NVIDIA BioNeMo Workshop

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自己紹介

- 2017年8月～現在、 シニア ディープラーニング ソリューションアーキテクト、ヘルスケア領域担当、エヌビディア合同会社
- 2016年4月～2017年8月、特別研究員、産業技術総合研究所人工知能研究センター
- 2015年4月～2016年3月、ポスドク研究員、京都大学化学研究所バイオインフォマティクスセンター
- 2012年４月～2015年3月、博士課程、京都大学情報学研究科知能情報学
- 2010年４月～2012年3月、修士課程、京都大学情報学研究科知能情報学

Introduction to BioNeMo Framework

NVIDIA BioNeMo Framework

Enables Data Scientists and and Researchers Train on DNA, Protein, Chemistry Data

Model Pre-Training

Foundation Model

Data Loaders

Optimized Training

Training Framework

Optimize

Model Fine-Tuning

Genomic

- DNABert[NEW]
- scGPT

Geometric

- Equidock[NEW]
- DiffDock[NEW]
- MegaMolBART
- MolMIIM

Structure

- ESM-2
- ProtT5
- OpenFold[NEW]

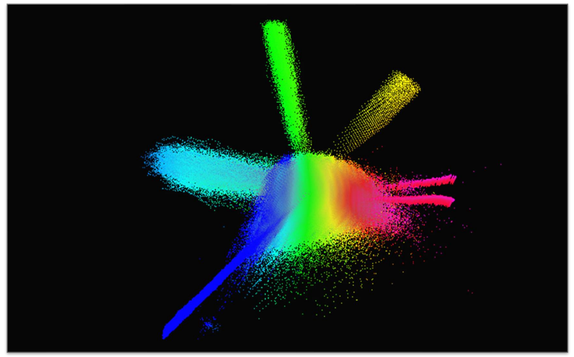
Pre-Trained Models

Microsoft Azure aws Google Cloud ORACLE

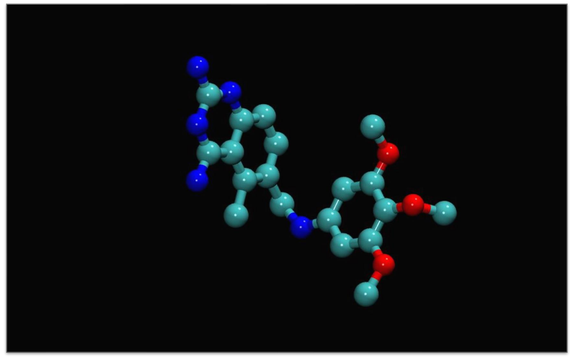
NVIDIA

BioNeMo Framework Supports Optimized Biomolecular Models

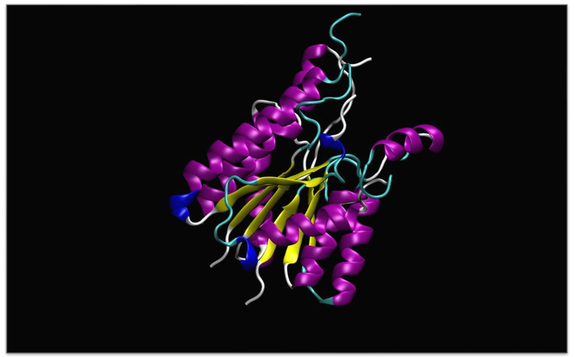
Proteins | Small Molecules | Genomics



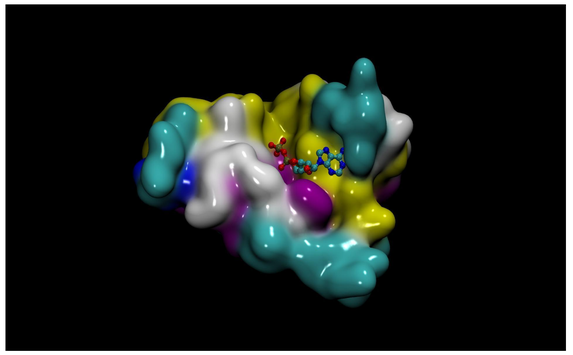
ESM-1 | ESM-2
Protein LLMs



MegaMolBART
Generative Chemistry Model



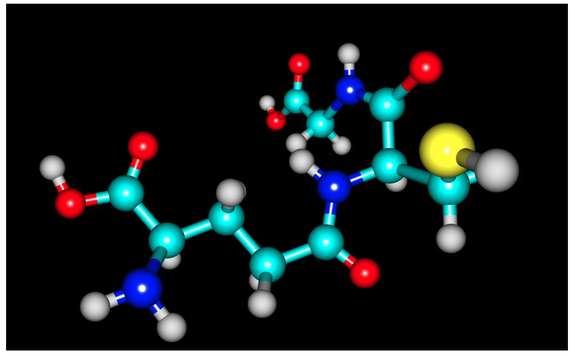
ProtT5
Protein Sequence Generation



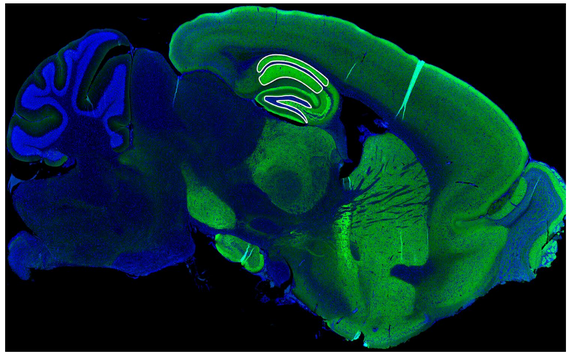
NEW: DiffDock | EquiDock
Docking Prediction

NEW: OpenFold
3D Protein Structure Prediction

NEW: DNABERT
DNA Sequence Model



NEW: MolMIM
Molecular Generation



COMING SOON: Single Cell BERT
Single Cell Expression Model

NVIDIA Training Times
Pre-Training from Scratch

Model	LLM Arch	Model Size (M Params)	Dataset	Training Time (Days) on 20 DGX	Experiments / Month
ESM	BERT	670	270M Proteins	7.5	4
ProtT5	T5	198	46M Proteins	7	4
MegaMolBART	BART	45	1.54B Compounds	1.5	20
GPT-3	GPT	5000	500B Tokens	5	6

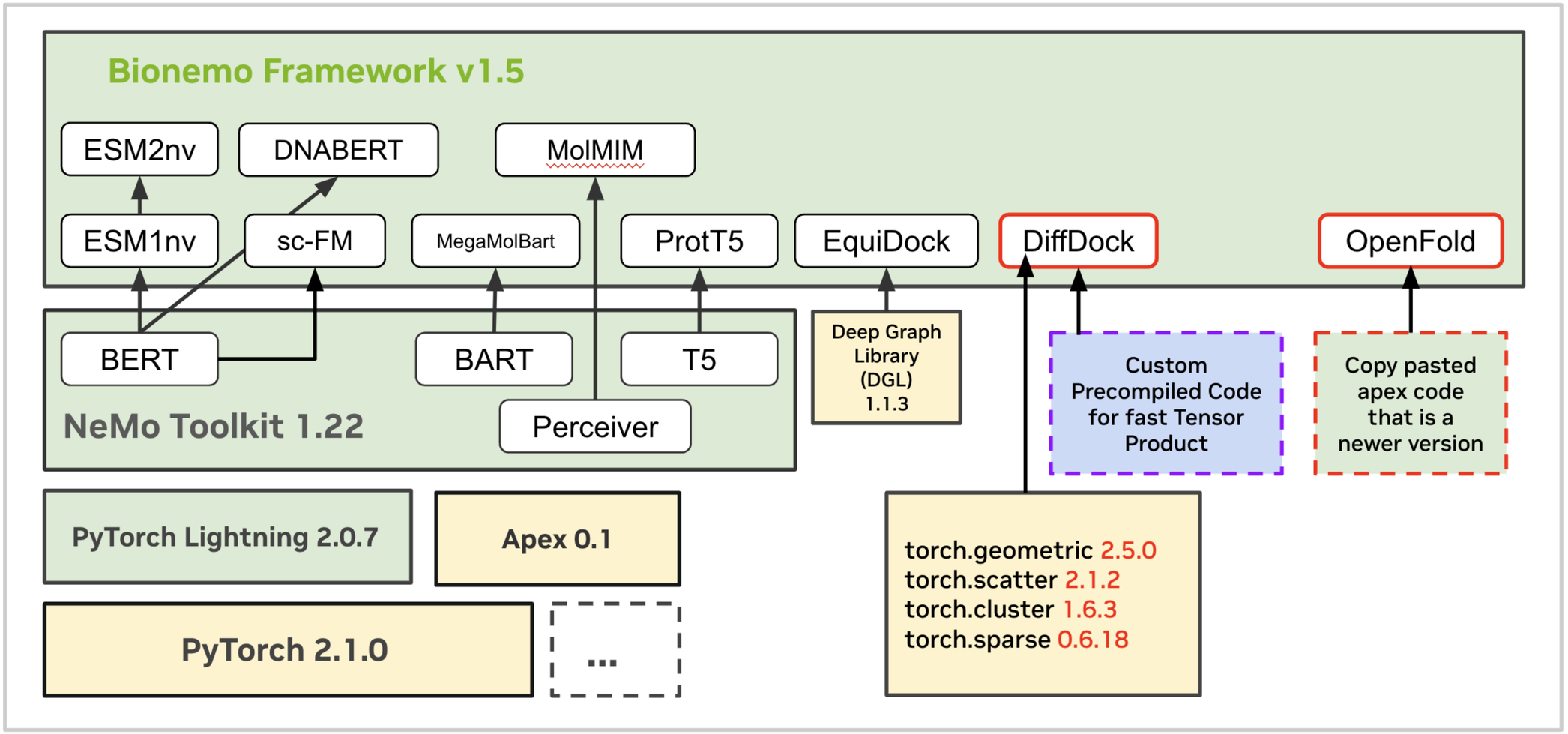
Example Workloads:

- **Infrastructure**
  - 20 DGX A100 Nodes
  - Base Command Platform Software
- **Software**
  - NVIDIA AI Enterprise for
    - BioNeMo
    - Nemo Megatron
    - Rapids

DGX Cloud Sample Sizing Guide

Analysis for Building Generative AI Models

BIONEMO FW STACK FOR V1.5 -- INSIDE CONTAINER



Public Release Container

Legend

Python Class/Module | Python code | Compiled binaries | Compiled/ Python Mix | Modified in this release (any red) | Temporary dependency that will need refactoring – tech debt (dashed)

DNABERT

- **Usage:** embedding, prediction of transcription factor binding sites, prediction of splice sites, prediction of functional genetic variants
- **Type of model**: BERT model trained on DNA sequences. The primary use case of DNABERT is for end-users to train from scratch on their own data, rather than using pre-trained checkpoints.

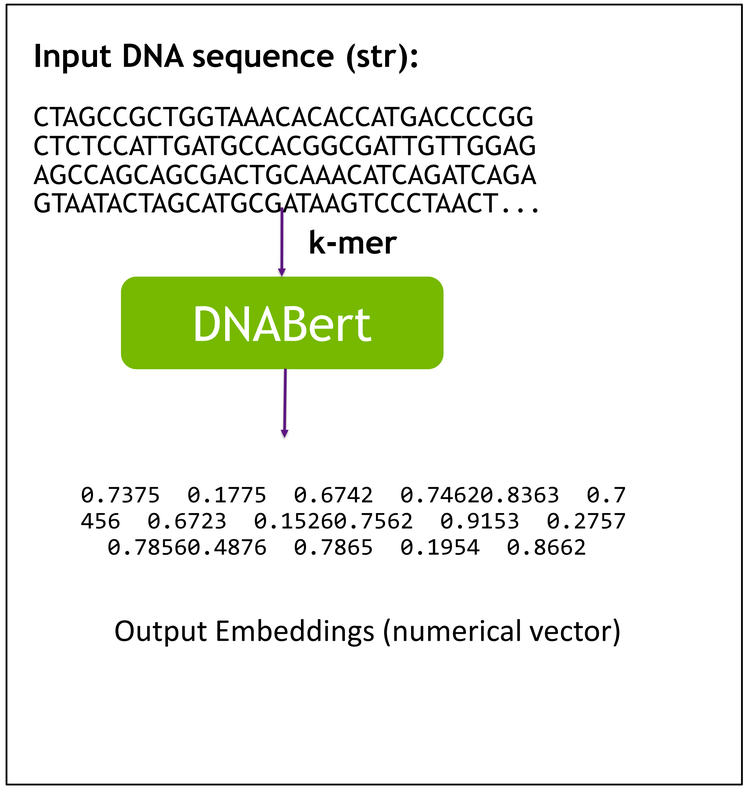
- **In scope deliverables**
  - DNABert training code.
    - Based on NeMo BERT, with tensor and pipeline parallelism support.
    - Downstream task support: Splice Site Prediction
  - Pretrained model checkpoint:
    - Checkpoint was trained from scratch, 86M parameters, not expected to match paper accuracy, because this is not relevant for typical DNABert users.

Training statistics

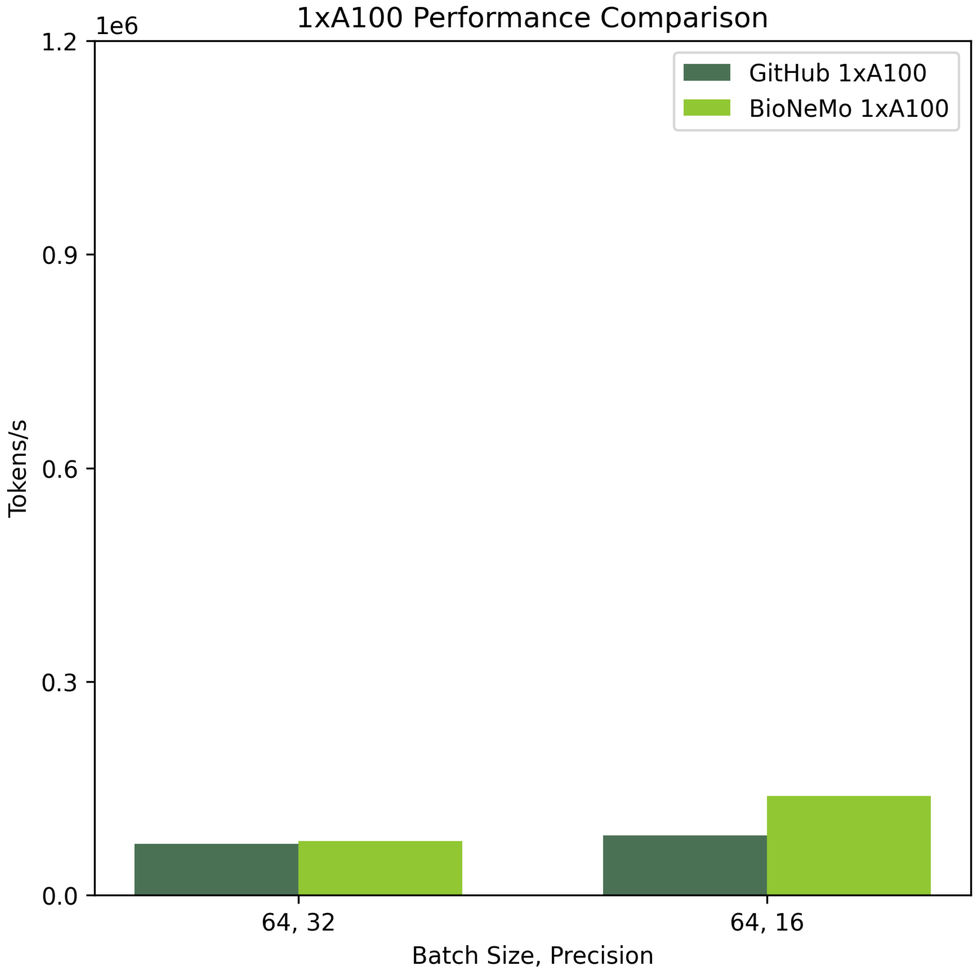
- Dataset: Homo sapiens genome assembly GRCh38.p13 - NCBI - NLM (nih.gov)

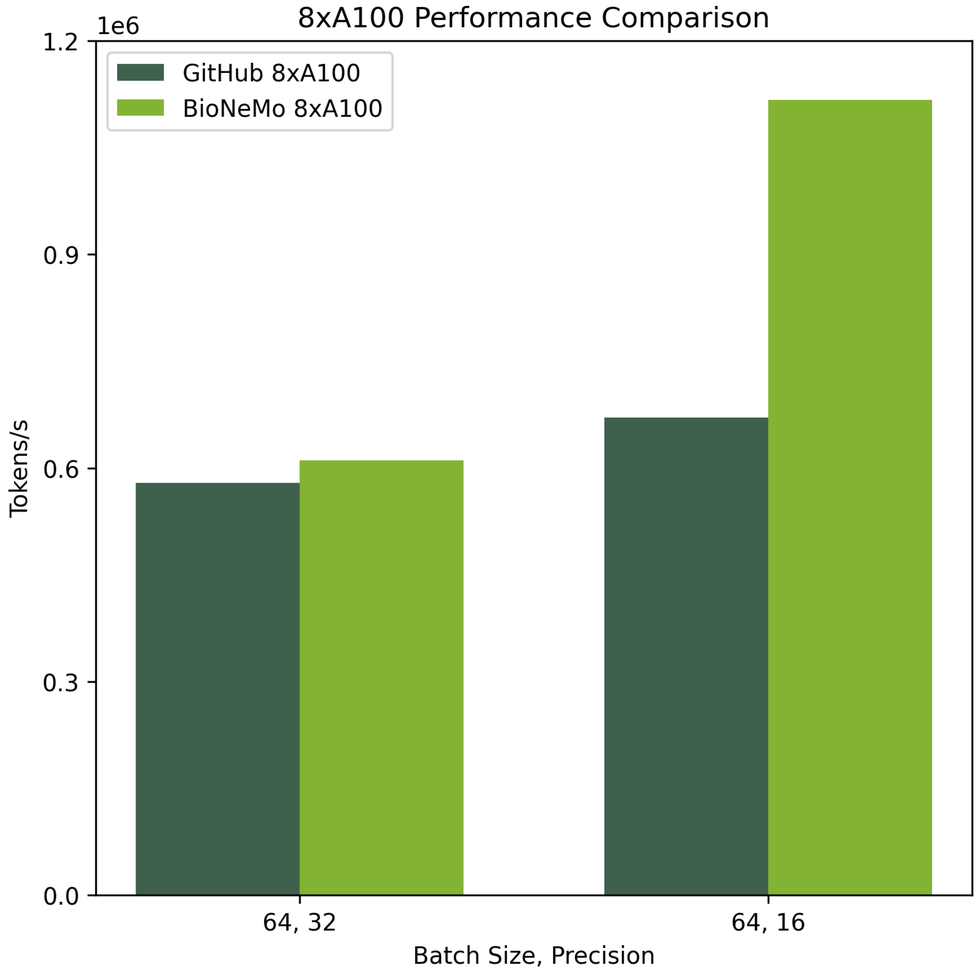
3.2B nucleotides of the human genome sequence.

- Input: Plain Text of nucleotide sequences (A, C, G, T).
- Output: Text predictions in the form of dense numerical embeddings.



DNABERT


1xA100 Performance Comparison
1e6
1.2
0.9
0.6
0.3
0.0
Tokens/s
GitHub 1xA100
BioNeMo 1xA100
64, 32
64, 16
Batch Size, Precision


8xA100 Performance Comparison
1e6
1.2
0.9
0.6
0.3
0.0
Tokens/s
GitHub 8xA100
BioNeMo 8xA100
64, 32
64, 16
Batch Size, Precision

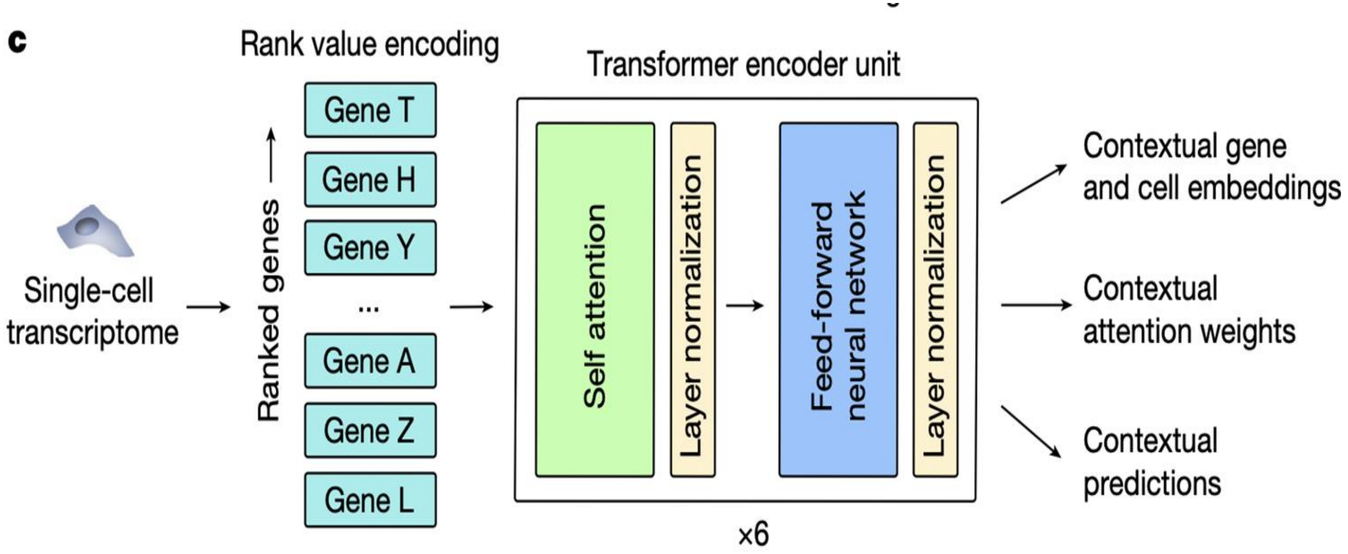
GENEFORMER

Enabling state of the art foundation models for single cell RNA-seq in BioNeMo

Objective:

Sc-FM (Single cell foundation models) primary usecase is to enable users to build and research single cell foundation models. This includes pre-training from scratch, customizing the model architecture, preprocessing methods, and re-training on their own datasets.

- **Architecture -** Geneformer-style BERT pre-training pipeline with restricted context length (1k genes)
  - Tensor, Pipeline Model parallelism, scale to 1B parameters.



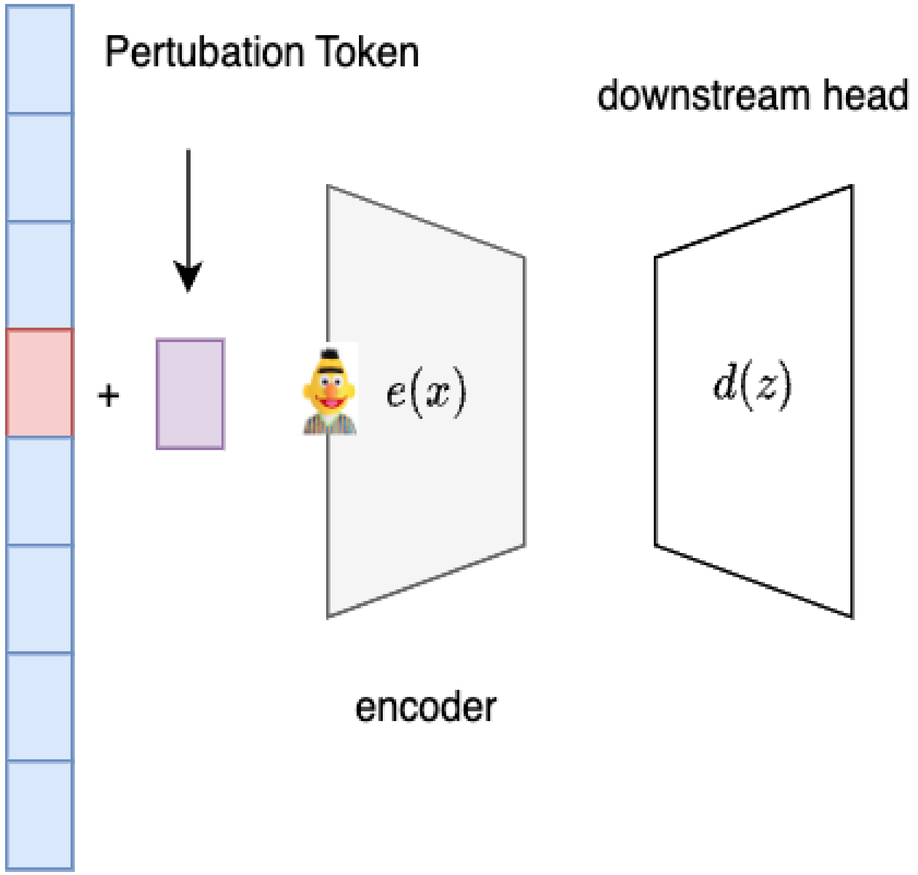
- **This method uses a simple normalization technique based on the rank of gene expression.**
- **Limitation: It hides all of the resolution involved in gene expression behind ranks.**

Theodoris, Christina V., et al. "Transfer learning enables predictions in network biology." *Nature* (2023): 1-9.

GENEFORMER

Downstream task

- **Downstream tasks -** Fine-tuning and zero-shot example using PERTURB-seq

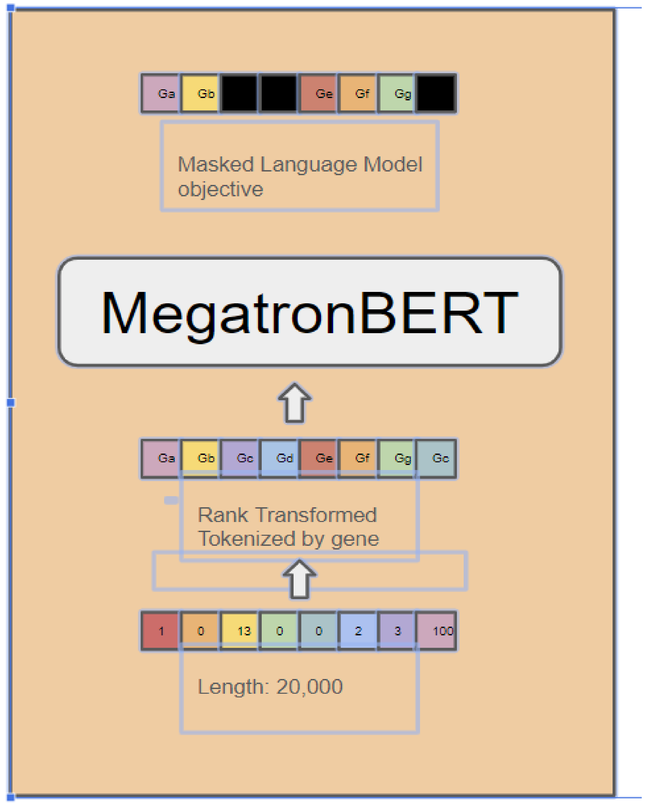


Requires modification to the input

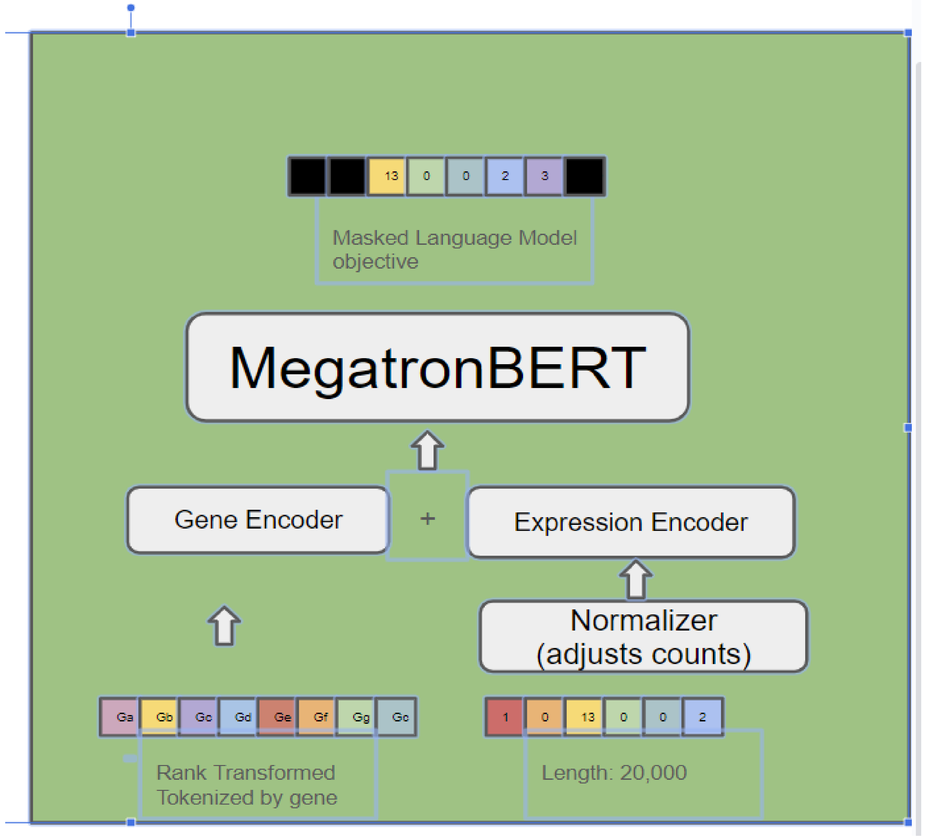
Option 1: use tokentype during fine tuning (BioNemo)

Option 2: add perturbed gene embedding @ output of the encoder

GENEFORMER



The model known as “geneformer”

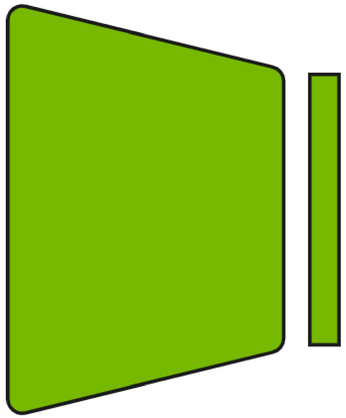


An example, users will want to use more than one encoder for single cell foundation models, which is not supported by BioNemo yet.

ESM-1nv

- **Usage:** embedding, prediction.
- **Type of model**: BERT and is based on ESM-1 model published by Meta AI, with layer normalization and Gaussian Error Linear Unit (GELU) activation used throughout

MHHHHHSSGLVPRGSGMKETAAAKFERQH
MDSPDLGTDDDDKAMADIGSENLYFQSMSK
IFVNPSAIRAGMADLEMAEETVDLINRNIE
DNQAHLQGEPIEVDSLPEDIENLYFQGMES
DKIVFKVNNQLVSVKPEVIVDQYEYKYPAI
QDHTKPSITLGKAPDLNKAYKSILSGMNAA
KLDPDDVCSYLAAAMELFEGVCPEDWTSYG
IMIARKGDKITPATLVDIKRTDIEGNWALT
GGQDLTRDPTVAEHASLVGLLFFSRVEHLY
SAIRVGTVVTAYEDCSGLVSFTGFIKQIN



0.7375 0.1775 0.6742 0.7462
0.8363 0.7456 0.6723 0.1526
0.7562 0.9153 0.2757 0.7856
0.4876 0.7865 0.1954 0.8662

- Downstream task models
- Physical properties
- Sequence-level tasks
- Residue-level tasks
- Clustering

RAPIDS

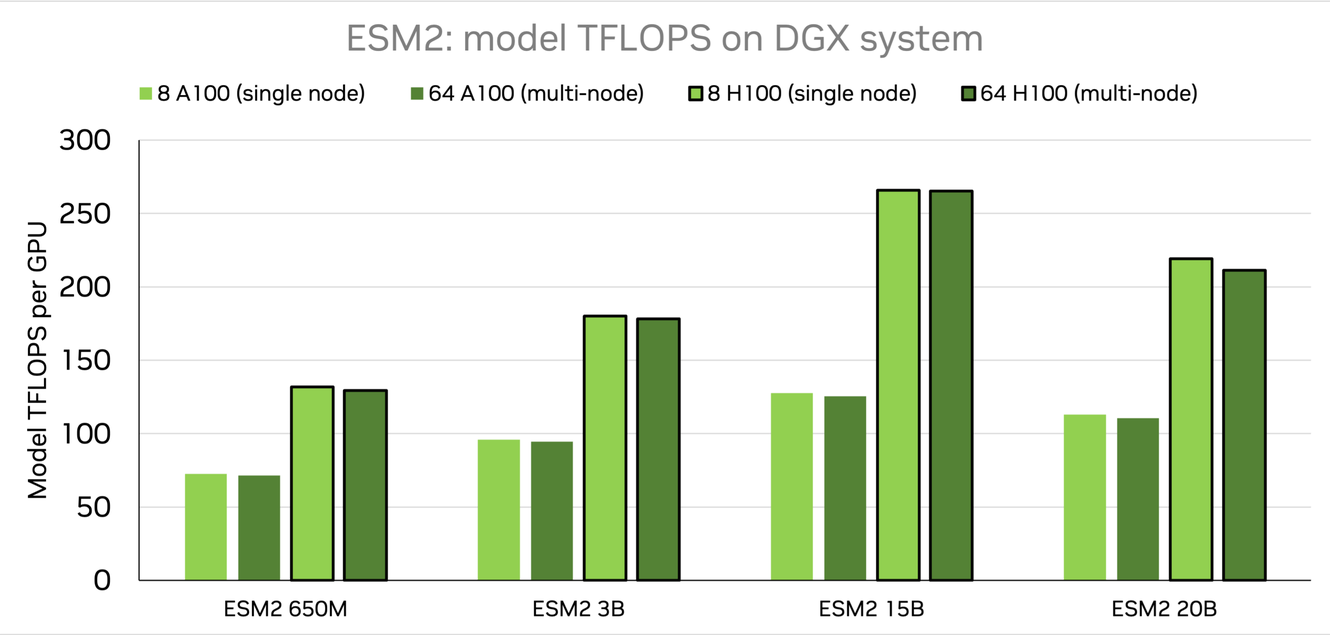
PyTorch

Training statistics

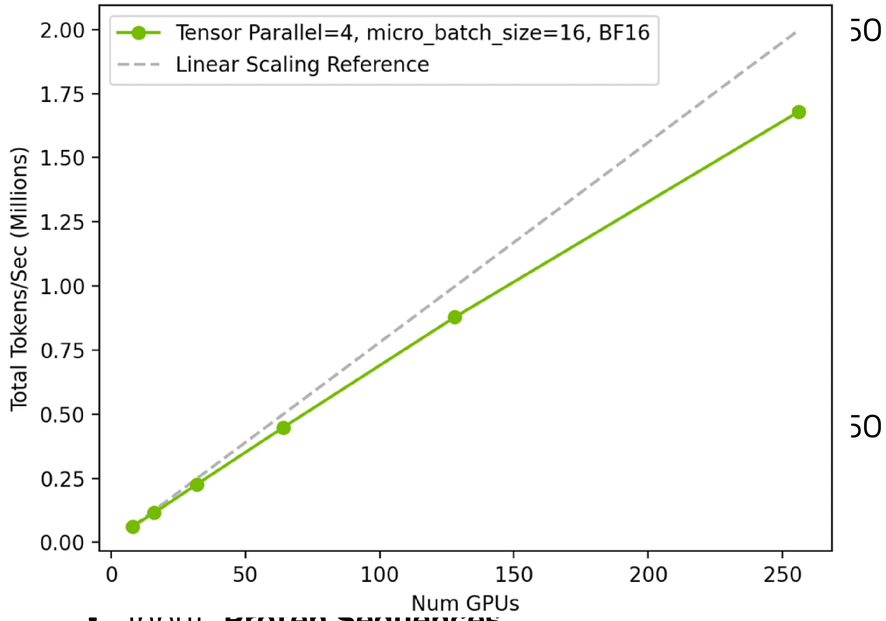
- Trained on **46 M** protein sequences from UniRef50
- **44 M** parameters
- Hidden dim size: **768**
- Maximum input length: **512**
- Maximum output length: **512**
- Input: **Proten Sequences**
- Output: **Protein Sequences**

ESM-2nv

- **Usage:** embedding, predict structure, function and other protein properties
- **Type of model**: BERT and is based on ESM-2 model published by Meta AI
- **Data**: Unlike ESM-2 pre-training data, the curated pre-training dataset provided with ESM-2nv release contains hits for de novo proteins, since sequences in UniRef100, UniRef90, and UniRef50 with high sequence similarity to a non-public 81 de novo proteins are not filtered.



Training statistics (ESM-2nv 3B model)



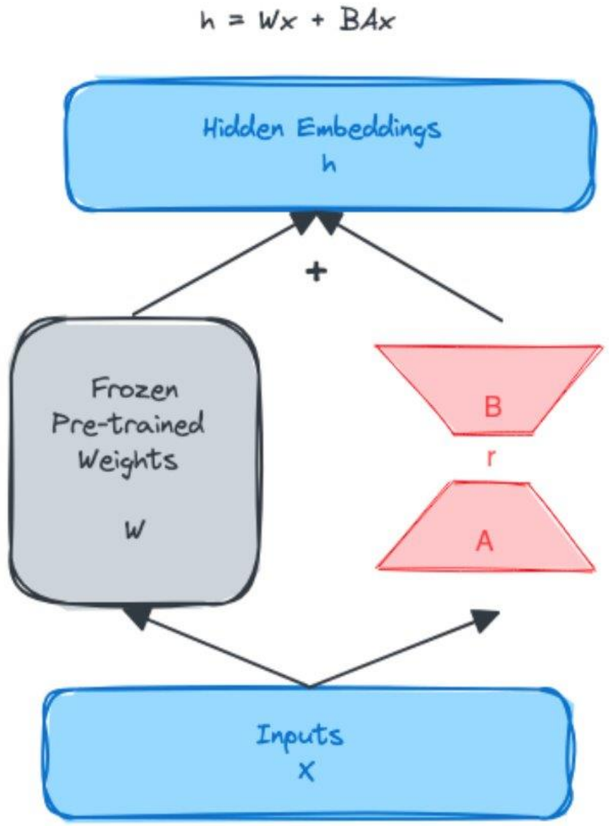
- Input: **Protein Sequences**
- Output: **Protein Sequences**

ESM2 LORA

Enabling parameter-efficient finetuning technique for ESM2

Objective:

LoRA addresses some of the drawbacks of fine-tuning by freezing the pre-trained model weights and injecting trainable rank decomposition matrices into each layer of the Transformer architecture. The key advantage of this decomposition is that it significantly reduces the number of trainable parameters.

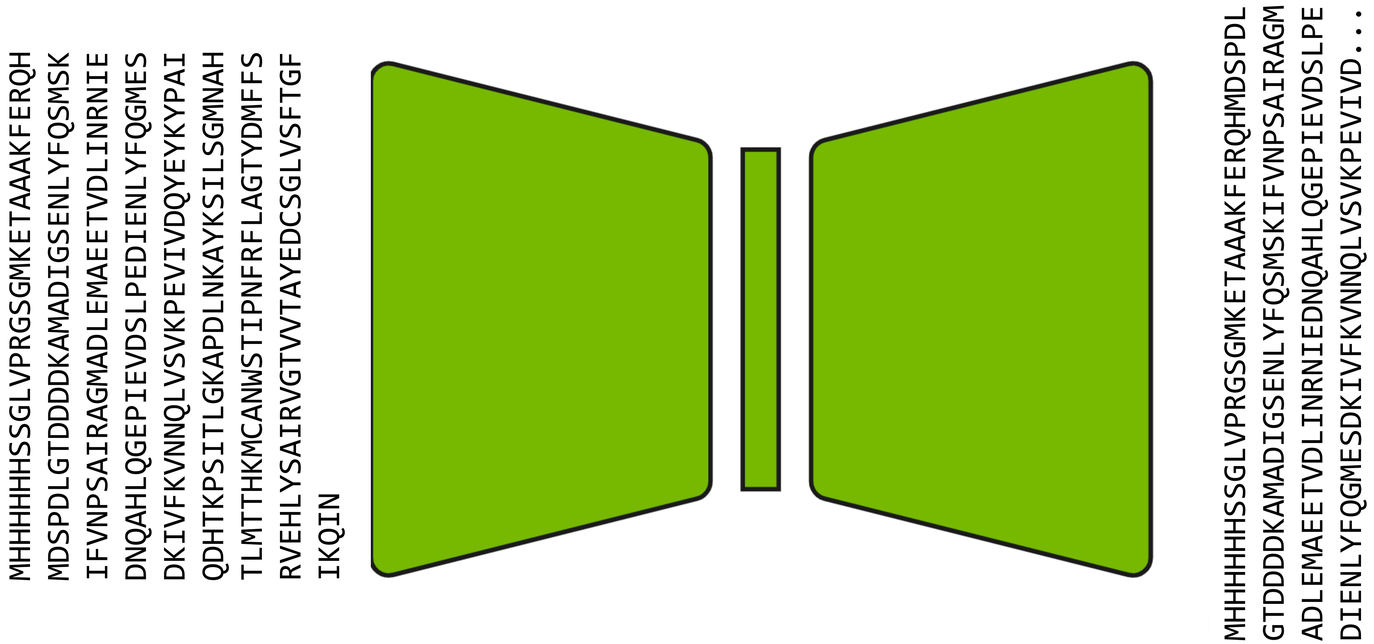


Performance

- Training speed, faster training step time compared to full finetuning (10-25% speedup), 1 node and 8 node A100
- Trainable parameter reduction, ~ 99% reduction compared to full finetuning

ProtT5nv

- **Usage:** embedding, prediction, protein sequence generation
- **Type of model**: T5 encoder-decoder with layer normalization and GELU activation used throughout. This model was developed in a collaboration led by the Technical University of Munich's RostLab and NVIDIA, and extends the capabilities of protein LLMs to sequence generation.



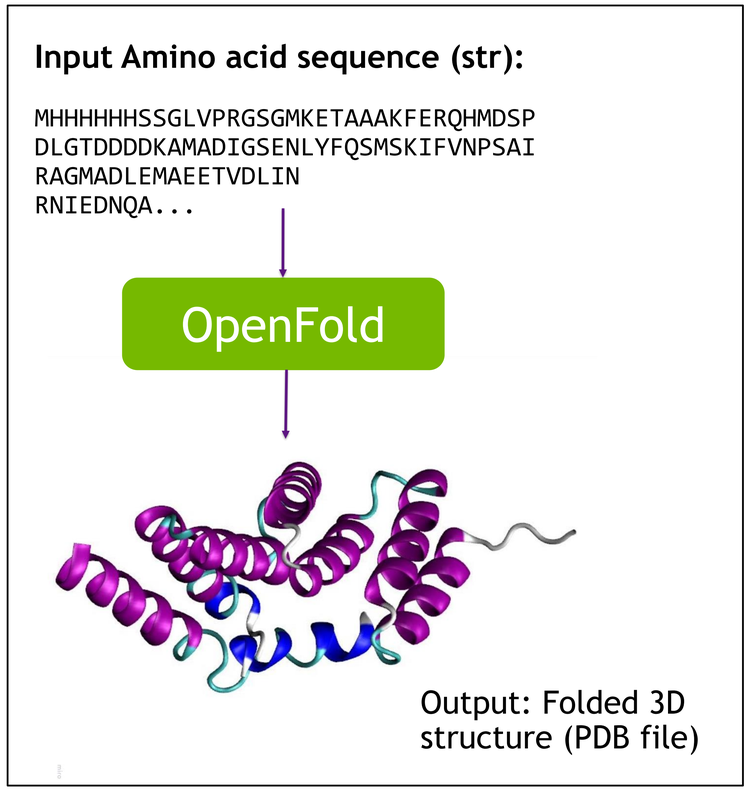
Training statistics

- Trained on **46 M** protein sequences from UniRef50
- **192 M** parameters
- Hidden dim size: **768**
- Maximum input length: **512**
- Maximum output length: **512**
- Input: **Protein Sequences**
- Output: [Protein Sequences, Score]

OPENFOLD RELEASE

OpenFold is the open-source version of AlphaFold, which predicts protein 3D structure from amino acid sequences.

- **In scope deliverables**
  - OpenFold training code, with finetuning capability
    - Compatible training data: MSA, PDB, HHR structural templates
  - Two checkpoints:
    - Public converted checkpoint, LDDTCa = 91.5 (min. required LDDTCa 90)
    - Public converted checkpoint + finetunes in the framework, LDDTCa = 91.5 (doesn't get worse)
- **Benchmarks**
  - Training performance, 16 node (128 GPU), A100. Up to 1.7x perf boost (compared to public OpenFold implementation).
  - Accuracy benchmarks for released checkpoints. Document that training from scratch yields LDDTCa = 90.5



Training statistics

- Trained on **200 k** protein structures from PDB-mmCIF dataset and **269 k** sequence alignments from OpenProtein Set
- Input: **Protein Sequences + MSA (optional) + HHR structural template (optional)**
- Output: **PDB + (optional) Confidence Metrics + (optional) Embeddings**

OpenFold: Gustaf *et. al.*, https://www.biorxiv.org/content/10.1101/2022.11.20.517210v1

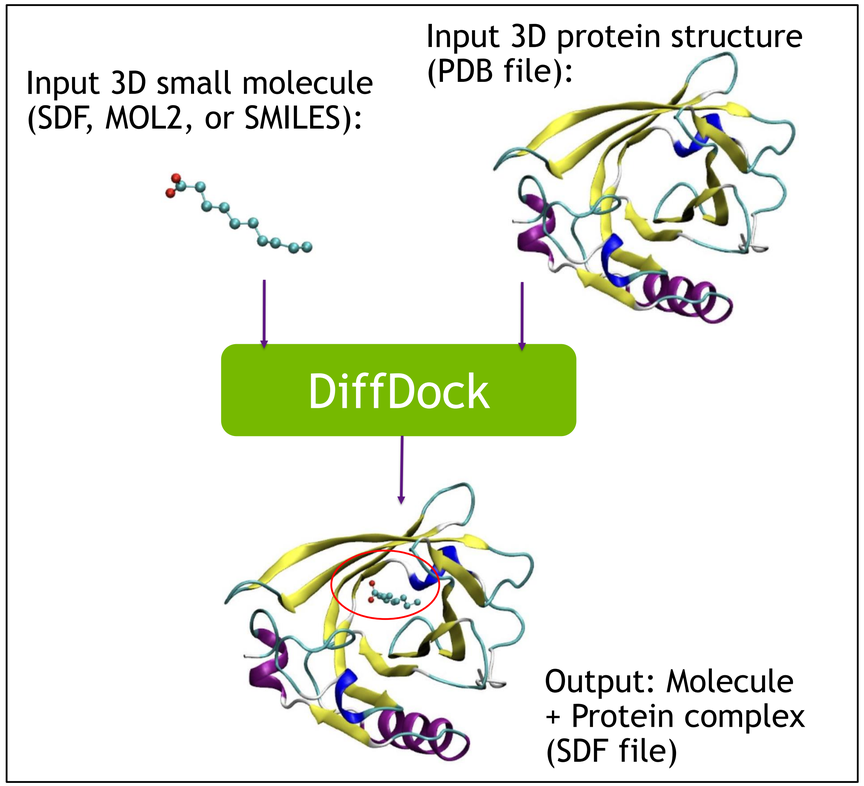
DIFFDOCK RELEASE

DiffDock is an equivariant diffusion model for small molecule – protein docking.

DiffDock consists of two models: the Score and Confidence models.

The Score model: a 6-graph-convolution-layer 3-dimensional equivariant graph neural network with 20M parameters. The Score model is used to generate a series of potential poses for protein-ligand binding by running the reverse diffusion process.

The Confidence model: a 5-graph-convolution-layer 3-dimensional equivariant graph neural network with 5M parameters. The Confidence model is used to rank the generated ligand poses from the Score model.

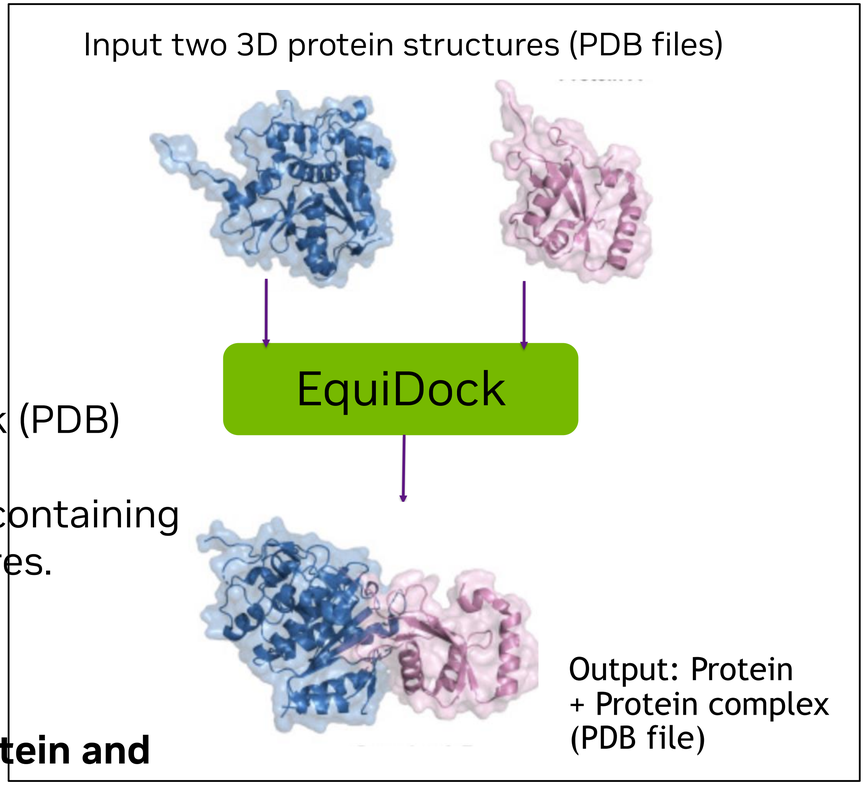


Training statistics

- Evaluated on **428** protein-ligand complexes manually curated using the PoseBusters benchmark (PDB) set
- Input: **Text (PDB, SDF, MOL2, SMILES)**
- Output: **Structural Data Files (SDF) + Confidence Score and the rank based on this score**

EQUIDOCK release

Equidock is an SE(3)-equivariant (GNN) rigid model for prediction of protein-protein complex formation.



Training statistics

- Dataset:
  - DB5.5 dataset consists of 253 protein structures built by mining the Protein Data Bank (PDB) for pairs of interacting proteins.
  - The Database for Interacting Proteins Structures (DIPS) has 41,876 binary complexes containing bound structures with rigid body docking, while DB5.5 includes unbound protein structures.
  - DB5.5 includes 203/25 training and validation data points, respectively.
  - DIPS includes 39,937/974 training and validation data points respectively.

- Input: **Text (Geometric Protein Structure), Maximum number of residues is 400 per protein and**
- **maximum number of atoms is 4000 per protein**

- Output: **Protein Data Bank (PDB)**

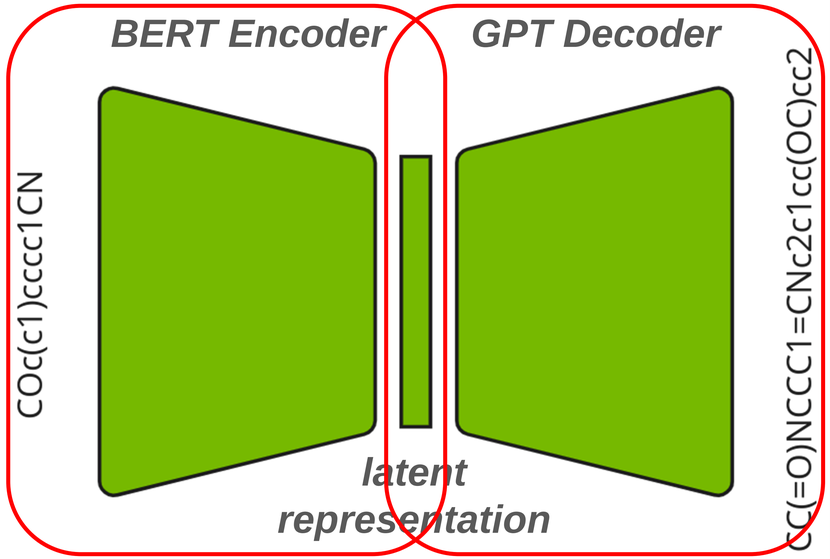
Images from: https://www.sciencedirect.com/topics/medicine-and-dentistry/docking-protein

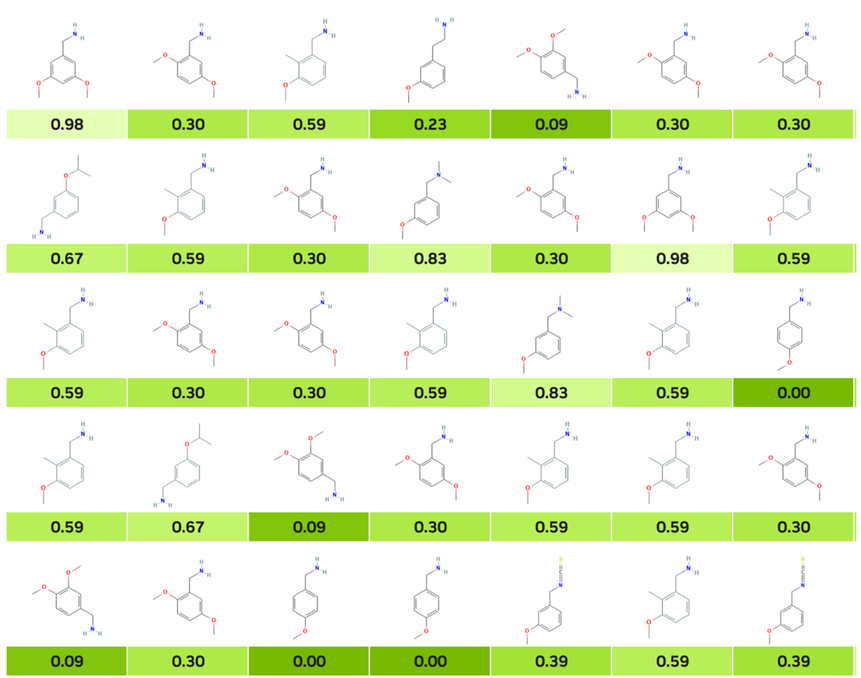
MegaMolBART

- **Usage:** embedding, reaction prediction, property prediction, de novo molecular generation
- **Type of model**: a BART model, seq2seq transformer with layer normalization and GELU activation used throughout
- **Representation**: variable-size representation for variable length SMILES

Training statistics

- Trained on **1.5B** molecules from ZINC15
- **45 M** parameters
- Hidden dim size: **256**
- Maximum input length: **512 tokens**
- Maximum output length: **512 tokens**
- Input: **SMILES**
- Output: **[SMILES, Score]**





MegaMolBART: NVIDIA & AstraZeneca; Bjerrum, Irvin, Engkvist, et al.

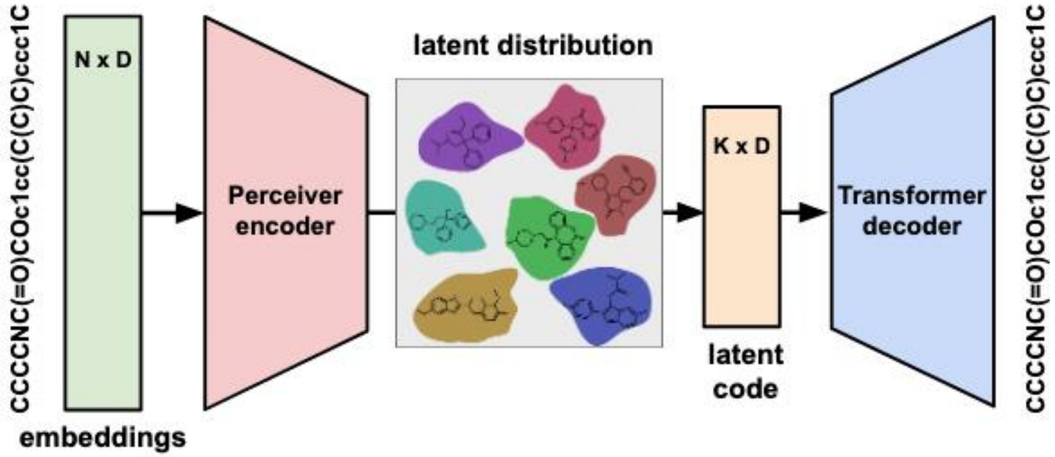
https://ngc.nvidia.com/catalog/models/nvidia:clara:megamolbart

MolMIM

Generative small molecule model developed by NVIDIA

- **Usage:** embedding, reaction prediction, property prediction, molecular optimization, de novo molecular generation
- **Type of model**: auto-encoder trained with mutual information machine learning (MIM)
- **Representation**: fixed-size representation for variable length SMILES

Architecture of MolMIM



Training statistics

- Trained on **730 M** molecules from ZINC15
- **65 M** parameters
- Hidden dim size: **512**
- Maximum input length: **128 tokens**
- Maximum output length: **512 tokens**
- Input: **SMILES**
- Output: **[SMILES, Score]**

The MIM part of MolMIM refers to the custom Mutual Information Machine (MIM) loss which overcomes some technical shortcomings of variational auto-encoders. MolMIM is uniquely able to sample valid, novel molecules with only slight perturbations of the latent code, due to its unique, dense latent space that clusters chemically similar molecules. These features lead to superior property guided optimization performance.

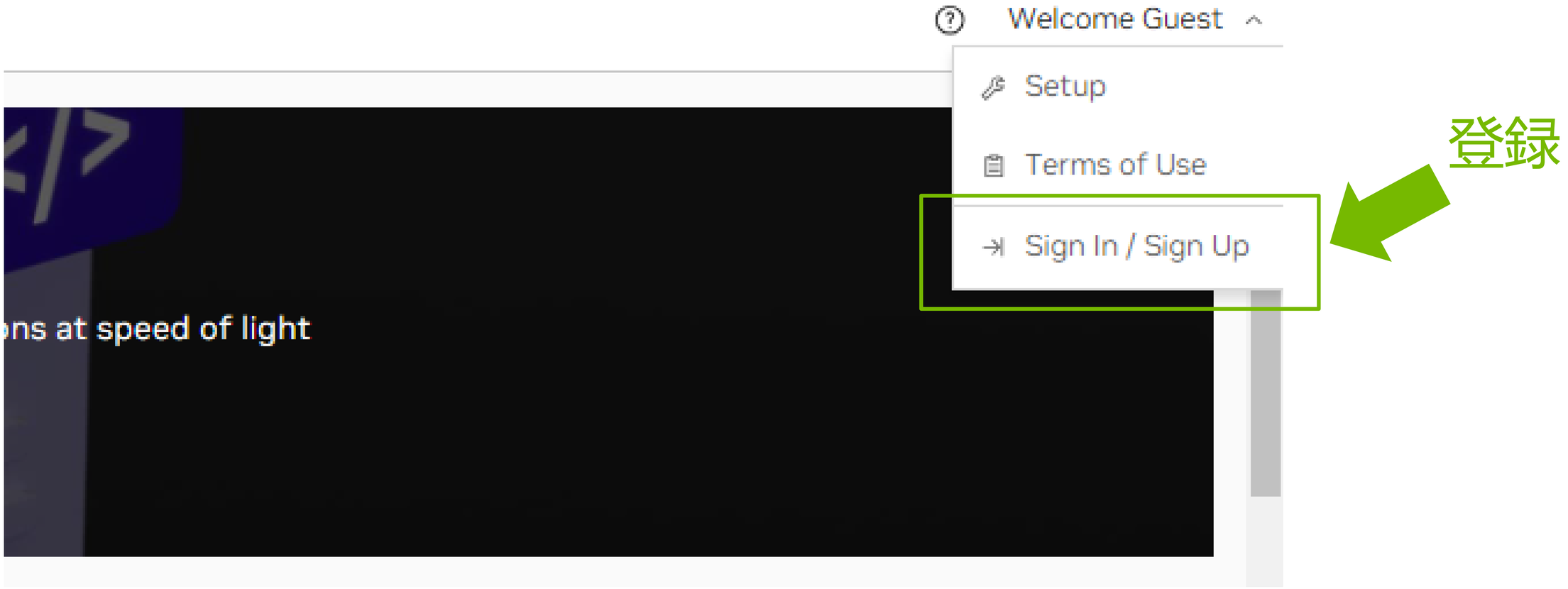
MolMIM: NVIDIA; Reidenbach *et. al.,*: https://arxiv.org/abs/2208.09016

SHIROKANEでの実機操作:

ESM-2nv、DNABERT と MolMIMモデル

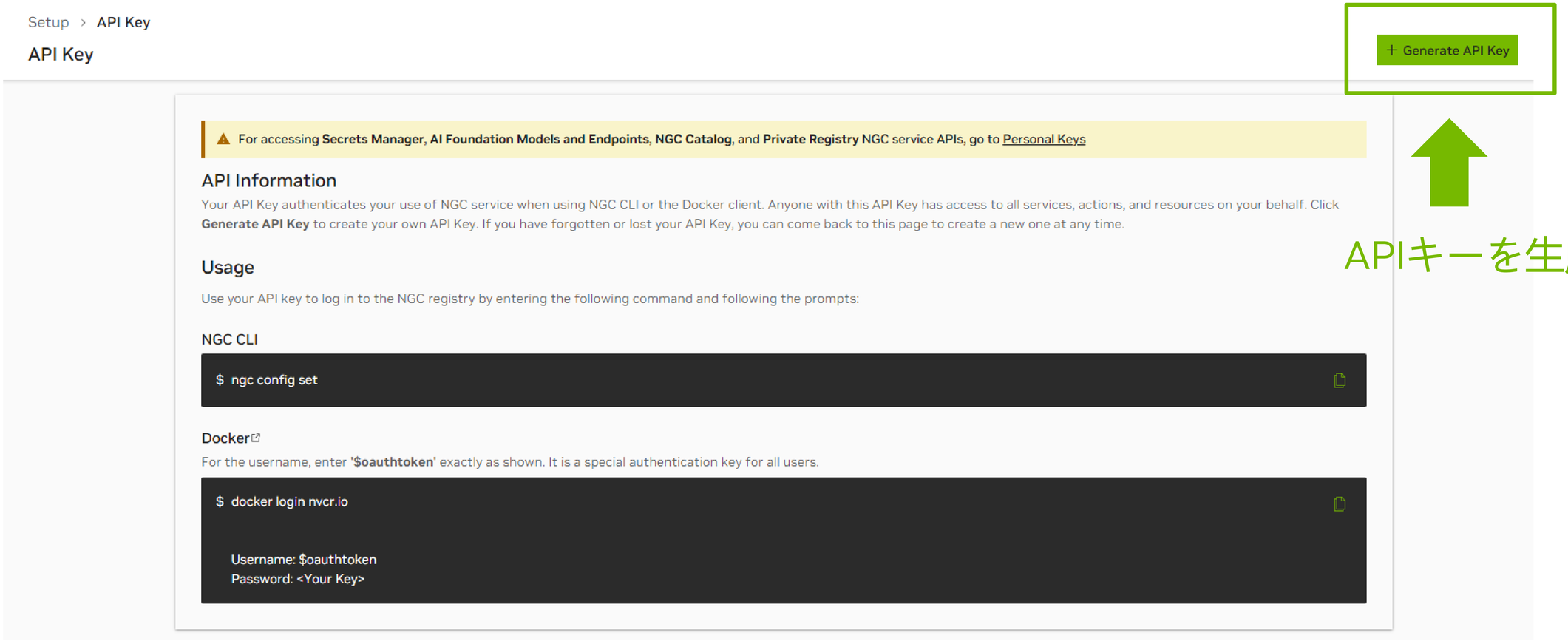
事前準備

- NGCの登録


Welcome Guest
Setup
Terms of Use
Sign In / Sign Up
登録
ons at speed of light

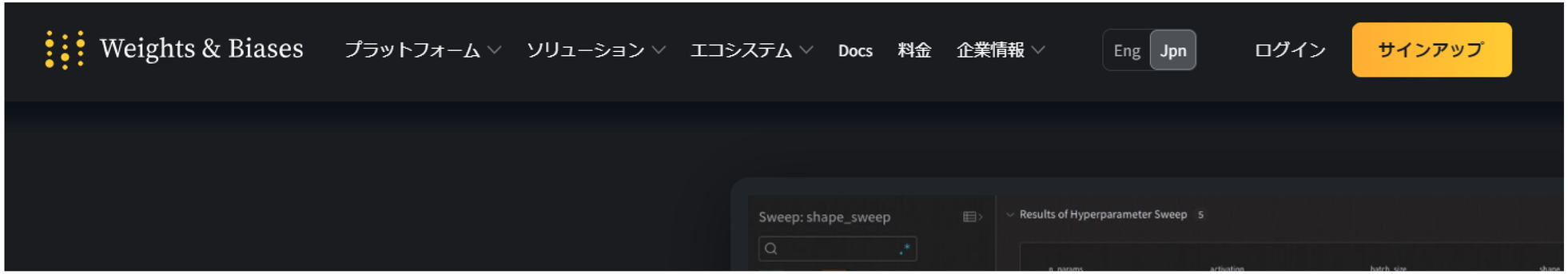
事前準備

- APIキーの取得



事前準備

- Weights and Biasesの登録とAPIキーの取得



SHIROKANEでの操作

1．BioNeMoのSingularity イメージを作成します

```
$ qlogin -l a100=2,s_vmem=200G,mem_req=200G
$ module load singularity/3.7.1
$ singularity pull --docker-login docker://nvcr.io/nvidia/clara/bionemo-framework:1.5
Username: $oauthtoken
Password: 「APIキーを入力」
```

2．BioNeMoフォルダを自分のホームディレクトリにコピーします。そうしないと、ファイルの書き込みエラーとなります

```
$ singularity shell --nv -e bionemo-framework_1.5.sif
$ cp -R $BIONEMO_HOME /home/cruan/
$ exit
```

3．BioNeMoコンテナを起動します

```
$ cd /home/cruan
$ singularity shell --nv -e -B bionemo:/workspace/bionemo/ bionemo-framework_1.5.sif
```

SHIROKANEでの操作

Jupyter Lab

1．BioNeMoはコマンドラインでも実行できますが、Jupyter Labを利用したい方は、コンテナ内で下記を入力してJupyterLabを起動してください

```
$ jupyter lab --allow-root --ip=* --port=8888 --no-browser --
NotebookApp.token='' --NotebookApp.allow_origin='*' --
ContentsManager.allow_hidden=True --notebook-dir=/workspace/bionemo & sleep
infinity
```

2．ローカルマシンのターミナルで以下を実行します。

```
$ ssh -N -L 8888:gcga01:8888 cruan@slogin.hgc.jp -i /path/to/id_rsa
```

** gcga01 は、ターミナルで BioNeMo コンテナを起動した SHIROKANE の計算ノードです*
** 二つ目の8888 は、起動した Jupyper lab が示す URL に記載のある “http://127.0.0.1:XXXX/lab” の XXXX を指します*
** /path/to/id_rsa は、ローカルにある認証に必要な秘密鍵 "id_rsa" ファイルのパスを指定します*

3．手順 1 で起動した Jupyper lab が示す URL http://127.0.0.1:XXXX/lab にローカルのウェブブラウザからアクセスします

今回のデモで利用するJupyter Notebook資料

- 自分のディレクトリのbionemoフォルダに下記の実行して、Jupyter Notebookの資料を取得してください

```
$ cd /home/cruan/bionemo
$ git clone https://github.com/colleenrpy/BioNeMo_FW_Hands-on.git
```

- Jupyter Notebook を順次実行

参考知識

CMA-ESを使用したMolMIMによる特性ガイド分子最適化

CMA-ES（Covariance Matrix Adaptation Evolution Strategy）は、進化計算における最も有力なブラックボックス最適化の手法の1つとして知られています。このアルゴリズムは多変量正規分布から解を生成し、その解の評価値を利用して、より良い解を生成するような分布に更新を行う手法です。

ハイパーパラメータ最適化の流れ

Validationエラーを小さくするように
ハイパーパラメータを決めるという問題

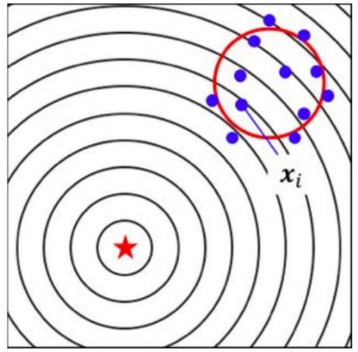
中身がブラックボックスな関数の最適化

= **Black-box最適化**

CMA-ES

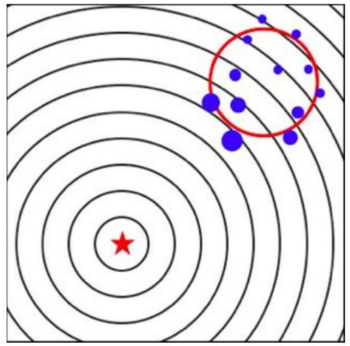
1. 正規分布から解を生成
2. 全ての解を評価して重み付けする
3. 正規分布のパラメータを更新
4. 1.～3.を繰り返す

CMA-ES



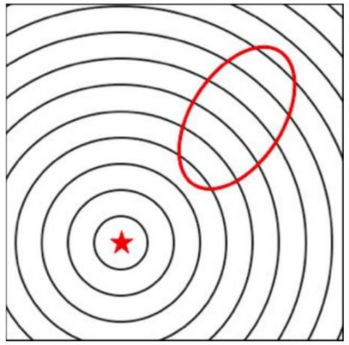
1. 正規分布から解を生成
2. 全ての解を評価して重み付けする
3. 正規分布のパラメータを更新
4. 1.～3.を繰り返す

CMA-ES



1. 正規分布から解を生成
2. 全ての解を評価して重み付けする
3. 正規分布のパラメータを更新
4. 1.～3.を繰り返す

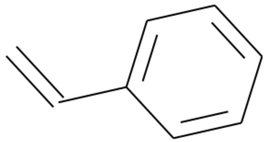
CMA-ES



1. 正規分布から解を生成
2. 全ての解を評価して重み付けする
3. 正規分布のパラメータを更新
4. 1.～3.を繰り返す

https://logmi.jp/tech/articles/322678

SMILESとCanonical SMILES



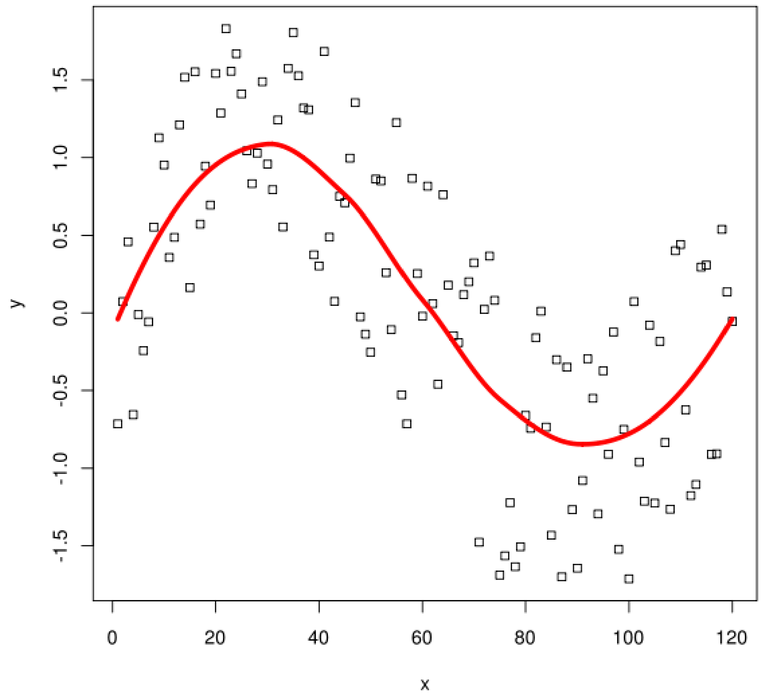
SMILES

- C=CC1=CC=CC=C1
- C1=CC=CC=C1C=C
- C1=C(C=C)C=CC=C1

ルールに従って並び順を決め（正規化 = canonicalize）、それに従って記述しましょう、というのがcanonical SMILESです。

LOWESS Smoothing

LOWESS（局所加重散布図平滑化）、時にはLOESS（局所加重平滑化）とも呼ばれますが、回帰分析で使用される一般的なツールです。これは、タイムプロットや散布図にスムーズな線を引き、変数間の関係を見やすくし、傾向を予測するのに役立ちます。



Tanimoto類似度

$$S_{AB} = \frac{c}{a + b - c}$$

- aは分子Aのビット配列で1が立っている数
- bは分子Bのビット配列で1が立っている数
- cは分子AとBで共通に1が立っている数

分子A:	1	0	1	1	1	0	1	1	0	0	1	1

分子B:	0	0	1	1	0	0	1	0	1	0	1	1

$$S_{AB} = \frac{5}{8 + 6 - 5} = 0.56$$

https://future-chem.com/rdkit-fingerprint/

QED

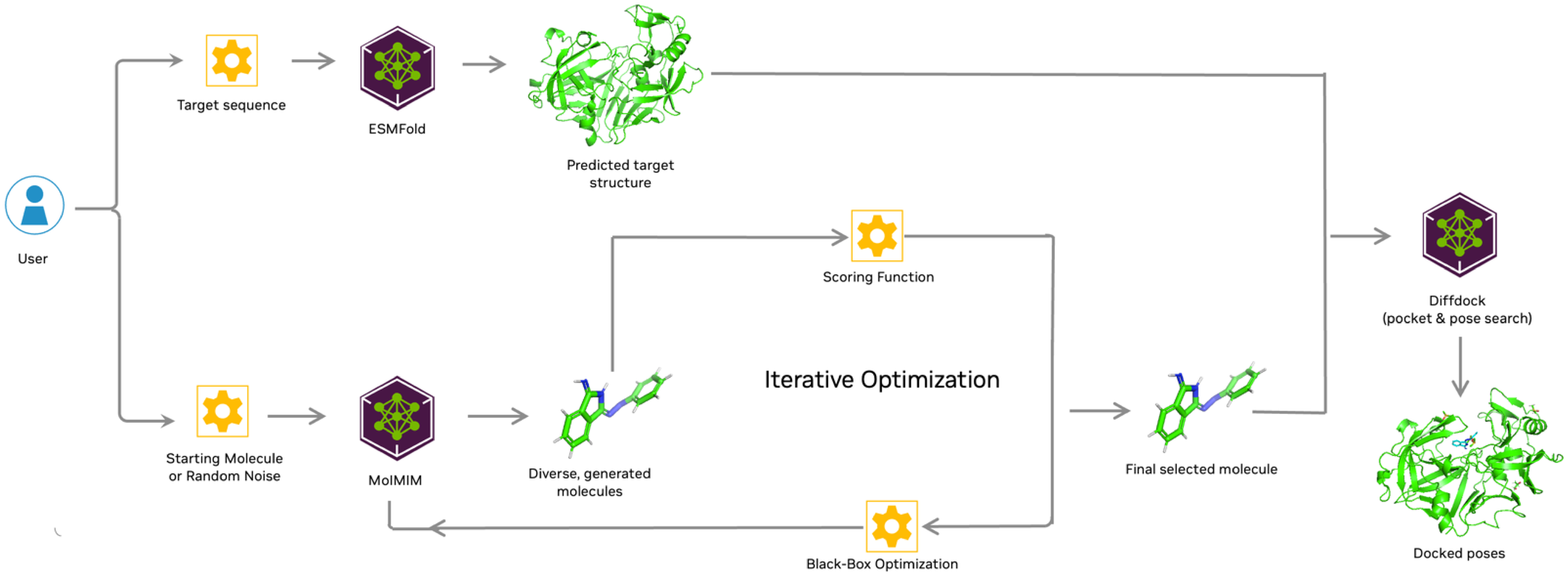
QED（Quantitative Estimate of Drug-likeness）は複数の分子記述子を組み合わせることで薬らしさを評価する方法の１つです。

QEDは771個の経口医薬品をデータセットに用いて，次の8つの記述子を用いてモデル化されました。QEDを用いることで，0（最も薬らしくない）から1（最も薬らしい）に定量化が可能です。

- 分子量（MW）
- logP（ALOGP）
- 水素結合ドナーの数（HBDs）
- 水素結合アクセプターの数（HBAs）
- 極性表面積（PSA）
- 回転可能結合数（ROTBs）
- 芳香環の数（AROMs）
- 忌避構造の数（ALERTS）

https://future-chem.com/rdkit-qed/

パイプライン：タンパク質標的の低分子生成とドッキング



参考情報

- BioNeMo Framework のドキュメンテーション
- BioNeMo Framework を使って最新のタンパク質言語モデルを作成する簡単な方法
- デモ資料のGithub
- NGCサイト