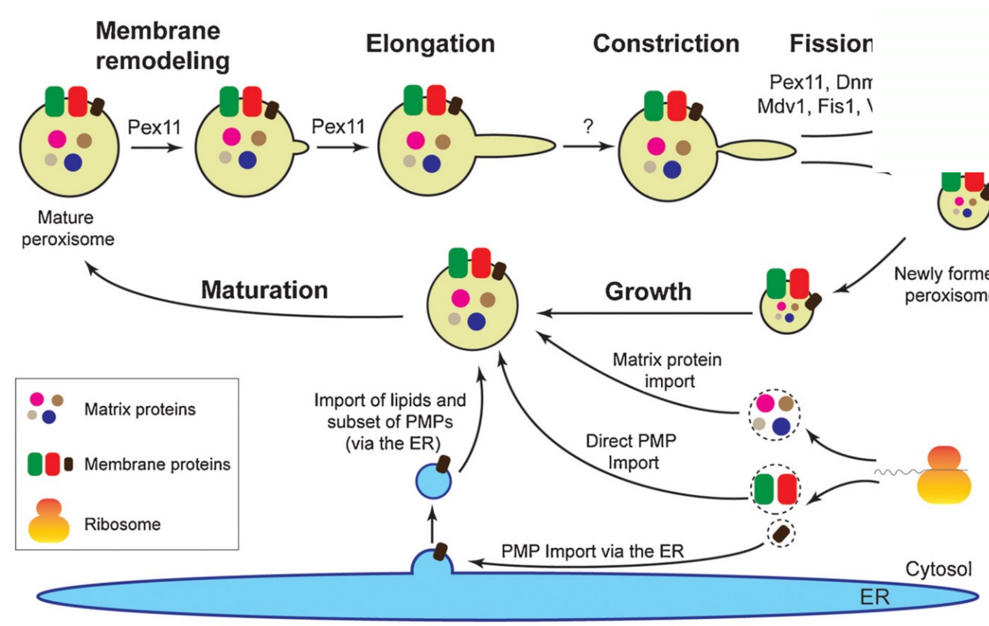
SynNotch
Specific activation of CAR-T



Understanding and programming self-organizing multicellular structures
with synthetic cell-cell signaling

Immune system AI-aided engineering

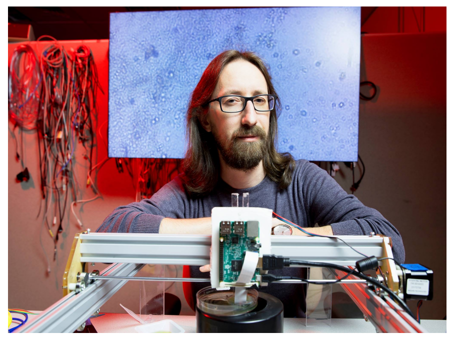




peroxisome proteins and membrane
involved in fusion, fission, maturation

Acknowledgements

IBM Cellular Engineering Group



Simone
Bianco

Shangying
Wang

Tom
Zimmerman

Thank you
for your attention

Open positions:

- IBM summer internship
- MD-AI postdoc

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or CCC slack

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