Developing a Modified version of Generative Adversarial Network for predicting Anti-Viral Drug of Covid-19

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Introduction

- The **coronavirus** was first discovered in the mid **1960s** causes common cold to severe illness.
- A new strain of the virus was discovered called the **Novel Coronavirus or COVID-19** in 2019 (Fig 1).
- This work will first develop a set of candidate drugs using deep reinforcement learning.
- Those drugs will be bonded with Covid-19 protein
- The drug with the best binding affinity will be a potential cure for the virus.

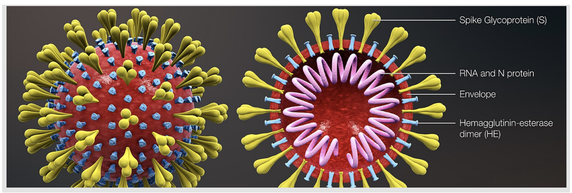

Figure 1: coronavirus virion structure showing spikes that form a "crown" like the solar corona

Literature Review

- Deep Belief Network (DBN), Hopfield network and Long Short-Term Memory(LSTM) and etc. are using to reach an integrated approach for drug design.
- This work uses **Objective-Reinforced Generative Adversarial Networks** (ORGAN) **[2]** to generate potential candidates' drugs.
- Research claims that **Chloroquine** and **remdesivir** are recognized as effective candidates to control the virus and others are used as referenced smiles.

Methodology

#1 Dataset Preprocessing

- A dataset of 677,044 SMILES strings with annotated nanomolar activities from ChEMBL.
- The SMILES are cleaned to remove salts, duplicates and stereochemical information.
- The model trained on 541,555 SMILES strings, with lengths from 34 to 74 tokens. **[3]**

#2 Model Struture and Training

- The ORGAN model has two neural networks:
- **Generator:** Generates molecules that closely follows the distribution of training data. For each epoch, the sequence is split into two and Generator predicts the next character and each time loss is calculated and the generator is optimized and parameters updated.

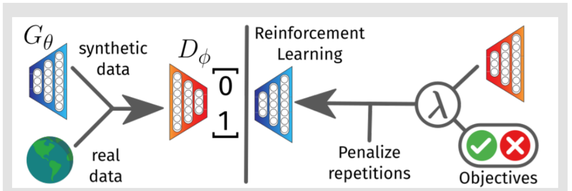

Figure 2: Schema for ORGAN. Left: D is trained as a classifier receiving as input a mix of real data and generated data by G. Right: G is trained by RL where the reward is a combination of D and the objectives, and is passed back to the policy function via Monte Carlo sampling. Non-unique sequences penalized .

- **Discriminator:** Trained to catch fake molecules generated by generator(G). It is trained first on the real training data , then trained on fake data labeled with fake generated by the generator, loss is calculated for both fake and real.
- First phase training is finished and invalid smiles are removed. Referenced smiles are used for policy gradient method, the loss of generator is computed via **policy gradient function** *P(f)* and for discriminator **Binary Cross Entropy** with **Logits loss**.
- First, get the rewards from the reward metrics for each predicted token by **(Eq 1).**

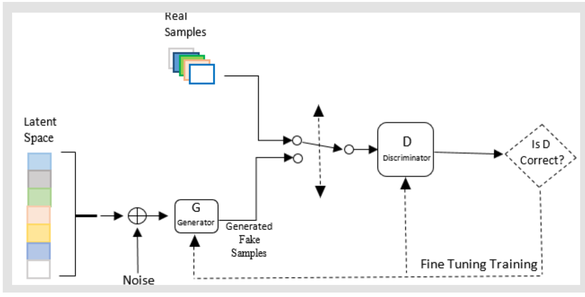

Figure 3: ORGAN Structure for training, how it is used to train. While G is training, D is freezed, same for D's training

- The generated sequence and rewards are forwarded to ***P(f)*** to calculate the loss by **(Eq. 2)**.

Reward Funtion (Equation - 01)

$$J(\theta) = E[R_T|s_\theta, \theta] = \sum_{x_i \in X} G_\theta(x_i|s_\theta) \cdot Q(s_\theta, x_i).....(1)$$

Policy gradient Loss Funtion (Equation - 02)

$$L = -Q(s,a)log(G(y_t|Y_{1:t-1})).....(2)$$

- Optimized the generator, backpropagate and calculate the gradient.
- Generated samples from the generator in batches. Iterated over all the batches and through each molecule to predict the probability of it being fake, determined the loss by (Eq. 2) and updated the gradients.

Results and Discussion

- After about 9 hours of training, with a λ of **0.2** and epochs of **240** and a sample set of 6400, **10 good samples** are generated.
- The Solubility or LogP of these samples is 0.7098 and other molecular matrices can be found in **(Table 1)**.

Novelty	**1.0000**
Hard Novelty	1.0000
Soft Novelty	1.0000
Diversity	0.4698
Conciseness	0.9866
Solubility	0.7098
Naturalness	0.5828
Synthesizability	0.6197

Table 1: Molecular Matrixes of good Candidate Samples

- Good sample candidates' drugs are collected, bonded to the coronavirus through the PyRX software. The binding affinities of each of the samples are recorded. **(Table 2)**
- The drug with the highest binding affinity is ***C18H15ClN4O2*** also known as **Olutasidenib** which is an active, selective inhibitor for treating acute myeloid leukaemia.

Ligand	*Binding Affinity*	*rmsd/ub*	*rmsd/lb*
$C_{18}H_{15}ClN_4O_2$	-7.3	0	0
$C_{23}H_{20}N_2O$	-6.9	0	0
$C_{21}F_{18}FNO$	-6.8	0	0
$C_{21}H_{18}O_2$	-6.4	0	0

Table 2. Binding Affinities of top four candidate drugs

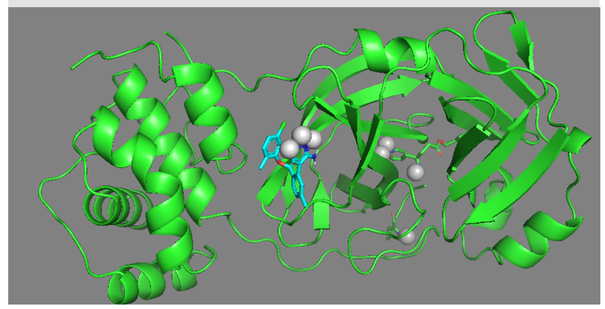

Figure 6: Olutasidenib been bonded with the corona virus.

Conclusion

1. ORGAN is able to identify ten sample molecules or LINGADS which are then bonded to the virus and the candidate molecule is found.

2. Further work should be approved by taking the candidate drug (Olutasidenib) to the lab to be synthesized and tested.

References

1. Benhenda, Mostapha. "ChemGAN challenge for drug discovery: can AI reproduce natural chemical diversity?." arXiv:1708.08227 (2017)

2. Objective-reinforced generative adversarial networks (ORGAN) for sequence generation models. arXiv preprint arXiv:1705.10843.

3. Implementation of the paper-"Generative Recurrent Networks for De Novo Drug Design." https://github.com/topazape/LSTM_Chem