

# Deep Generative Models for Drug Discovery : Variational Auto-Encoder and Generative Adversarial Network

---

NLP연구팀 | 장영걸  
2020-11-09

## 1. VAE 및 GAN 개략적 설명

- Generative 모델의 종류 및 설명
- 수식 모델링 및 해석

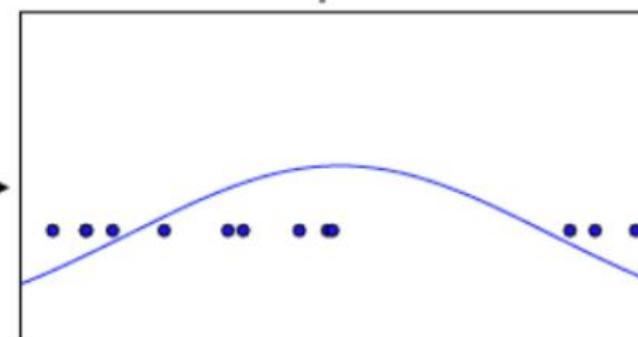
## 2. 약물 생성에서의 VAE 및 GAN 활용

- VAE 관련 사례
- GAN 관련 사례
- 요약 및 Tips

# What is Generative Model

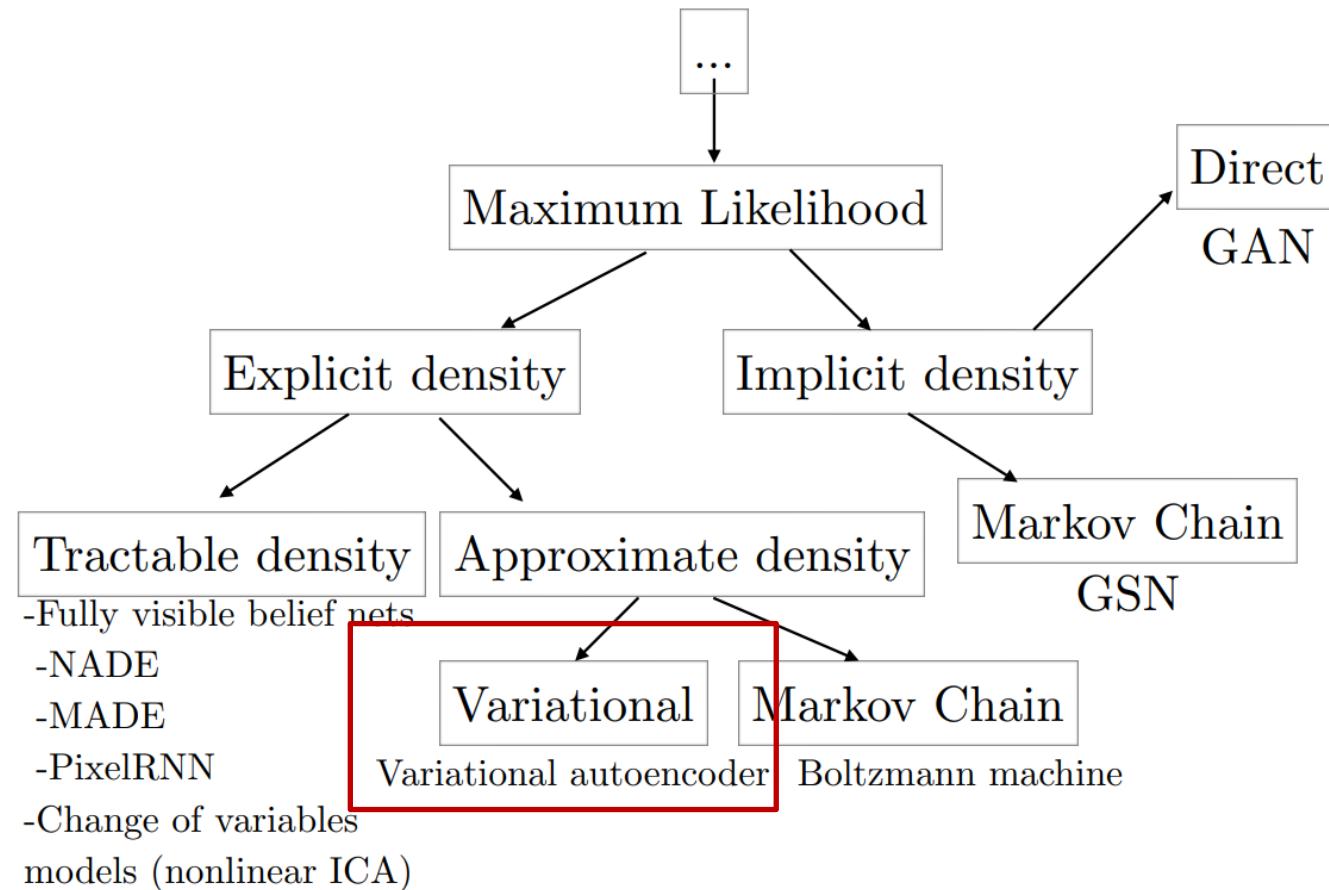


Training Examples



Density Estimation

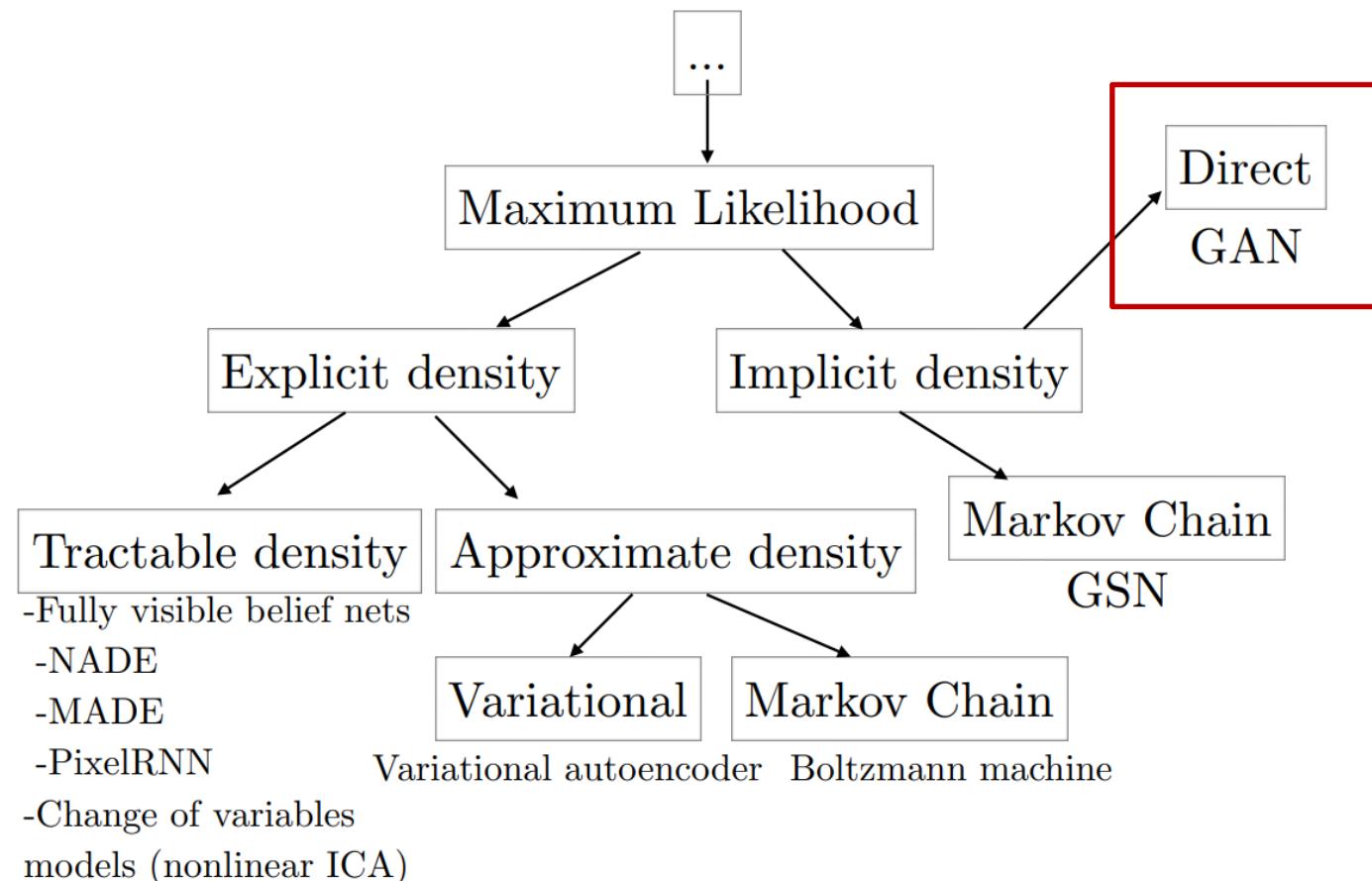
Sampling



- Latent z와 함께 density function 정의
- $p_{model}(x; \theta)$ 을 직접 모델링 (어려움)  
 $p_\theta(x) = \int p_\theta(x|z)p_\theta(z) dz \rightarrow$  intractable
- 하한을 최대화 → 우회적으로 접근
- Variational approximation  

$$L(x; \theta) \leq \log p_{model}(x; \theta)$$

## ⟨Taxonomy of Deep Generative Models⟩



- Transition function  $q$  및 Sample  $x$ ,
- do sampling  $x'$  and update  $x' \sim q(x'|x)$
- $x'$  converge to  $p_{data}(x)$

## ⟨Taxonomy of Deep Generative Models⟩

# Variational Auto-Encoder

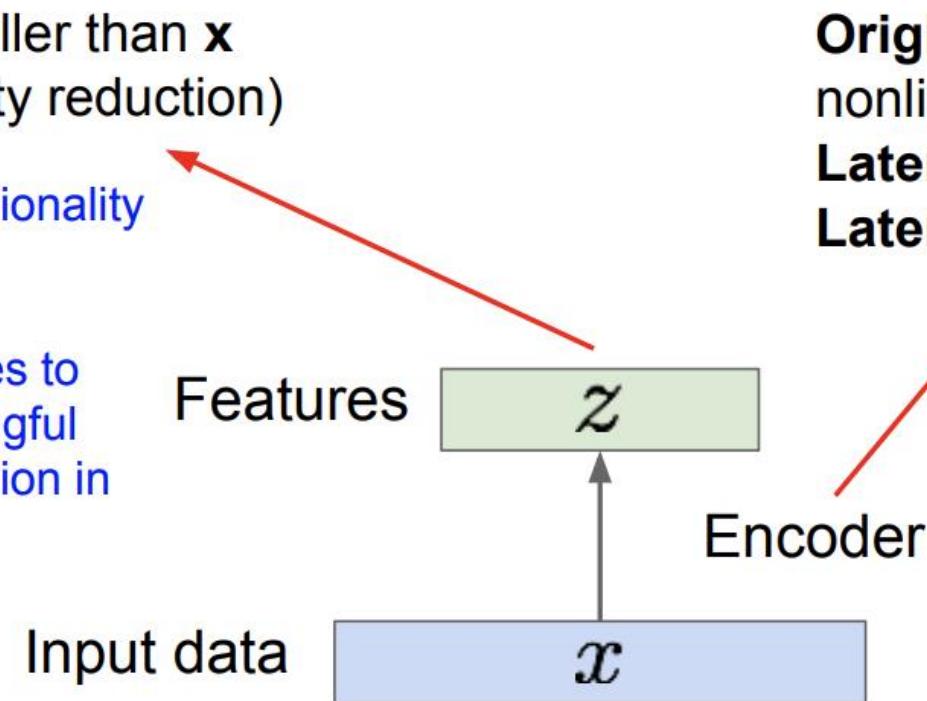
---

Unsupervised approach for learning a lower-dimensional feature representation from unlabeled training data

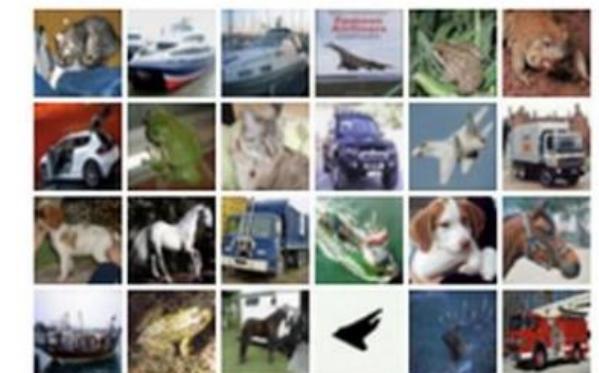
$z$  usually smaller than  $x$   
(dimensionality reduction)

Q: Why dimensionality reduction?

A: Want features to capture meaningful factors of variation in data



**Originally:** Linear +  
nonlinearity (sigmoid)  
**Later:** Deep, fully-connected  
**Later:** ReLU CNN



Train such that features can be used to reconstruct original data

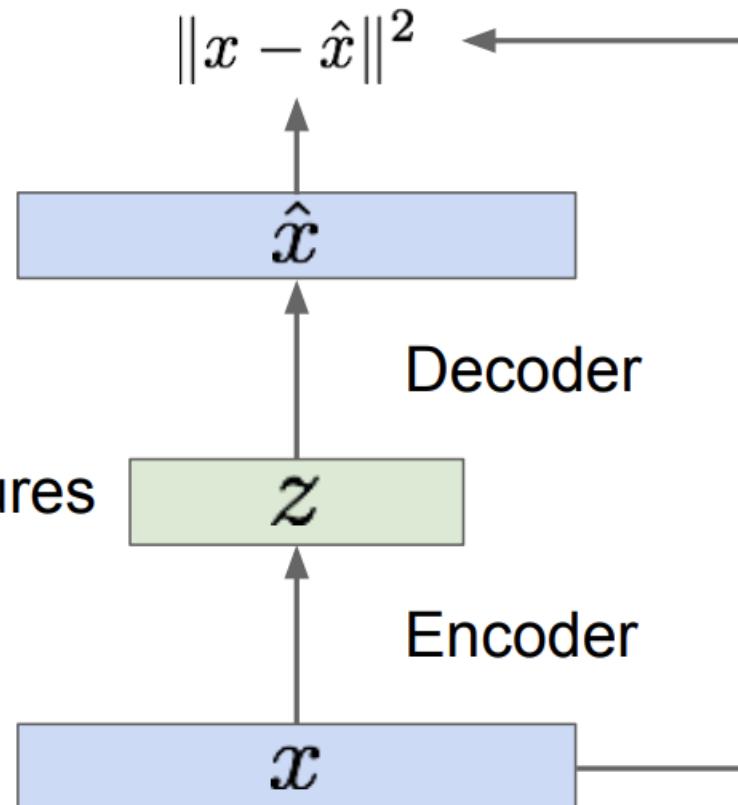
Reconstructed input data

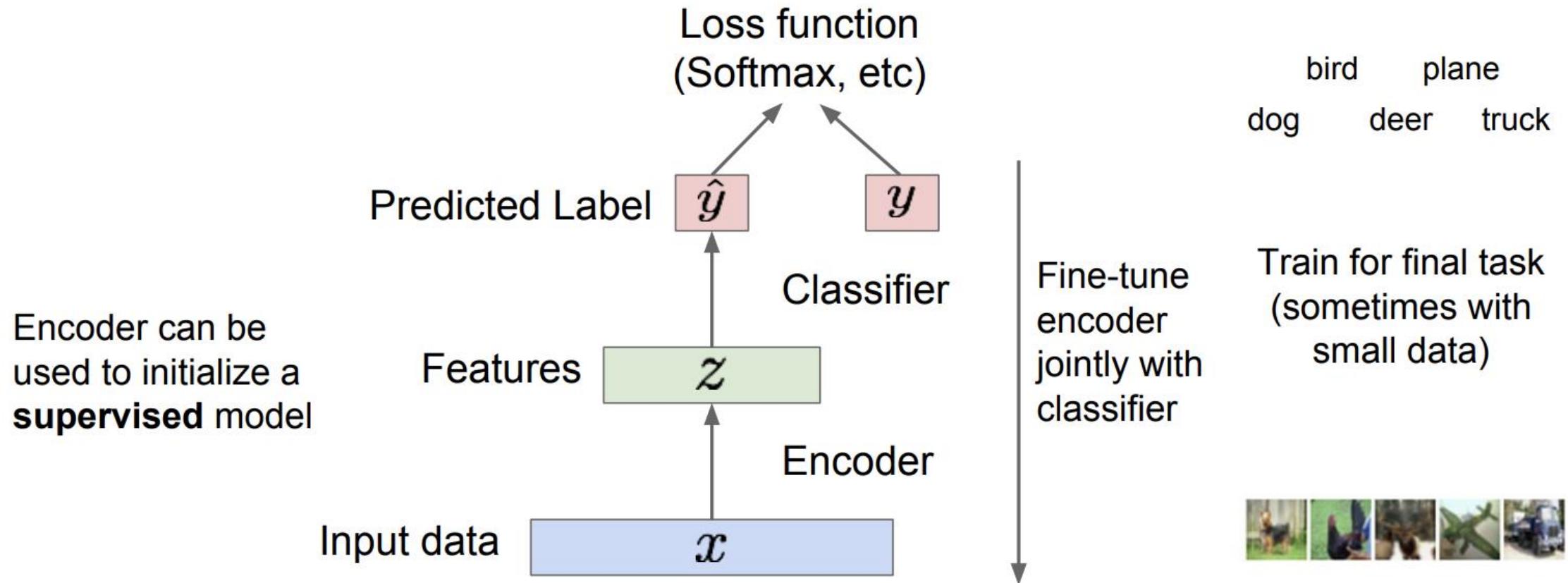
Features

Input data

Doesn't use labels!

L2 Loss function:

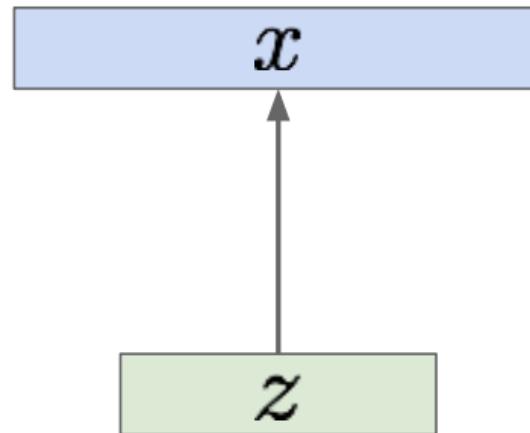




Probabilistic spin on autoencoders - will let us sample from the model to generate data!

Assume training data  $\{x^{(i)}\}_{i=1}^N$  is generated from underlying unobserved (latent) representation  $z$

Sample from  
true conditional  
 $p_{\theta^*}(x | z^{(i)})$



**Intuition (remember from autoencoders!):**  
 $x$  is an image,  $z$  is latent factors used to generate  $x$ : attributes, orientation, etc.

Sample from  
true prior  
 $p_{\theta^*}(z)$

Data likelihood:  $p_\theta(x) = \int p_\theta(z) p_\theta(x|z) dz$



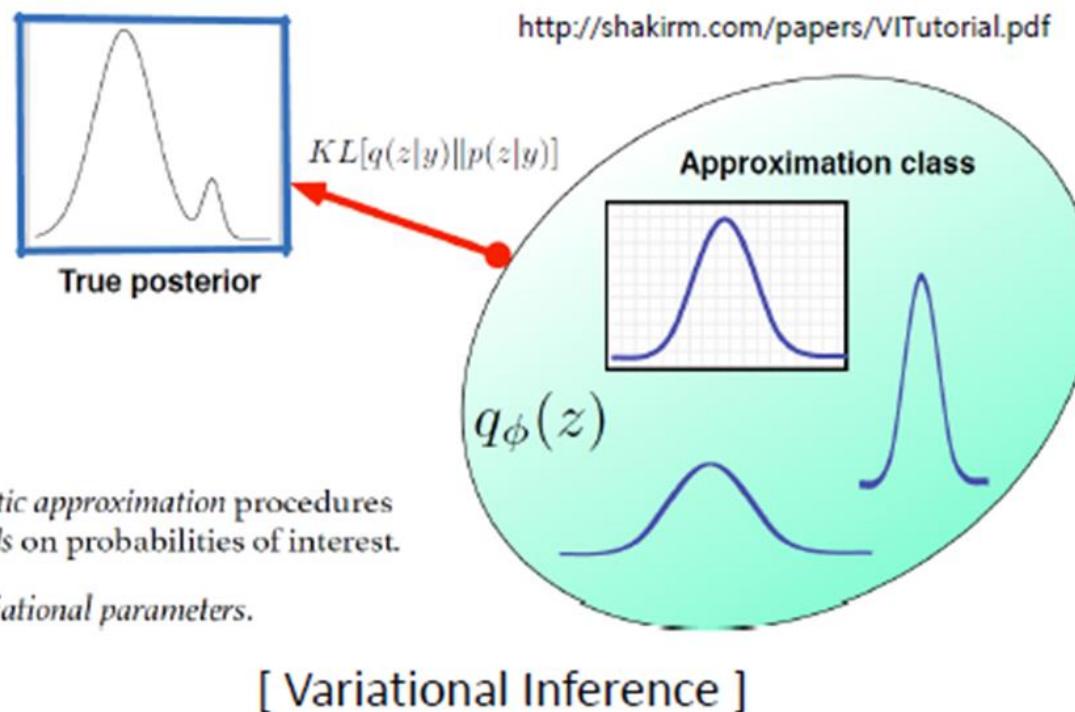
Intractible to compute  
 $p(x|z)$  for every  $z$ !

Posterior density also intractable:  $p_\theta(z|x) = p_\theta(x|z)p_\theta(z)/p_\theta(x)$

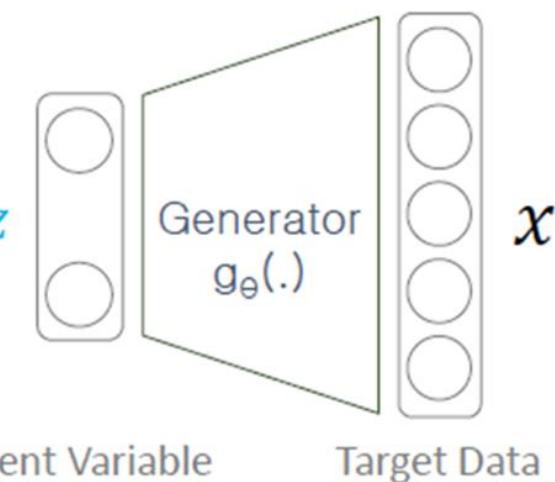


### ⟨Solution⟩

- Define additional encoder network  $q_\theta(z|x)$  that approximates  $p_\theta(z|x)$
- It derives a lower bound on the data likelihood that is tractable, which we can optimize



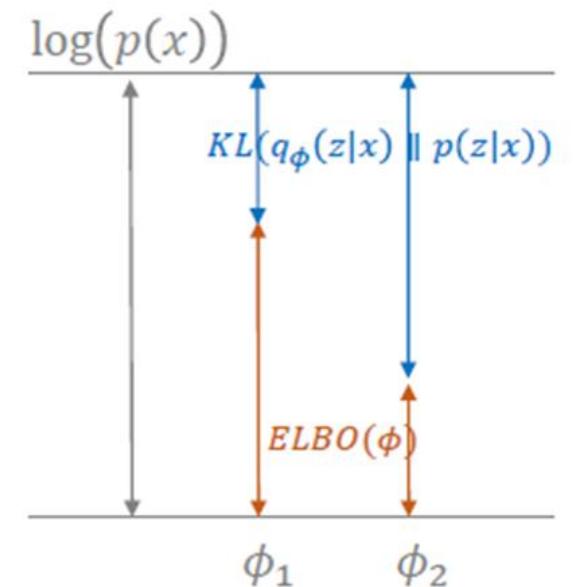
$$p(z|x) \approx q_\phi(z|x) \sim z$$



$$\begin{aligned}
 \log(p(x)) &= \int \log(p(x)) q_{\phi}(z|x) dz \quad \leftarrow \int q_{\phi}(z|x) dz = 1 \\
 &= \int \log\left(\frac{p(x,z)}{p(z|x)}\right) q_{\phi}(z|x) dz \quad \leftarrow p(x) = \frac{p(x,z)}{p(z|x)} \\
 &= \int \log\left(\frac{p(x,z)}{q_{\phi}(z|x)} \cdot \frac{q_{\phi}(z|x)}{p(z|x)}\right) q_{\phi}(z|x) dz \\
 &= \int \log\left(\frac{p(x,z)}{q_{\phi}(z|x)}\right) q_{\phi}(z|x) dz + \int \log\left(\frac{q_{\phi}(z|x)}{p(z|x)}\right) q_{\phi}(z|x) dz
 \end{aligned}$$


---


$$\begin{array}{c}
 \text{ELBO}(\phi) \\
 \hline
 \text{KL}\left(q_{\phi}(z|x) \parallel p(z|x)\right)
 \end{array}$$



$$\arg \min_{\phi, \theta} \sum_i -\mathbb{E}_{q_\phi(z|x_i)} [\log(p(x_i|g_\theta(z)))] + KL(q_\phi(z|x_i) || p(z))$$

$L_i(\phi, \theta, x_i)$

원 데이터에 대한 likelihood

$$L_i(\phi, \theta, x_i) = -\mathbb{E}_{q_\phi(z|x_i)} [\log(p(x_i|g_\theta(z)))] + KL(q_\phi(z|x_i) || p(z))$$

### Reconstruction Error

- 현재 샘플링 용 함수에 대한 negative log likelihood
- $x_i$ 에 대한 복원 오차 (AutoEncoder 관점)

Variational inference를 위한 approximation class 중 선택

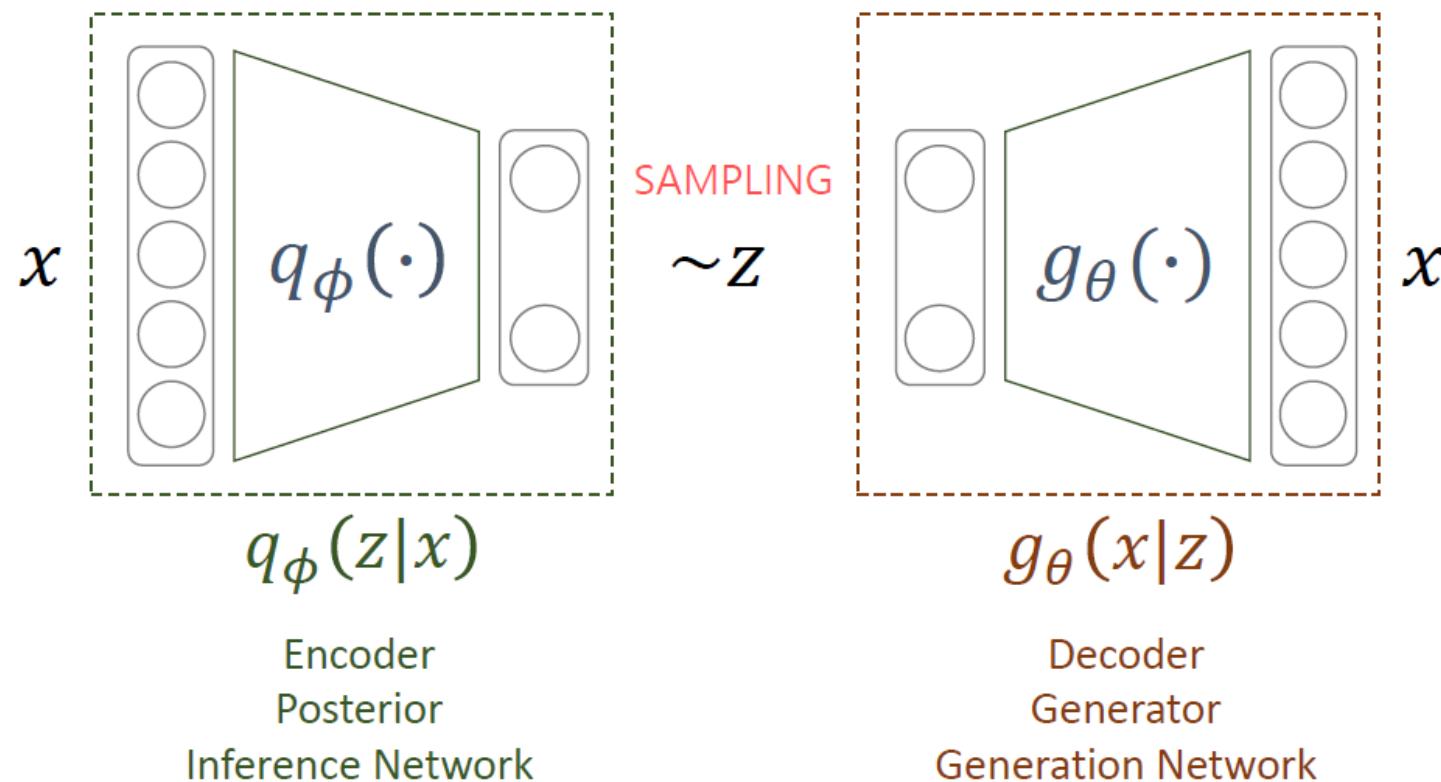
다루기 쉬운 확률 분포 중 선택

### Regularization

- 현재 샘플링 용 함수에 대한 추가 조건
- 샘플링의 용의성/생성 데이터에 대한 통제성을 위한 조건을 prior에 부여하고 이와 유사해야 한다는 조건을 부여

$$\arg \min_{\phi, \theta} \sum_i -\mathbb{E}_{q_\phi(z|x_i)} [\log(p(x_i|g_\theta(z)))] + KL(q_\phi(z|x_i) || p(z))$$

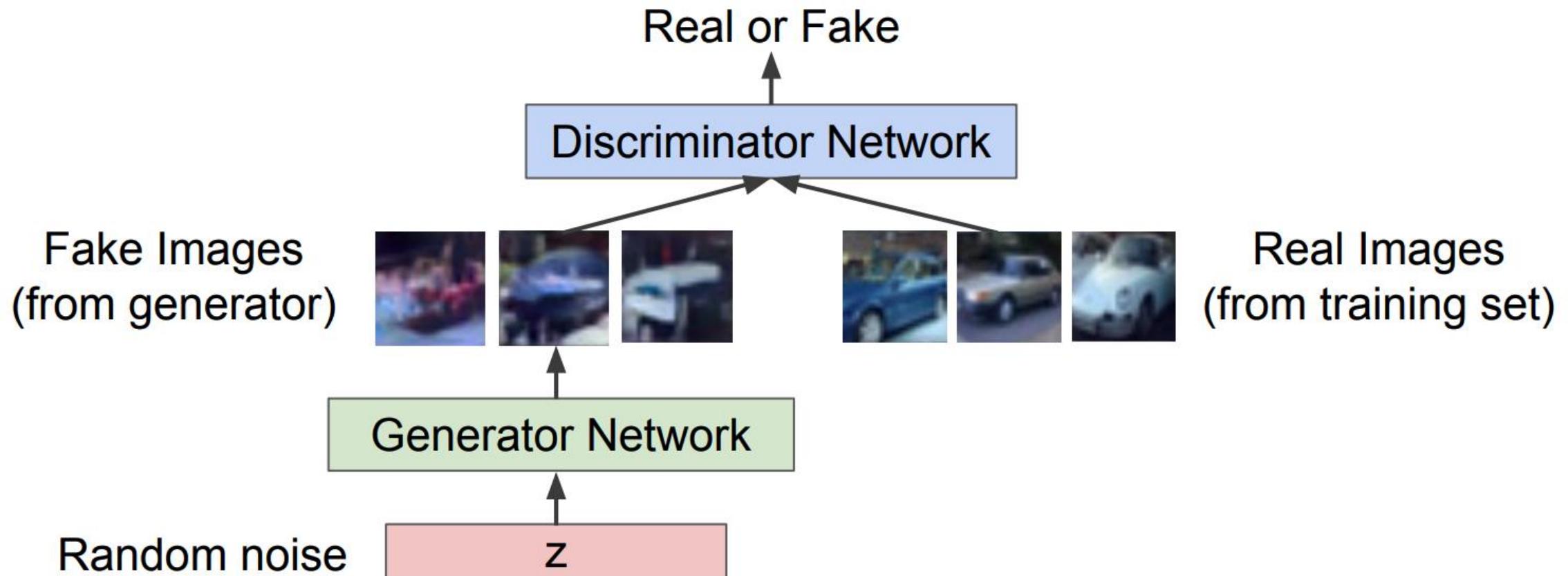
$L_i(\phi, \theta, x_i)$



The mathematical basis of VAEs actually has relatively little to do with classical autoencoders

# Generative Adversarial Network

---



## Train jointly in **minimax game**

Minimax objective function:

$$\min_{\theta_g} \max_{\theta_d} \left[ \mathbb{E}_{x \sim p_{data}} \log \underbrace{D_{\theta_d}(x)}_{\text{Discriminator output for real data } x} + \mathbb{E}_{z \sim p(z)} \log(1 - \underbrace{D_{\theta_d}(G_{\theta_g}(z))}_{\text{Discriminator output for generated fake data } G(z)}) \right]$$

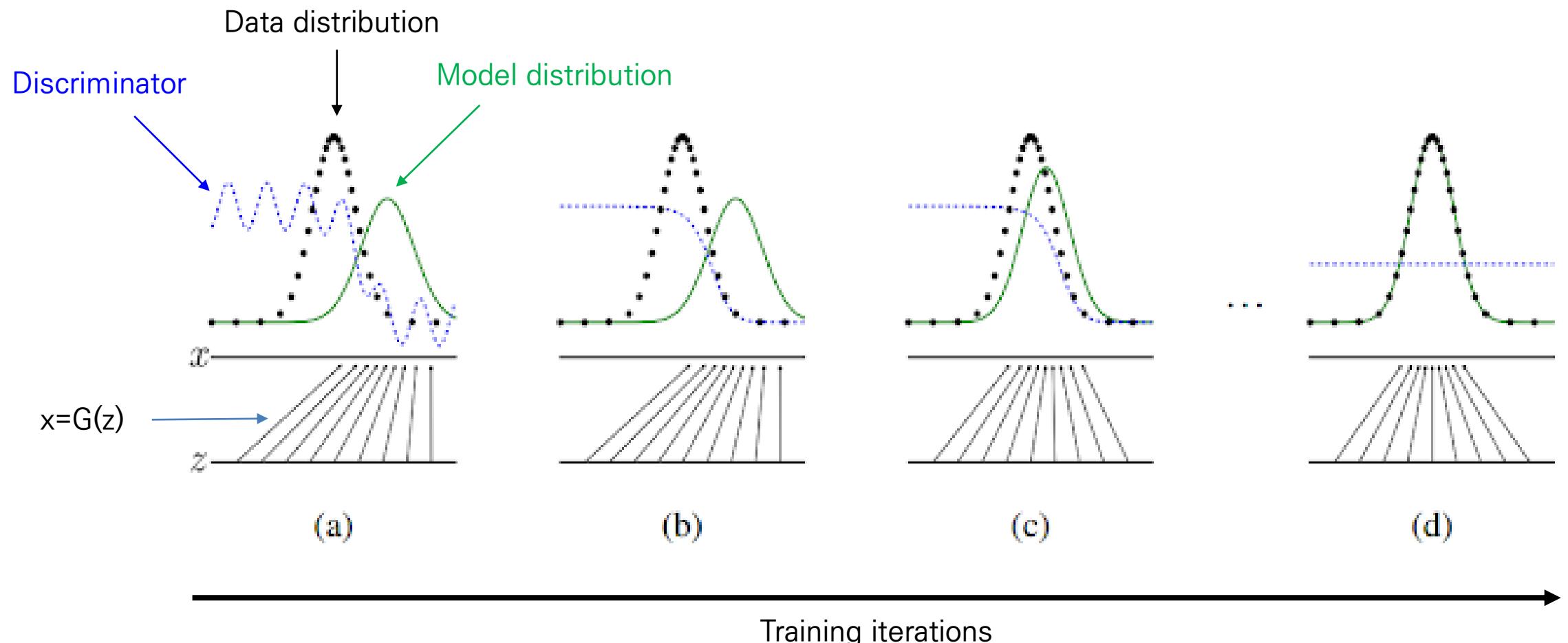
Discriminate wants to maximize objective

- $D(x) \rightarrow 1$  (real)
- $D(G(z)) \rightarrow 0$  (fake)

Generate wants to minimize objective

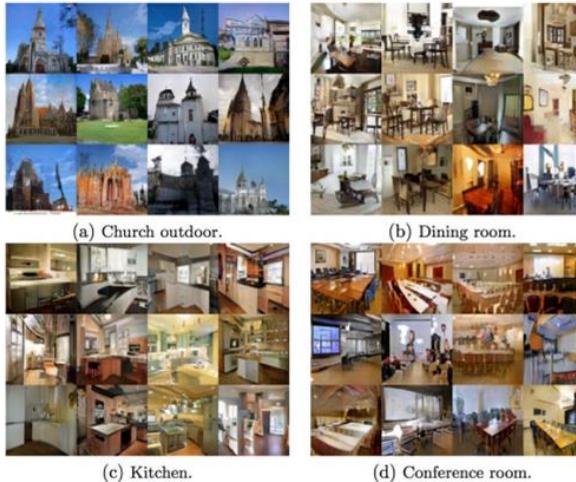
- $D(G(z)) \rightarrow 1$
- Fool discriminator (fake  $\rightarrow$  real)

$$\min_G \max_D V(D, G) = \mathbb{E}_{x \sim p_{data}(x)}[\log D(x)] + \mathbb{E}_{z \sim p_x(z)}[\log(1 - D(G(z)))]$$



## 2017: Year of the GAN

Better training and generation

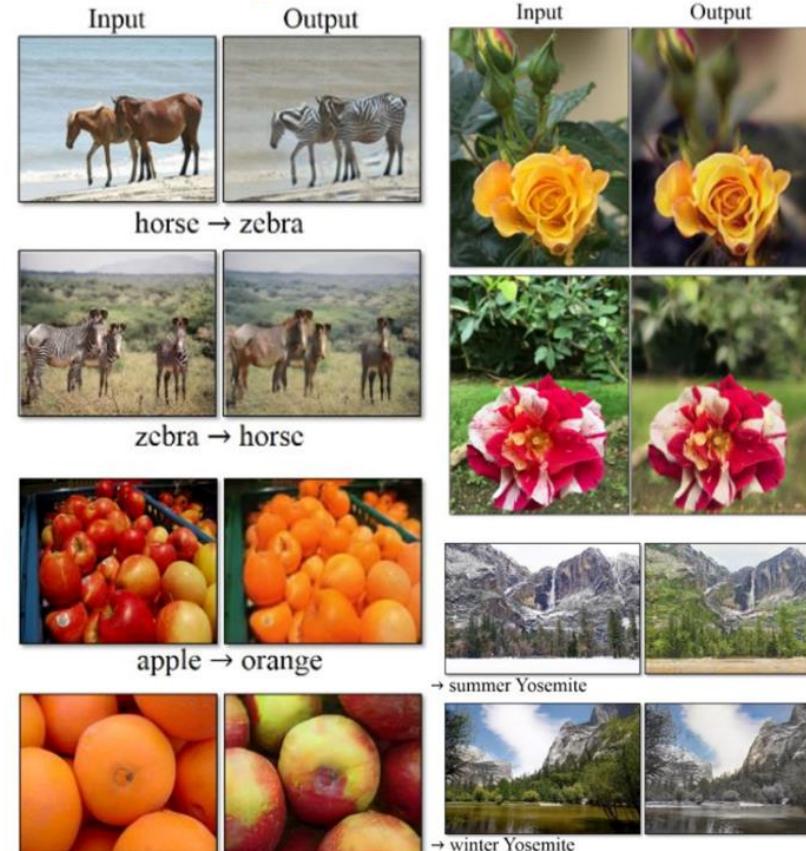


LSGAN. Mao et al. 2017.



BEGAN. Bertholet et al. 2017.

Source->Target domain transfer



CycleGAN. Zhu et al. 2017.

Text -> Image Synthesis

this small bird has a pink breast and crown, and black primaries and secondaries.

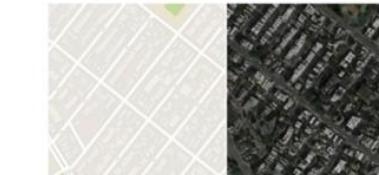


this magnificent fellow is almost all black with a red crest, and white cheek patch.



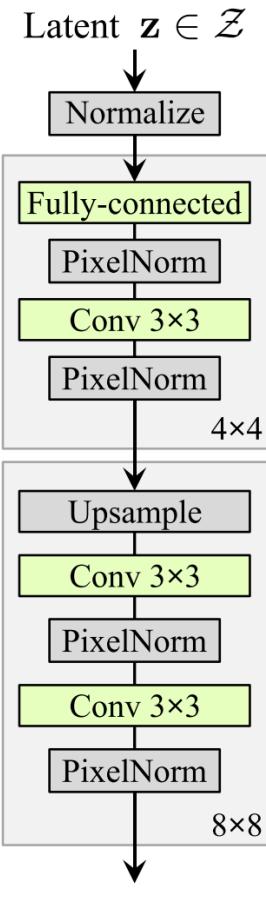
Reed et al. 2017.

Many GAN applications

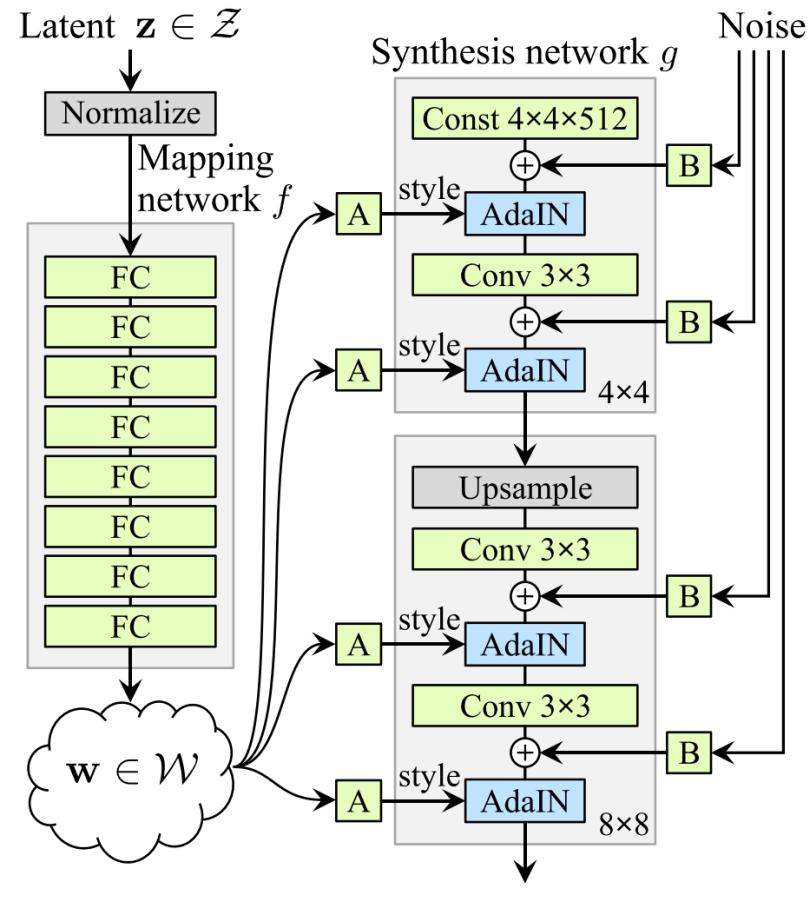


Pix2pix. Isola 2017. Many examples at <https://phillipi.github.io/pix2pix/>

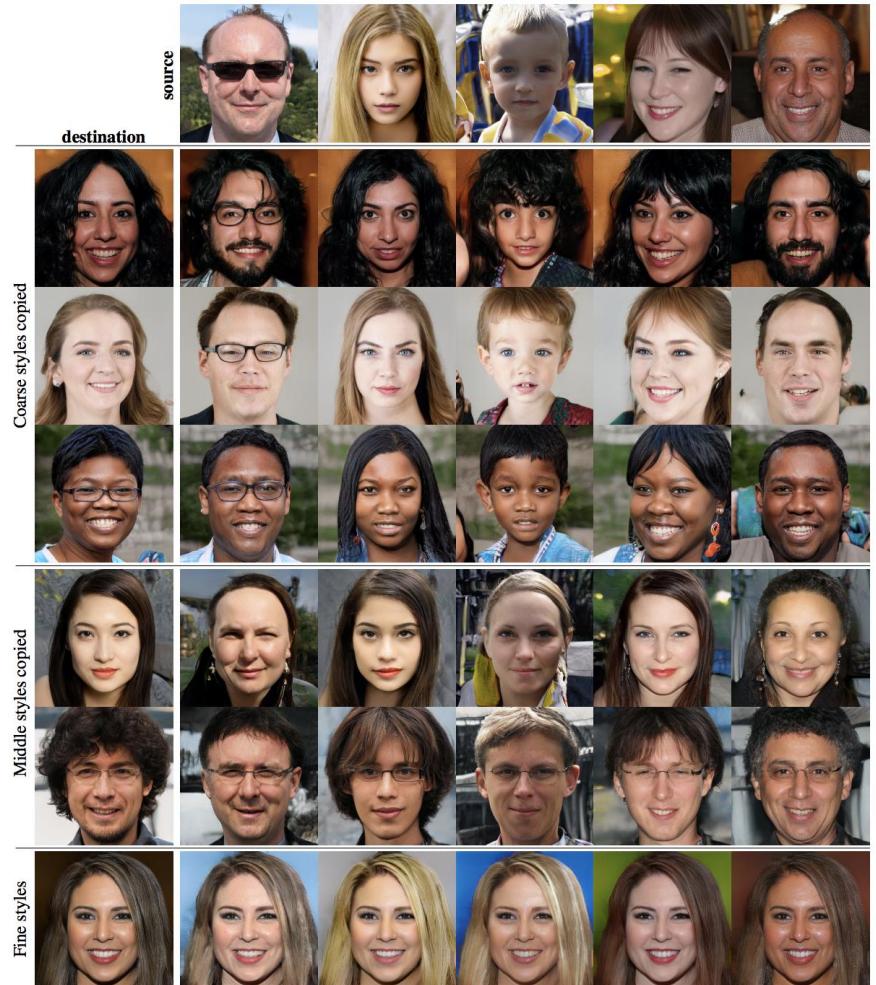
# Various GANs and Its applications: Style GAN (2019)



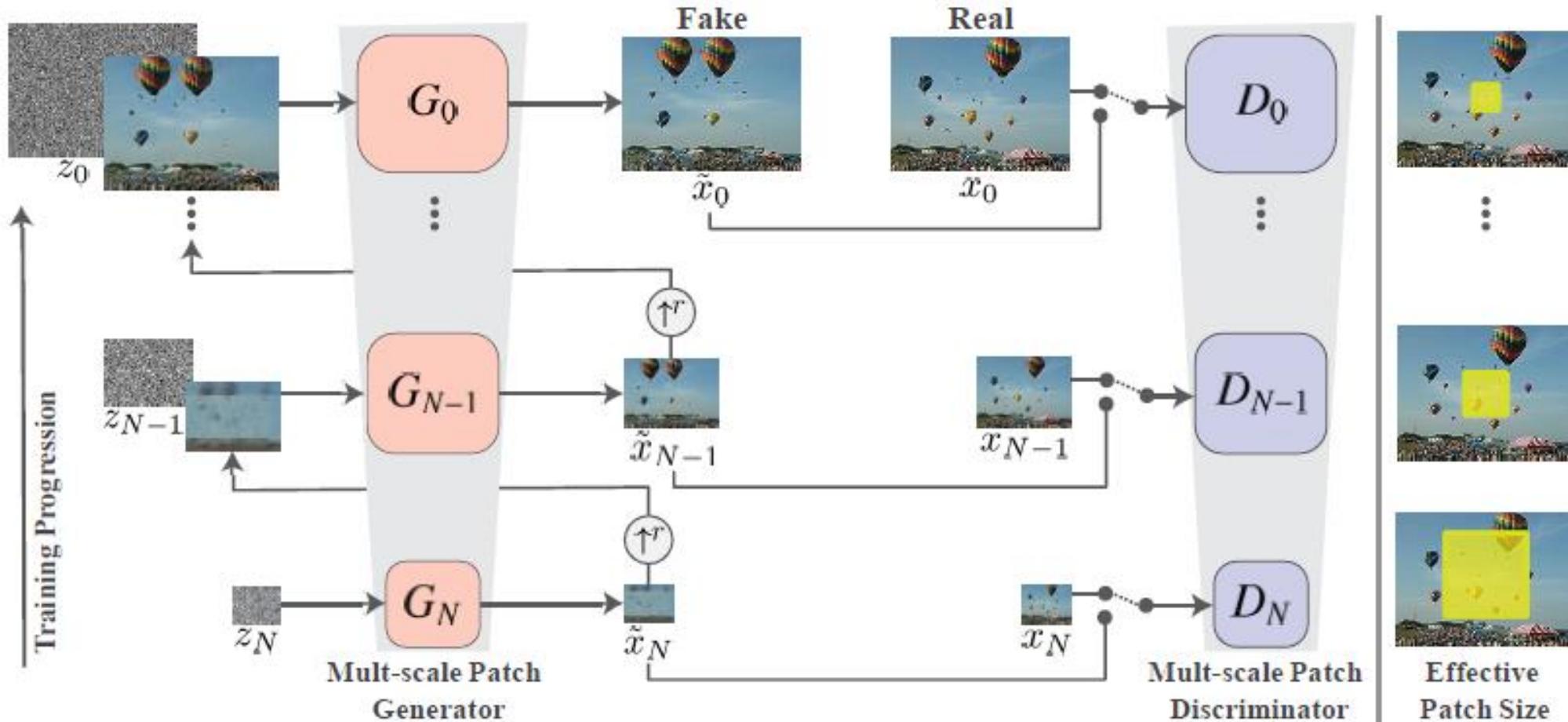
(a) Traditional



(b) Style-based generator

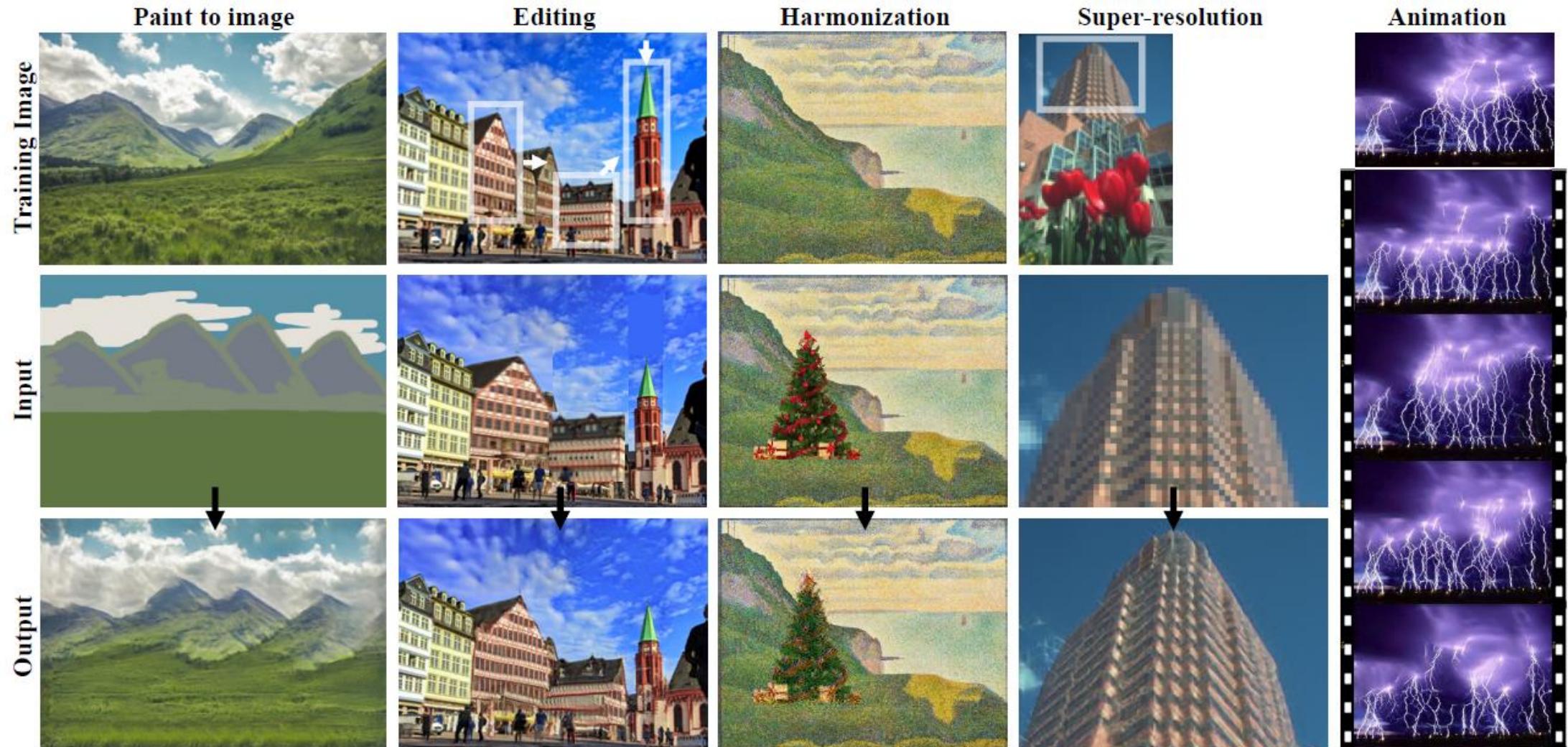


## SinGAN: Learning a Generative Model from a Single Natural Image

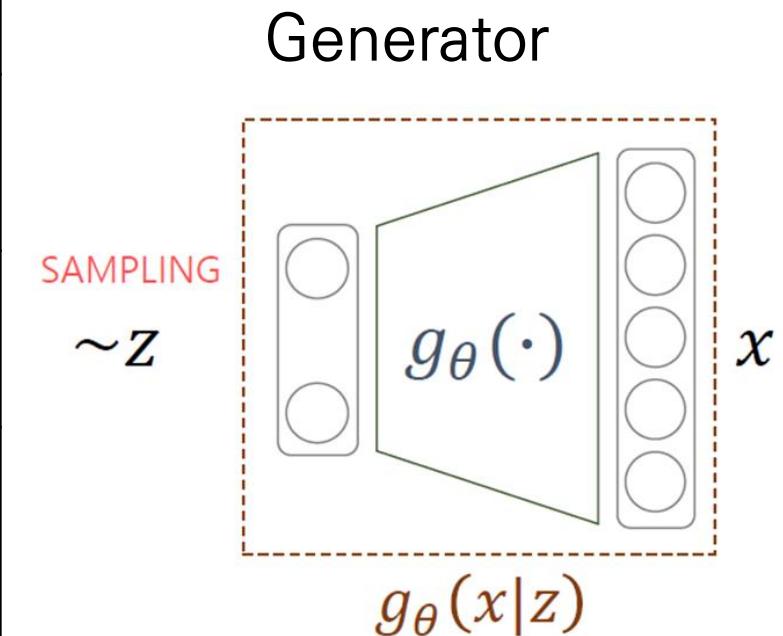


$$\min_{G_n} \max_{D_n} \mathcal{L}_{\text{adv}}(G_n, D_n) + \alpha \mathcal{L}_{\text{rec}}(G_n).$$

# Various GANs and Its applications: SinGAN (2019)



	VAE	GAN
모델링	<ul style="list-style-type: none"> <li>Explicit density</li> <li>원론적인 접근 방식</li> </ul>	<ul style="list-style-type: none"> <li>Implicit density</li> <li>게임 이론적 접근 (2-players game)</li> </ul>
학습 안정성	<ul style="list-style-type: none"> <li>Posterior collapse</li> <li>KL annealing 등 개선 기법</li> </ul>	<ul style="list-style-type: none"> <li>Mode collapse</li> <li>Tricky 학습법, 최근 많이 개선됨</li> </ul>
성능	<ul style="list-style-type: none"> <li>GAN과 비교해 불만족스런 성능</li> <li>Blur &amp; low-quality sample</li> </ul>	<ul style="list-style-type: none"> <li>State-of-the art 성능</li> <li>선명한 고화질 영상도 생성</li> </ul>
응용 연구	<ul style="list-style-type: none"> <li>(z x)에 대한 inference 제공 → feature representation</li> <li>Flexible approximation → Adversarial AE 등</li> <li>Conditional VAE</li> </ul>	<ul style="list-style-type: none"> <li>p(x) 및 p(z x) Inference 불가</li> <li>WGAN, Sphere GAN, LSGAN 등 안정적 학습을 위한 다양한 연구</li> <li>여러 분야/다양한 문제에 적용</li> <li>Continuous data에만 적용 가능 → 최근 latent vector로 우회적 적용</li> </ul>



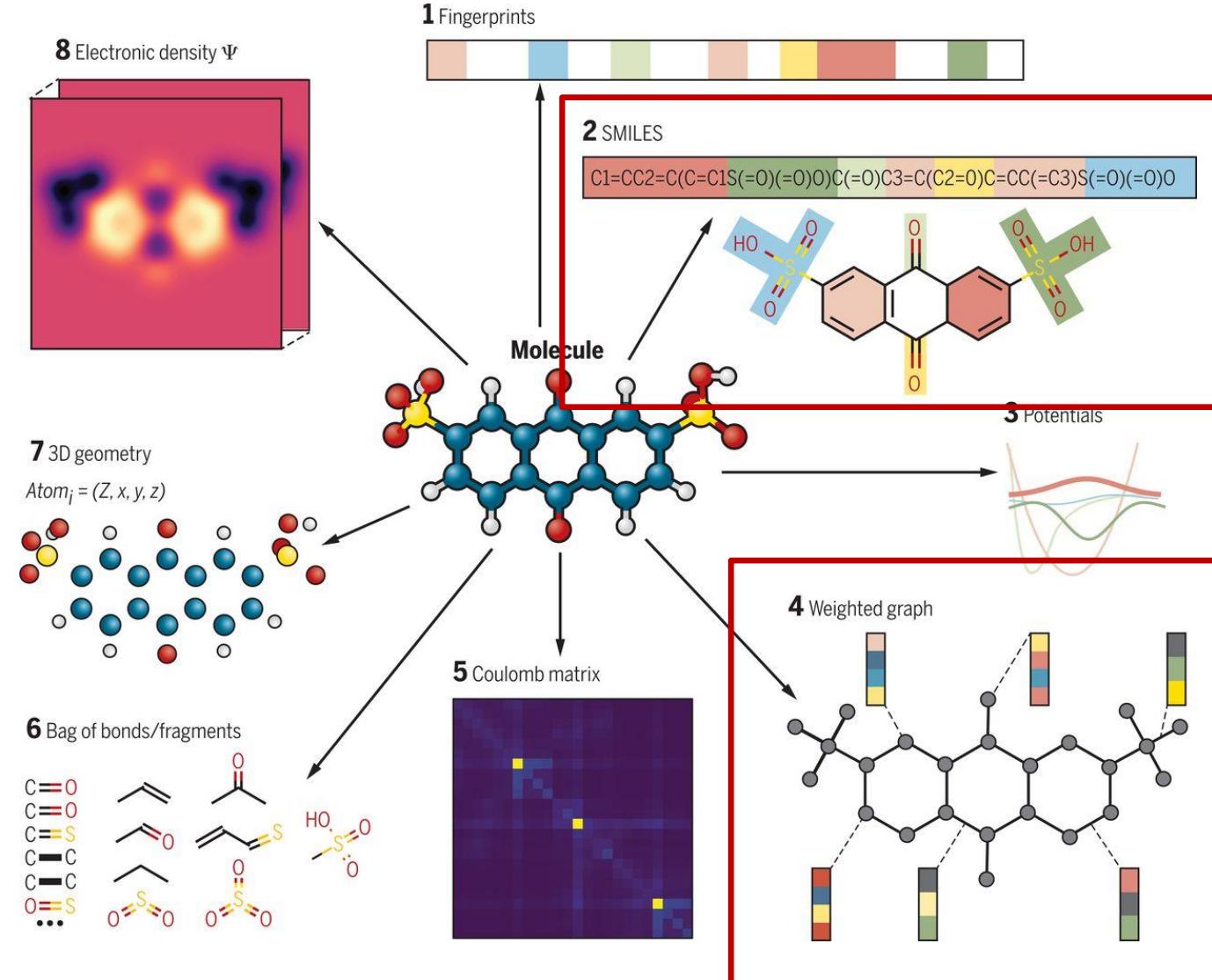
# VAE and GAN in Drug discovery

---

Goal : ‘**타겟 기능**’을 가진 ‘**새로운**’ ‘**최적**’의 분자 구조식 생성

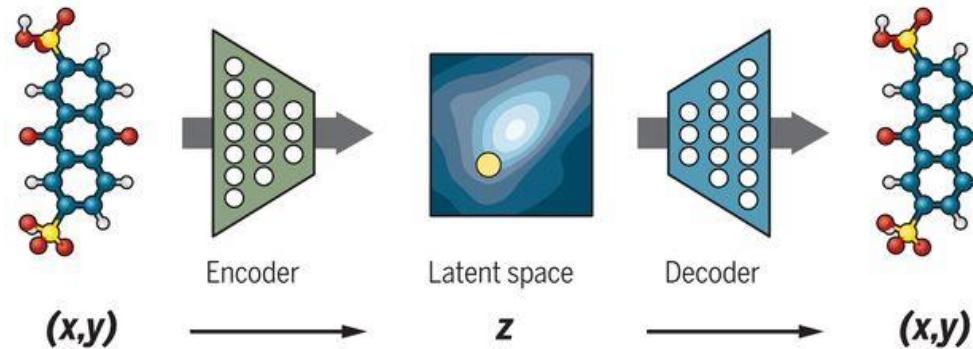
- 1) 특정 물질에 결합해 기능을 억제/활성화 → 타겟 기능 달성
- 2) 기존 물질과 다른 신규 분자 구조식 → 물질 특허 회피
- 3) 물질 최적화 → 체내 독성 최소화 등 생체 적합성

# Molecule representations

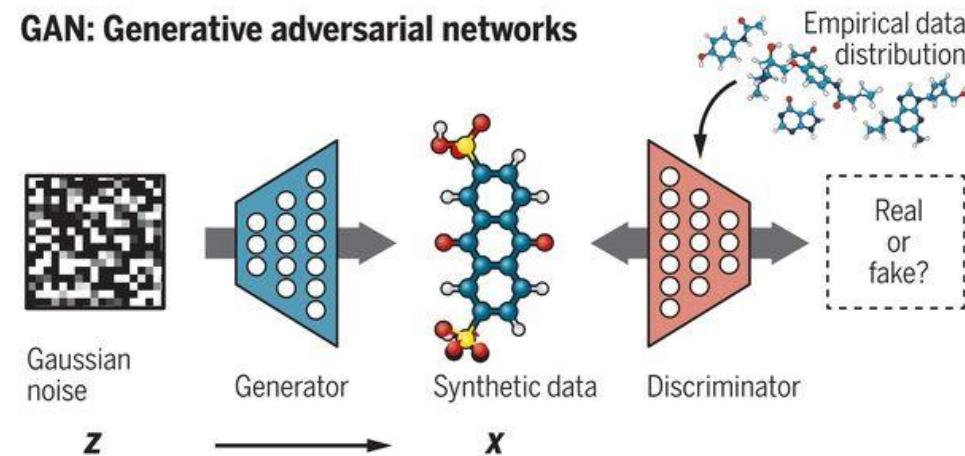


출처: Sanchez-Lengeling et al, "Inverse molecular design using machine learning: Generative models for matter engineering." Science 361.6400 (2018): 360–365.

## VAE: Variational autoencoders

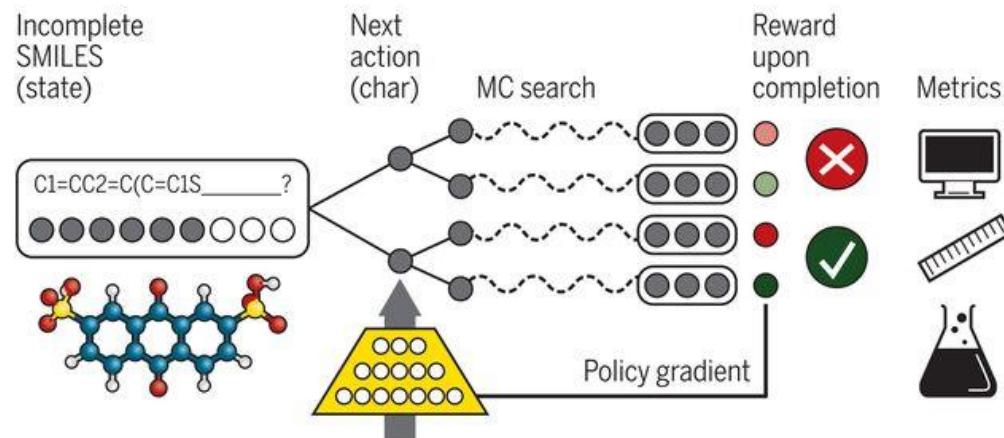


## GAN: Generative adversarial networks

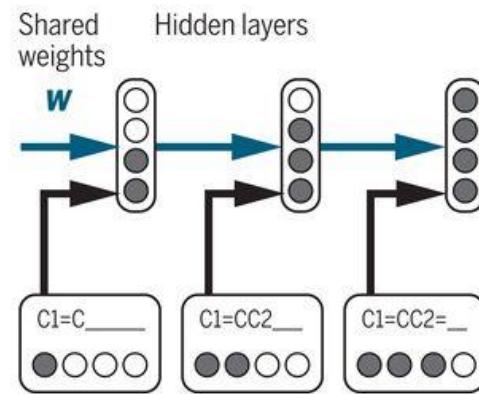


## RL: Reinforcement learning

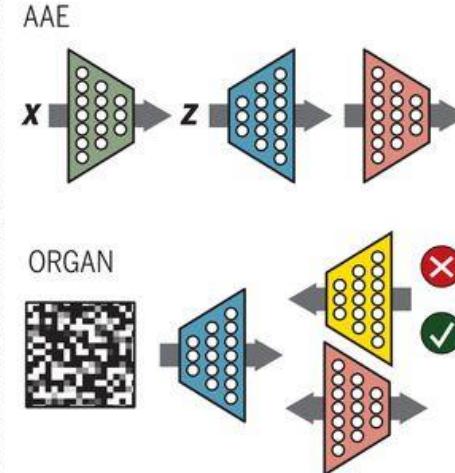
Policy gradient with Monte Carlo tree search (MCTS)



## RNN: Recurrent neural network



## Hybrid approaches



# Continuous Representation of Molecules using VAE (1/3)

Cite This: ACS Cent. Sci. 2018, 4, 268–276

## Automatic Chemical Design Using a Data-Driven Continuous Representation of Molecules

Rafael Gómez-Bombarelli,<sup>†,‡,§,¶</sup> Jennifer N. Wei,<sup>‡,§,¶</sup> David Duvenaud,<sup>¶,||</sup> José Miguel Hernández-Lobato,<sup>§,¶</sup> Benjamín Sánchez-Lengeling,<sup>‡</sup> Dennis Sheberla,<sup>‡,¶</sup> Jorge Aguilera-Iparraguirre,<sup>†</sup> Timothy D. Hirzel,<sup>†</sup> Ryan P. Adams,<sup>¶,||</sup> and Alán Aspuru-Guzik<sup>\*‡,§,¶</sup>

<sup>†</sup>Kyulux North America Inc., 10 Post Office Square, Suite 800, Boston, Massachusetts 02109, United States

<sup>‡</sup>Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138, United States

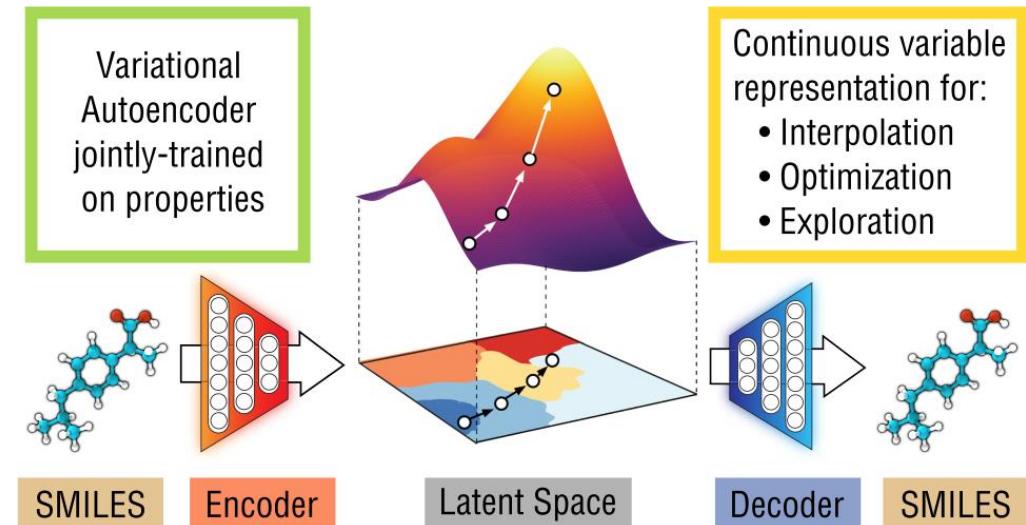
<sup>¶</sup>Department of Computer Science, University of Toronto, 6 King's College Road, Toronto, Ontario M5S 3H5, Canada

<sup>§</sup>Department of Engineering, University of Cambridge, Trumpington Street, Cambridge CB2 1PZ, U.K.

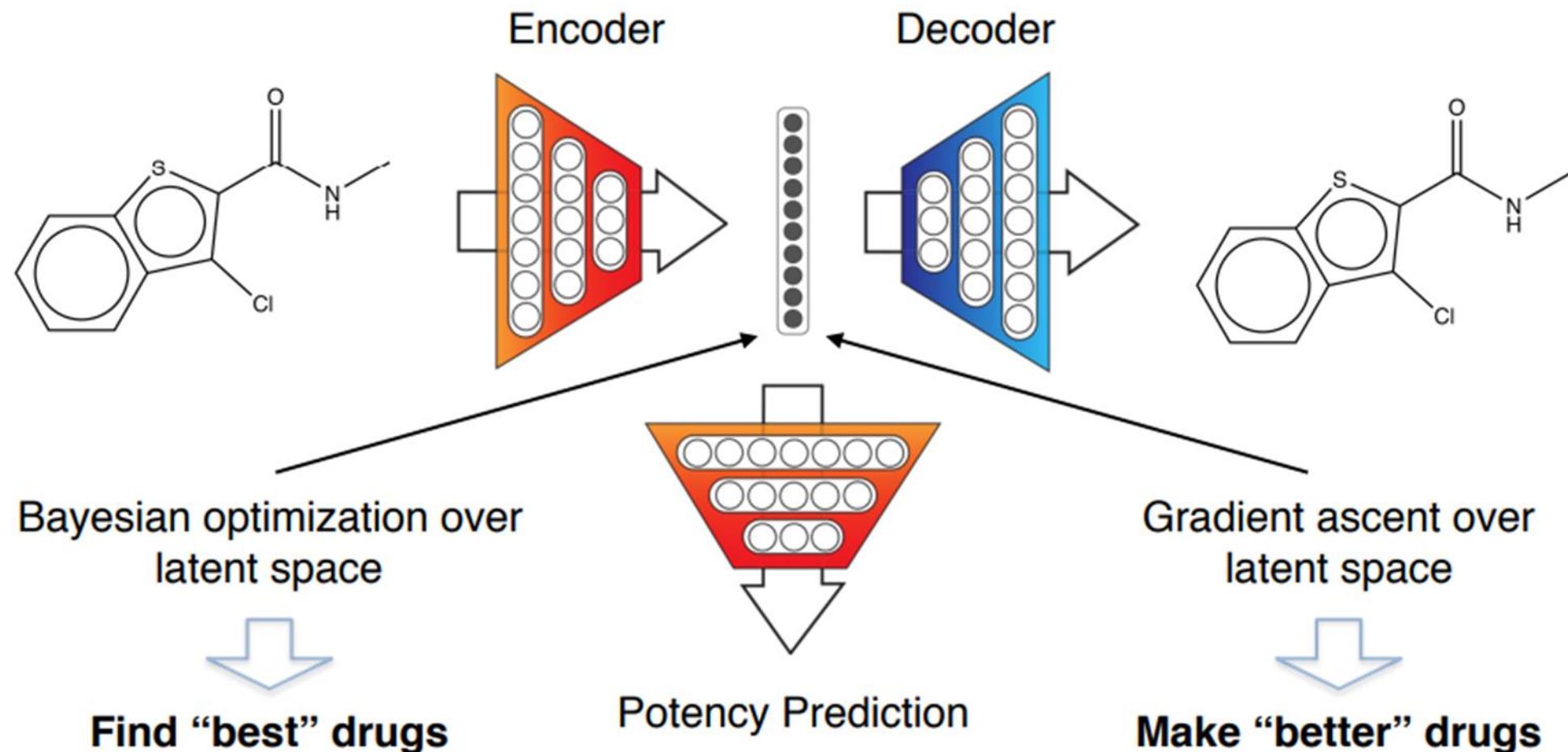
<sup>||</sup>Google Brain, Mountain View, California, United States

<sup>\*Princeton University, Princeton, New Jersey, United States</sup>

<sup>Biologically-Inspired Solar Energy Program, Canadian Institute for Advanced Research (CIFAR), Toronto, Ontario M5S 1M1, Canada</sup>



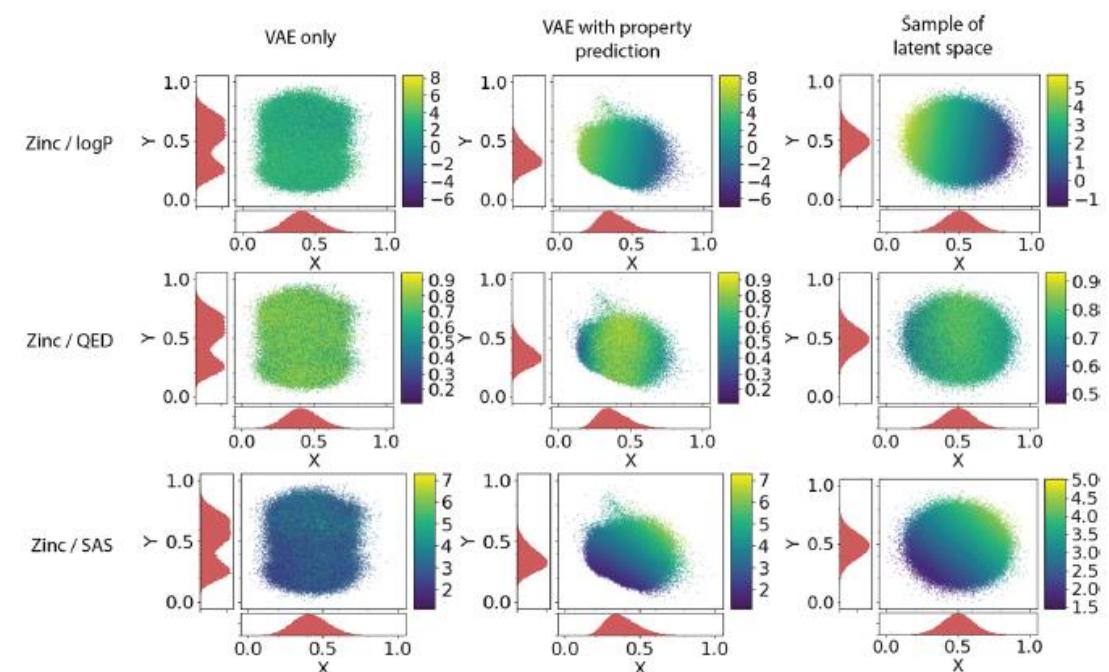
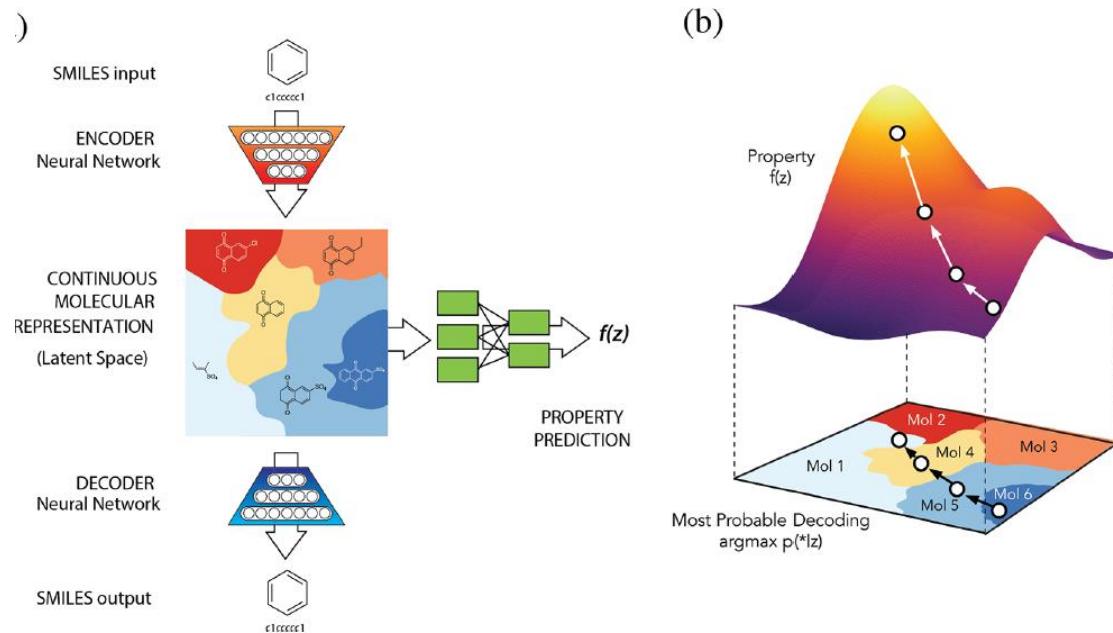
# Continuous Representation of Molecules using VAE (1/3)



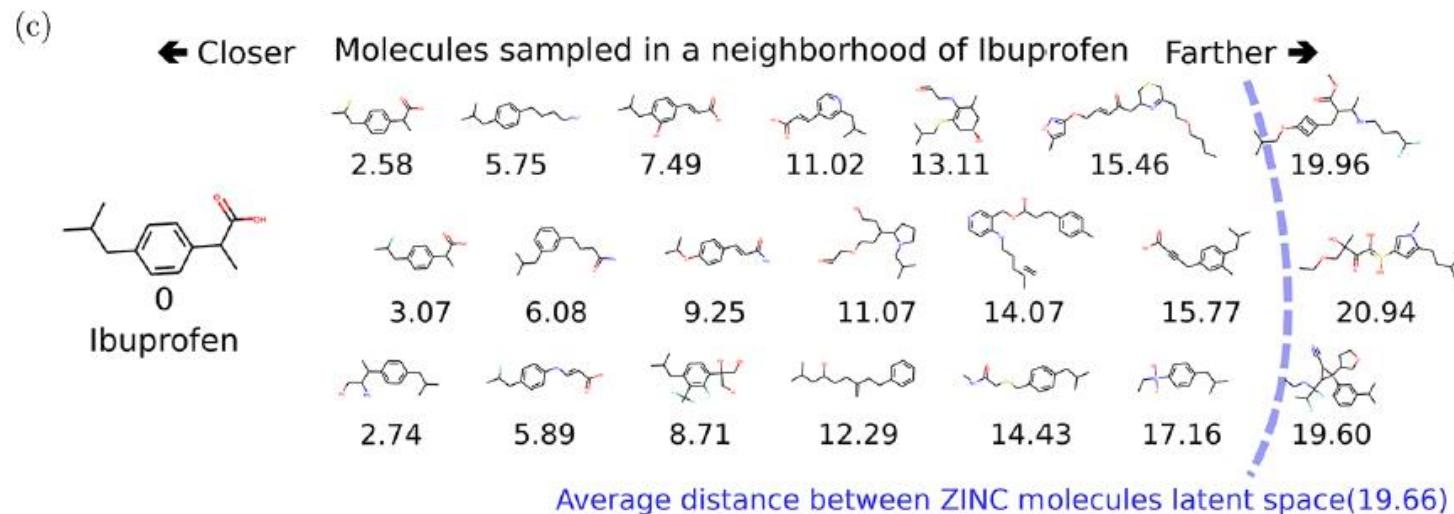
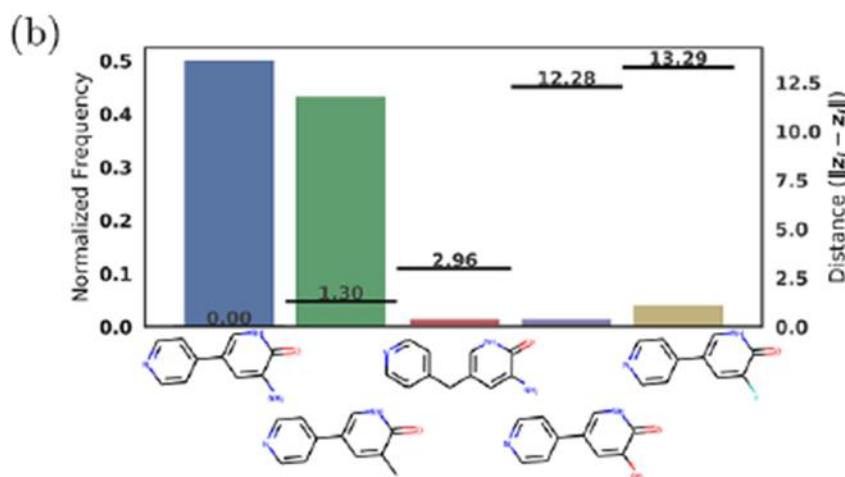
# Continuous Representation of Molecules using VAE (2/3)

Table 1. Comparison of Molecule Generation Results to Original Datasets

source <sup>a</sup>	data set <sup>b</sup>	samples <sup>c</sup>	logP <sup>d</sup>	SAS <sup>e</sup>	QED <sup>f</sup>	% in ZINC <sup>g</sup>	% in emol <sup>h</sup>
Data	ZINC	249k	2.46 (1.43)	3.05 (0.83)	0.73 (0.14)	100	12.9
GA	ZINC	5303	2.84 (1.86)	3.80 (1.01)	0.57 (0.20)	6.5	4.8
VAE	ZINC	8728	2.67 (1.46)	3.18 (0.86)	0.70 (0.14)	5.8	7.0
Data	QM9	134k	0.30 (1.00)	4.25 (0.94)	0.48 (0.07)	0.0	8.6
GA	QM9	5470	0.96 (1.53)	4.47 (1.01)	0.53 (0.13)	0.018	3.8
VAE	QM9	2839	0.30 (0.97)	4.34 (0.98)	0.47 (0.08)	0.0	8.9



# Continuous Representation of Molecules using VAE (3/3)





Cite This: Mol. Pharmaceutics XXXX, XXX, XXX-XXX

pubs.acs.org/molecularpharmaceutics



Article

## Entangled Conditional Adversarial Autoencoder for de Novo Drug Discovery

Daniil Polykovskiy,<sup>\*,†,‡,§,||</sup> Alexander Zhebrak,<sup>†,||</sup> Dmitry Vetrov,<sup>‡,||</sup> Yan Ivanenkov,<sup>†,‡,||,¶</sup> Vladimir Aladinskiy,<sup>†,||,¶</sup> Polina Mamoshina,<sup>†,||</sup> Marine Bozdaganyan,<sup>†,||</sup> Alexander Aliper,<sup>†,||</sup> Alex Zhavoronkov,<sup>†,||</sup> and Artur Kadurin<sup>†,§,||</sup>

<sup>†</sup>Insilico Medicine, Rockville, Maryland 20850, United States

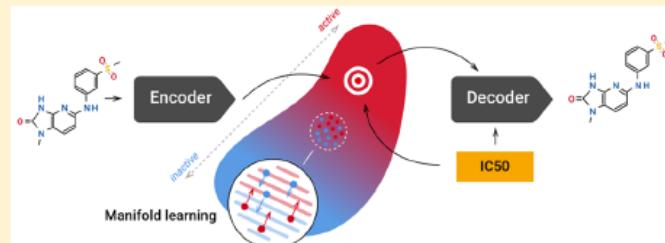
<sup>‡</sup>National Research University Higher School of Economics, Moscow 101000, Russia

<sup>§</sup>Insilico Taiwan, Taipei City 115, Taiwan R.O.C.

<sup>¶</sup>Institute of Biochemistry and Genetics Russian Academy of Science, Ufa, 450054, Russia

<sup>||</sup>Moscow Institute of Physics and Technology (State University), Moscow Region, 141700, Russia

**ABSTRACT:** Modern computational approaches and machine learning techniques accelerate the invention of new drugs. Generative models can discover novel molecular structures within hours, while conventional drug discovery pipelines require months of work. In this article, we propose a new generative architecture, entangled conditional adversarial autoencoder, that generates molecular structures based on various properties, such as activity against a specific protein, solubility, or ease of synthesis. We apply the proposed model to generate a novel inhibitor of Janus kinase 3, implicated in rheumatoid arthritis, psoriasis, and vitiligo. The discovered molecule was tested in vitro and showed good activity and selectivity.



**KEYWORDS:** adversarial autoencoders, disentanglement, conditional generation, Janus kinase

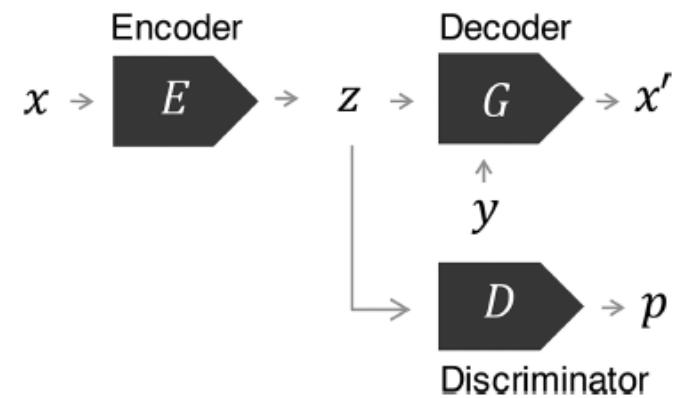


Figure 2. Supervised adversarial autoencoder (SAAE) model.

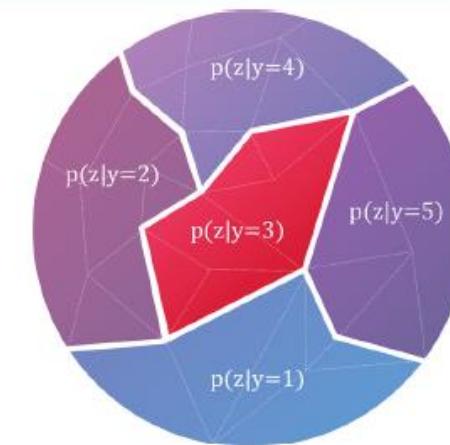
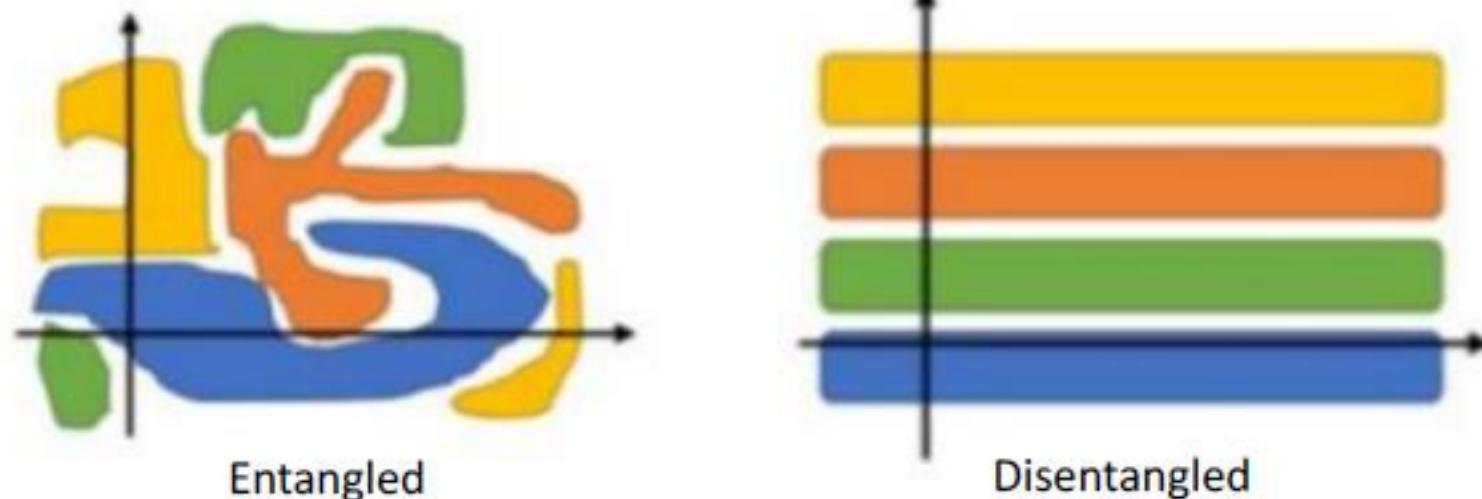


Figure 3. Motivation for the disentanglement. The marginal distribution of latent codes is  $p(z)$ , but conditional distributions differ from the marginals.

- Disentanglement는 적합 X
- 오히려 latent representation에 대한 structure에 제약을 부여
- Latent feature의 해석가능성에 부정적 효과
- 예) ImageNet → object class와 color간의 관계는 완전히 다름.



**Table 1. Performance of Models Trained with Different Disentanglement Techniques Using Fingerprint Vectors as the Condition<sup>a</sup>**

disentanglement	Tanimoto (%)	Hamming (%)	exact (%)	remaining MI (%)
no	80.0	10.49	4.4	2.75
predictive	86.2	7.13	11.4	0.64
joint	88.7	5.78	17.4	1.56
combined	91.8	4.18	27.8	0.32
entangled, no predictive	93.5	3.31	40.9	2.51
entangled	93.6	3.28	41.3	1.30

<sup>a</sup>Notice the large gap between the model with no disentanglement (corresponding to ref 18) and other models.

**Table 2. Performance for Continuous Properties<sup>a</sup>**

disentanglement	logP, <i>r</i>	SA, <i>r</i>
no	$0.088 \pm 0.005$	$0.004 \pm 0.006$
predictive	$0.661 \pm 0.005$	$0.060 \pm 0.01$
joint	$0.432 \pm 0.006$	$0.034 \pm 0.01$
combined	$0.654 \pm 0.004$	$0.113 \pm 0.003$
entangled	$0.613 \pm 0.004$	$0.431 \pm 0.005$

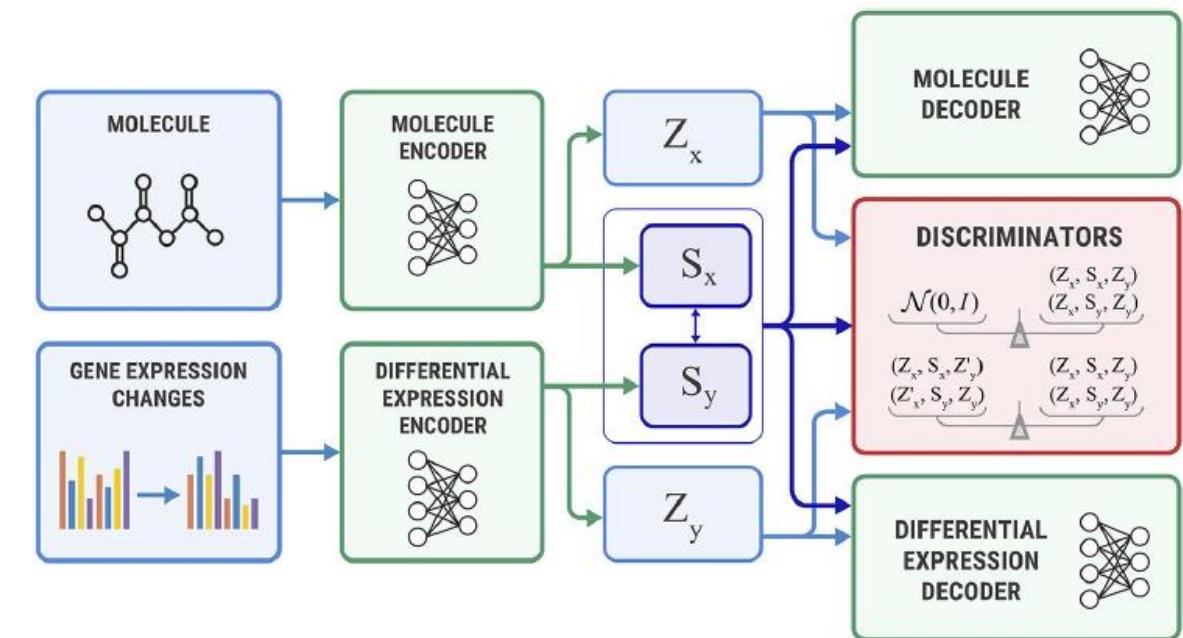
<sup>a</sup>We report the Pearson correlation *r* between the actual value for the generated molecules and the requested one.

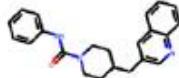
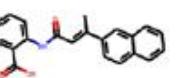
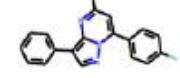
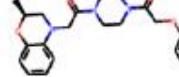
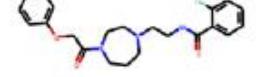
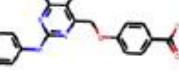
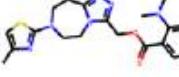
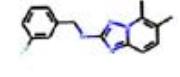


## Molecular Generation for Desired Transcriptome Changes With Adversarial Autoencoders

Rim Shayakhmetov<sup>1†</sup>, Maksim Kuznetsov<sup>1†</sup>, Alexander Zhebrak<sup>1</sup>, Artur Kadurin<sup>1</sup>, Sergey Nikolenko<sup>1,2</sup>, Alexander Aliper<sup>1</sup> and Daniil Polykovskiy<sup>1\*</sup>

<sup>1</sup> Insilico Medicine, Hong Kong, Hong Kong, <sup>2</sup> Neuromation OU, Tallinn, Estonia



gene	FAAH	ALOX15	TERT	SLC12A5	STAT1
target protein	Anandamide amidohydrolase	Arachidonate 15-lipoxygenase	Telomerase reverse transcriptase	Solute carrier family 12 member 5	Signal transducer and activator of transcription 1-alpha/beta
template					
generated					

**FIGURE 8 |** The examples of generated molecules conditioned on gene expression changes from a protein inhibitor; Real most similar inhibitors from ChEMBL are provided for comparison.

BRIEF COMMUNICATION

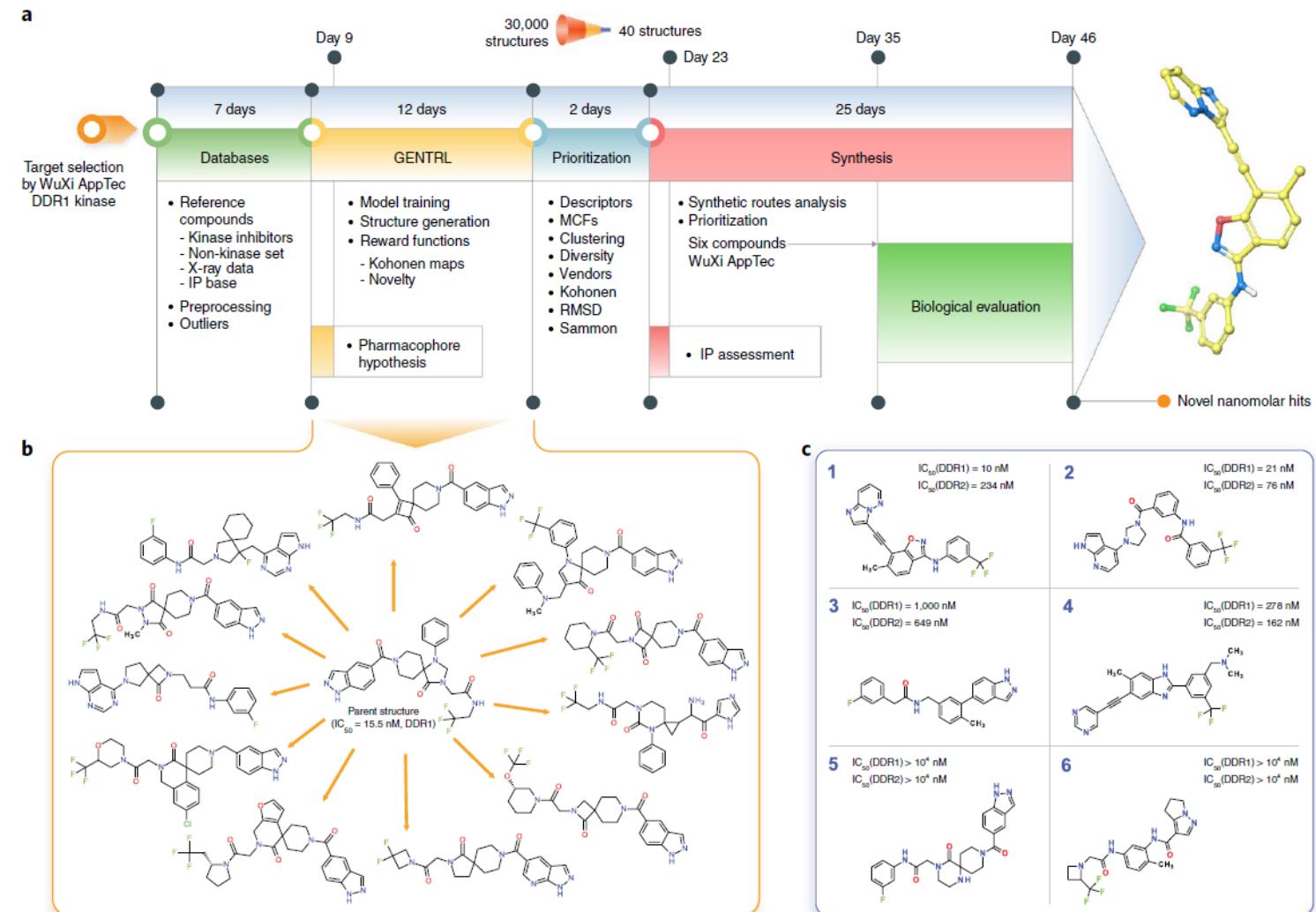
<https://doi.org/10.1038/s41587-019-0224-x>

nature  
biotechnology

# Deep learning enables rapid identification of potent DDR1 kinase inhibitors

Alex Zhavoronkov<sup>1\*</sup>, Yan A. Ivanenkov<sup>1</sup>, Alex Aliper<sup>1</sup>, Mark S. Veselov<sup>1</sup>, Vladimir A. Aladinskiy<sup>1</sup>, Anastasiya V. Aladinskaya<sup>1</sup>, Victor A. Terentiev<sup>1</sup>, Daniil A. Polykovskiy<sup>1</sup>, Maksim D. Kuznetsov<sup>1</sup>, Arip Asadulaev<sup>1</sup>, Yury Volkov<sup>1</sup>, Artem Zholus<sup>1</sup>, Rim R. Shayakhmetov<sup>1</sup>, Alexander Zhebrak<sup>1</sup>, Lidiya I. Minaeva<sup>1</sup>, Bogdan A. Zagribelnyy<sup>1</sup>, Lennart H. Lee<sup>1,2</sup>, Richard Soll<sup>2</sup>, David Madge<sup>2</sup>, Li Xing<sup>2</sup>, Tao Guo<sup>1,2</sup> and Alán Aspuru-Guzik<sup>3,4,5,6</sup>

# Deep learning enables rapid identification of potent DDR1 kinase inhibitors (2/5)



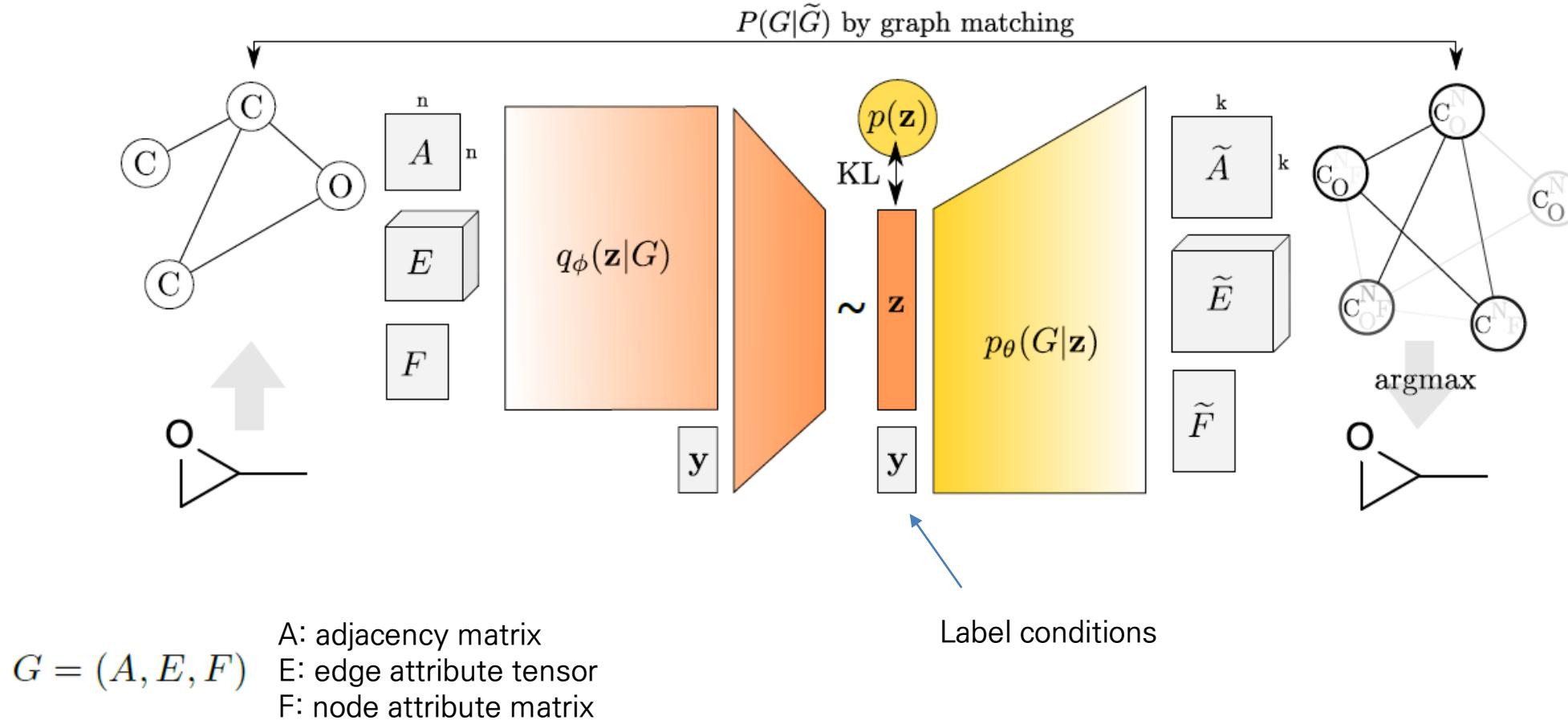
**Fig. 1 | GENTRL model design, workflow, and nanomolar hits. a,** The general workflow and timeline for the design of lead candidates using GENTRL. IP, intellectual property. **b,** Representative examples of generated structures compared to the parent DDR1 kinase inhibitor. **c,** Generated compounds with the highest inhibition activity against human DDR1 kinase.

---

## GraphVAE: Towards Generation of Small Graphs Using Variational Autoencoders

---

Martin Simonovsky<sup>1</sup> Nikos Komodakis<sup>1</sup>



## ⟨Reconstruction loss⟩

$$\begin{aligned}
 -\log p(G|\mathbf{z}) = & -\lambda_A \log p(A'|\mathbf{z}) - \lambda_F \log p(F|\mathbf{z}) - \\
 & - \lambda_E \log p(E|\mathbf{z})
 \end{aligned} \tag{3}$$

$$\begin{aligned}
 \log p(A'|\mathbf{z}) = & \\
 = & 1/k \sum_a A'_{a,a} \log \tilde{A}_{a,a} + (1 - A'_{a,a}) \log(1 - \tilde{A}_{a,a}) + \\
 + & 1/k(k-1) \sum_{a \neq b} A'_{a,b} \log \tilde{A}_{a,b} + (1 - A'_{a,b}) \log(1 - \tilde{A}_{a,b})
 \end{aligned}$$

$$\log p(F|\mathbf{z}) = 1/n \sum_i \log F_{i,\cdot}^T \tilde{F}_{i,\cdot}.$$

$$\log p(E|\mathbf{z}) = 1/(||A||_1 - n) \sum_{i \neq j} \log E_{i,j,\cdot}^T \tilde{E}_{i,j,\cdot}, \tag{2}$$

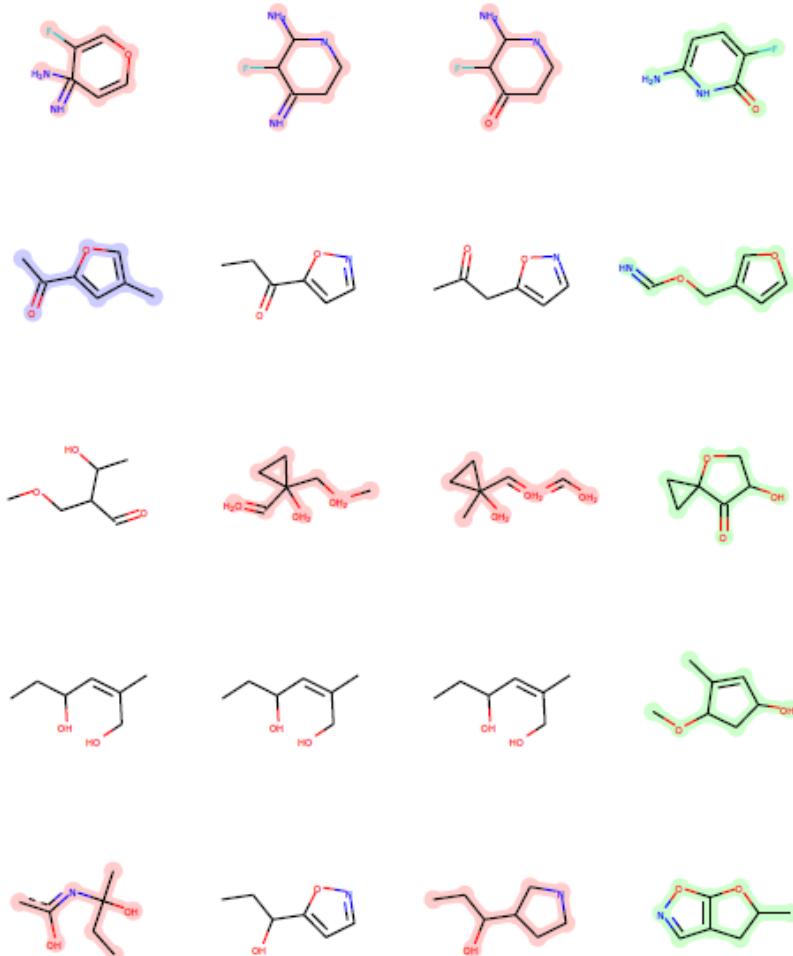
Matrix representation of graphs is not invariant to permutations of nodes

→ Approximate graph matching

$$\begin{aligned}
 S((i, j), (a, b)) = & \\
 = & (E_{i,j,\cdot}^T \tilde{E}_{a,b,\cdot}) A_{i,j} \tilde{A}_{a,b} \tilde{A}_{a,a} \tilde{A}_{b,b} [i \neq j \wedge a \neq b] + \\
 + & (F_{i,\cdot}^T \tilde{F}_{a,\cdot}) \tilde{A}_{a,a} [i = j \wedge a = b]
 \end{aligned} \tag{4}$$

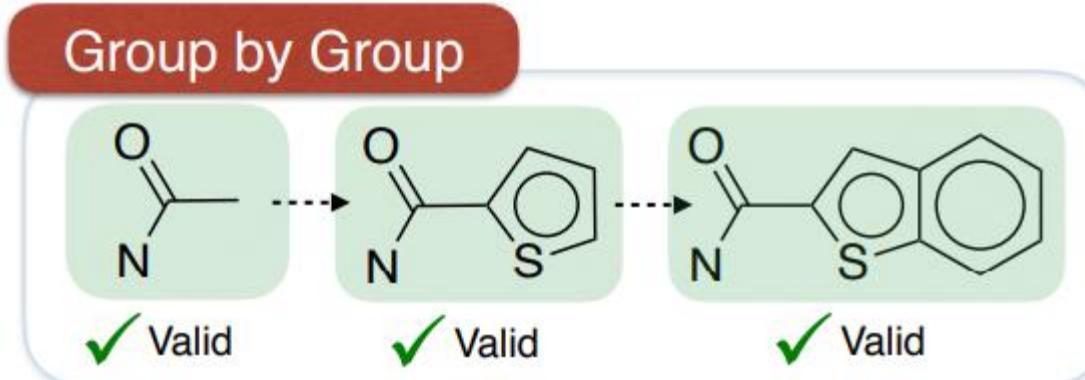
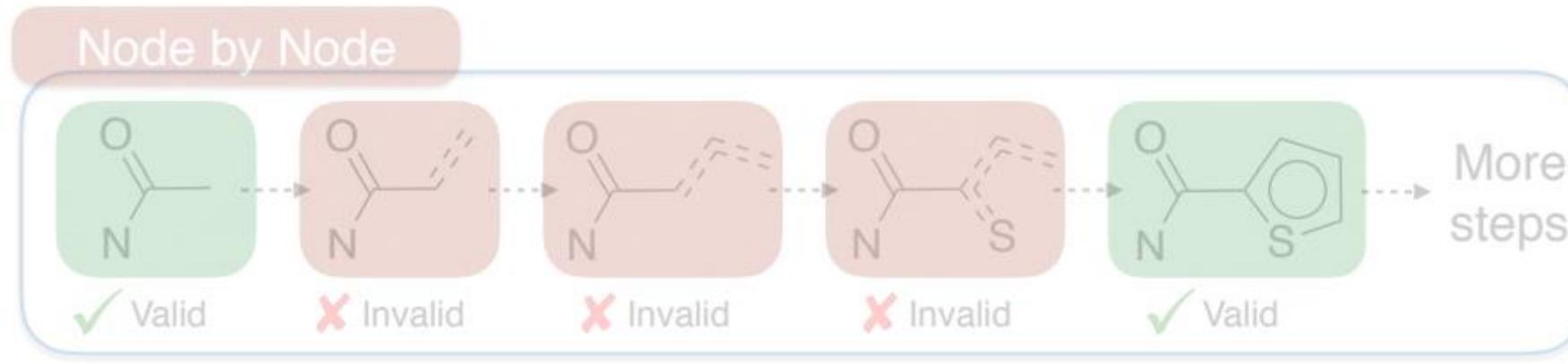
- Graph matching을 approximation
- 고정된 크기의 molecule만 복원 가능, 작은 그래프에서만 잘됨
- 복원 성능은 크게 만족스러운 수준은 아님

	$\log p_\theta(G z)$	ELBO	Valid	Accurate	Unique	Novel
Cond.	Ours $c = 20$	-0.578	-0.722	0.565	0.467	0.314
	Ours $c = 40$	-0.504	-0.617	0.511	0.416	0.484
	Ours $c = 60$	-0.492	-0.585	0.520	0.406	0.583
	Ours $c = 80$	-0.475	-0.557	0.458	0.353	0.666
Unconditional	Ours $c = 20$	-0.660	-0.916	0.485	0.485	0.457
	Ours $c = 40$	-0.537	-0.744	0.542	0.542	0.618
	Ours $c = 60$	-0.486	-0.656	0.517	0.517	0.695
	Ours $c = 80$	-0.482	-0.628	0.557	0.557	0.760
	NoGM $c = 80$	-2.388	-2.553	0.810	0.810	0.241
	CVAE $c = 60$	—	—	0.103	0.103	0.675
	GVAE $c = 20$	—	—	0.602	0.602	0.093
						0.809

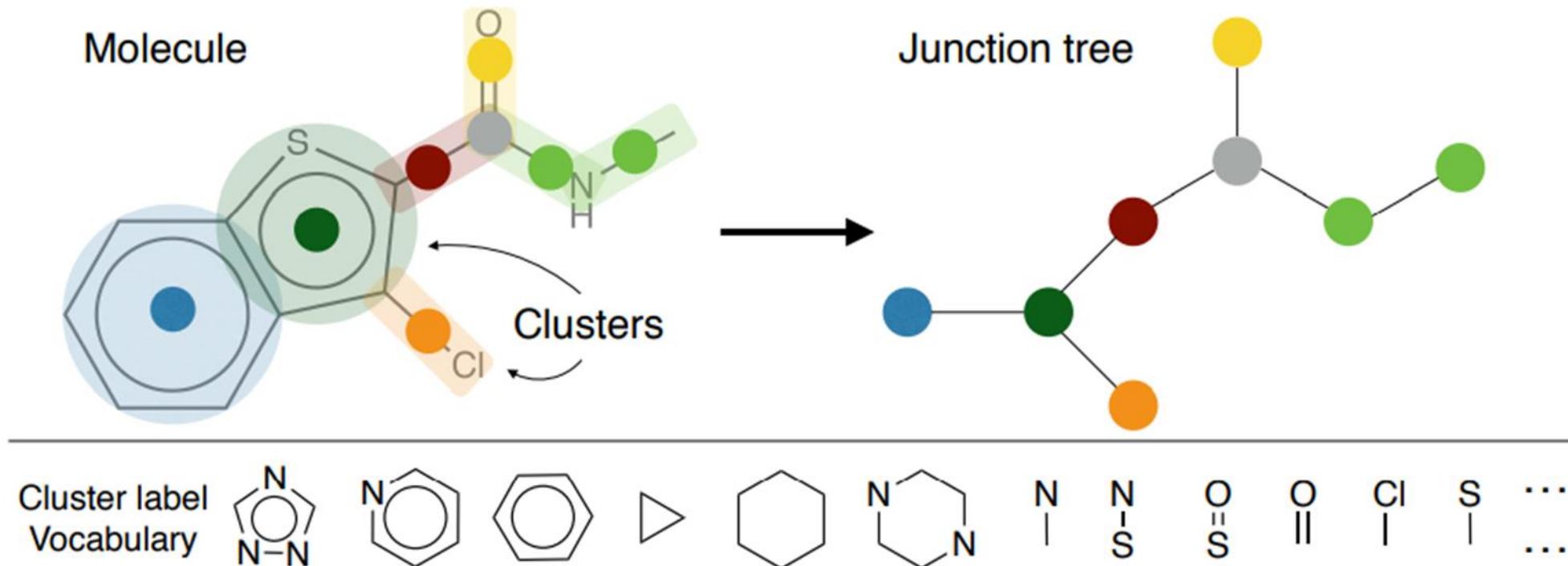


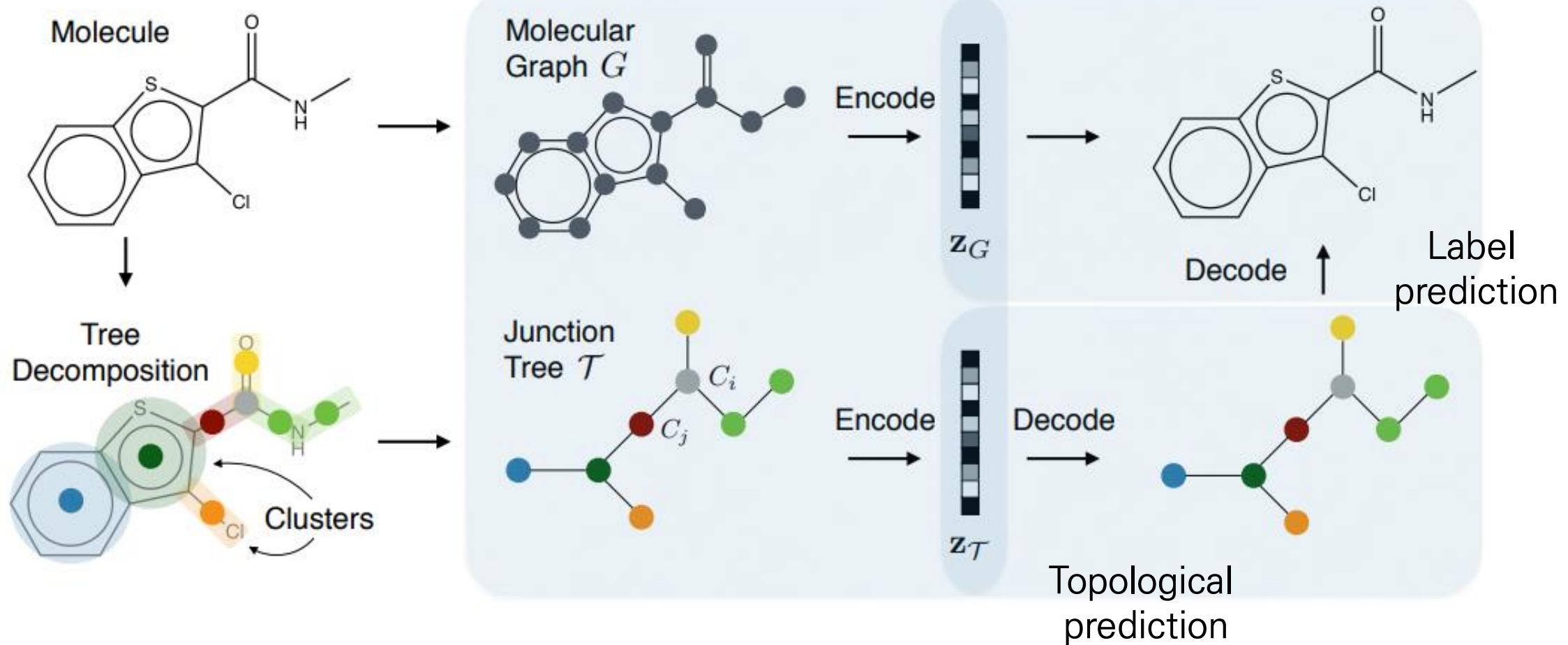
# Junction Tree Variational Autoencoder for Molecular Graph Generation

*Wengong Jin, Regina Barzilay, Tommi Jaakkola* ; Proceedings of the 35th International Conference on Machine Learning, PMLR 80:2323-2332, 2018.



- Shorter action sequence
- Easy to check validity





**Table 1.** Reconstruction accuracy and prior validity results. Baseline results are copied from Kusner et al. (2017); Dai et al. (2018) Simonovsky & Komodakis (2018).

Method	Reconstruction	Validity
CVAE	44.6%	0.7%
GVAE	53.7%	7.2%
SD-VAE <sup>3</sup>	76.2%	43.5%
GraphVAE	-	13.5%
JT-VAE	<b>76.7%</b>	<b>100.0%</b>

**Table 3.** Predictive performance of sparse Gaussian Processes trained on different VAEs. Baseline results are copied from Kusner et al. (2017) and Dai et al. (2018).

Method	LL	RMSE
CVAE	$-1.812 \pm 0.004$	$1.504 \pm 0.006$
GVAE	$-1.739 \pm 0.004$	$1.404 \pm 0.006$
SD-VAE	$-1.697 \pm 0.015$	$1.366 \pm 0.023$
JT-VAE	<b><math>-1.658 \pm 0.023</math></b>	<b><math>1.290 \pm 0.026</math></b>

<sup>4</sup> $y(m) = logP(m) - SA(m) - cycle(m)$  where  $cycle(m)$  counts the number of rings that have more than six atoms.

Chemical  
Science

EDGE ARTICLE



[View Article Online](#)  
[View Journal](#) | [View Issue](#)



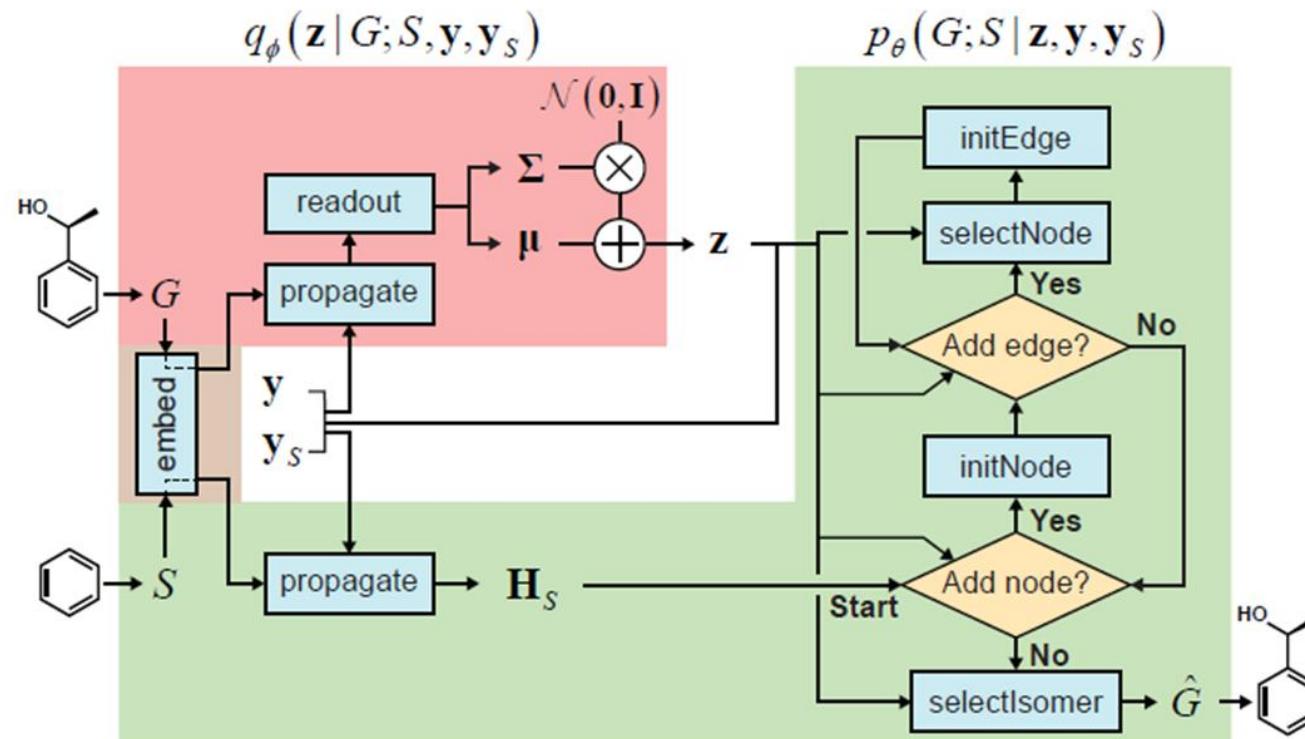
[Check for updates](#)

Cite this: *Chem. Sci.*, 2020, **11**, 1153

All publication charges for this article have been paid for by the Royal Society of Chemistry

## Scaffold-based molecular design with a graph generative model†

Jaechang Lim,<sup>‡<sup>a</sup></sup> Sang-Yeon Hwang,<sup>‡<sup>a</sup></sup> Seokhyun Moon,<sup>a</sup> Seungsu Kim<sup>b</sup> and Woo Youn Kim<sup>‡<sup>a</sup>\*ac</sup>



Objective function: the log-likelihood of an ordinary VAE

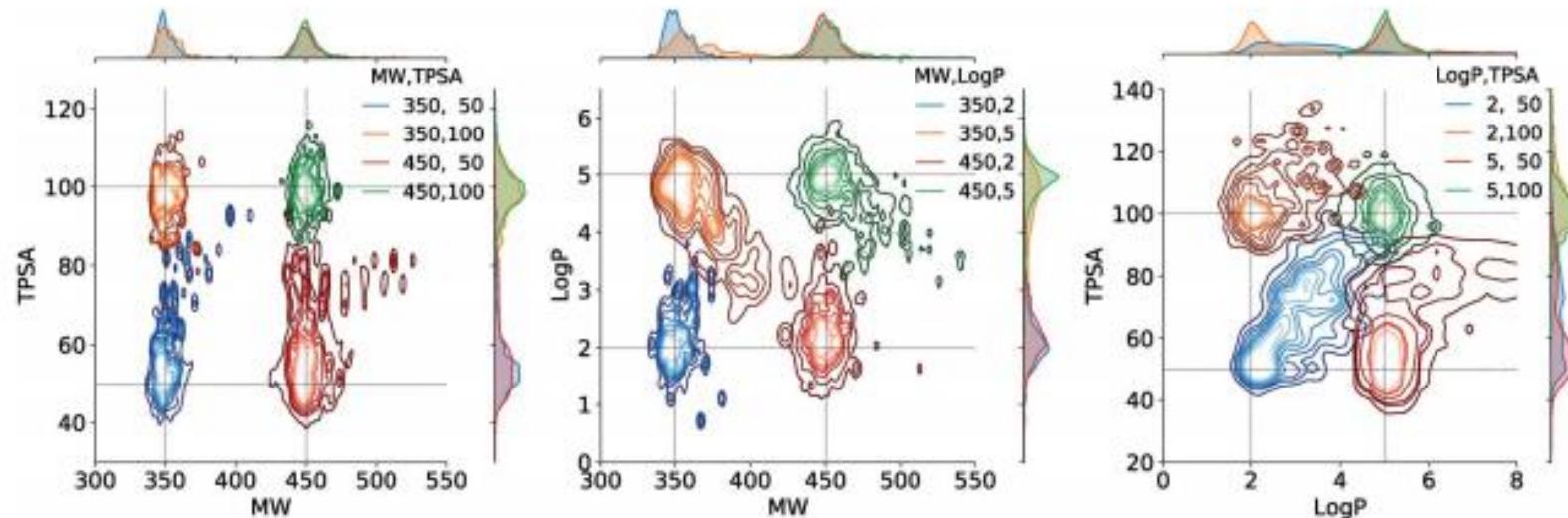
$$\log p(G; S) \geq \mathbb{E}_{z \sim q_\phi} [\log p_\theta(G; S | z)] - D_{\text{KL}} [q_\phi(z | G; S) \| p(z)], \quad (12)$$

Reconstruction (decoder)

Regularization (encoder + prior)

# Scaffold-based molecular design using graph generative model (3/3)

Model	Validity (%)	Uniqueness	
		(%)	Novelty (%)
Ours (MW)	98.6	85.4	98.7
Ours (TPSA)	93.0	84.9	99.1
Ours ( $\log P$ )	97.8	86.4	99.3
GraphVAE <sup>31</sup>	55.7	87.0	61.6
MolGAN <sup>31</sup>	98.1	10.4	94.2
JTVAE <sup>24</sup>	100.0	—	—
MolMP <sup>27</sup>	95.2–97.0	—	91.2–95.1
SMILES VAE <sup>27</sup>	80.4	—	79.3
SMILES RNN <sup>27</sup>	93.2	—	89.9



## Objective-Reinforced Generative Adversarial Networks (ORGAN) for Sequence Generation Models

Gabriel Guimaraes<sup>\*,†</sup> Benjamin Sanchez-Lengeling<sup>\*</sup> Carlos Outeiral<sup>\*,§</sup>

Pedro Luis Cunha Farias<sup>\*</sup> Alán Aspuru-Guzik<sup>\*,‡</sup>

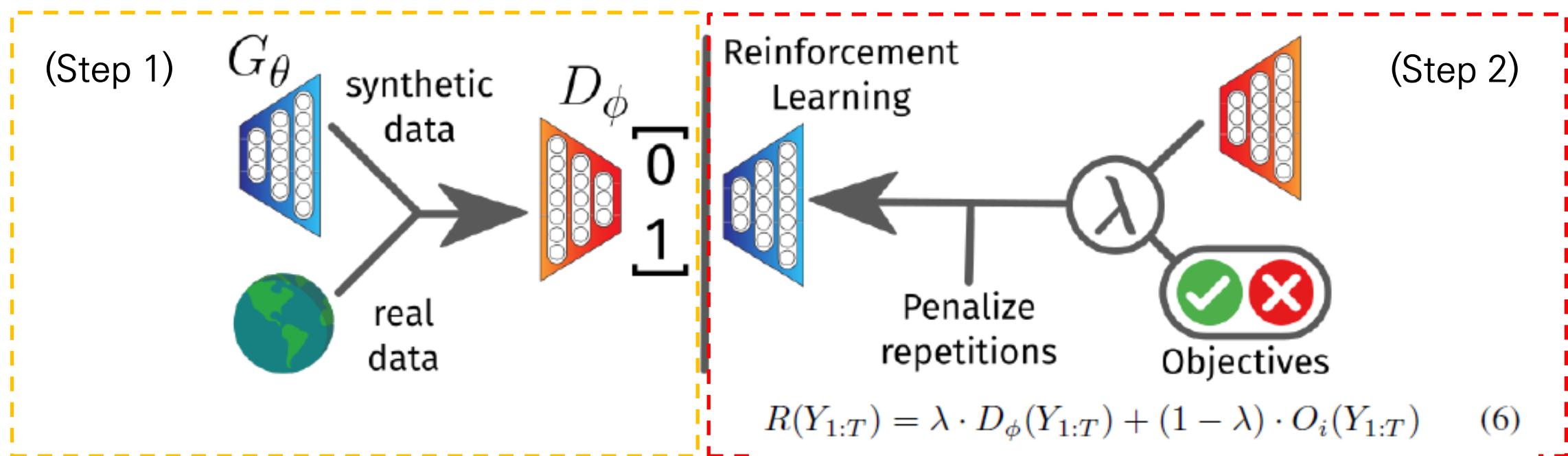
\* Harvard University

† Pagedraw

§ The University of Manchester

‡ Canadian Institute for Advanced Research (CIFAR) Senior Fellow

- GAN(절대적 생성 신경망)은 discrete data에는 적용 X
- RL의 reward 형태로 discrete data 생성에 적용
- 기존의 objective(target property) + GAN 결합된 reward 사용
- 두 단계 학습 진행: (Step1) GAN학습 → (Step2) GAN + RL 학습



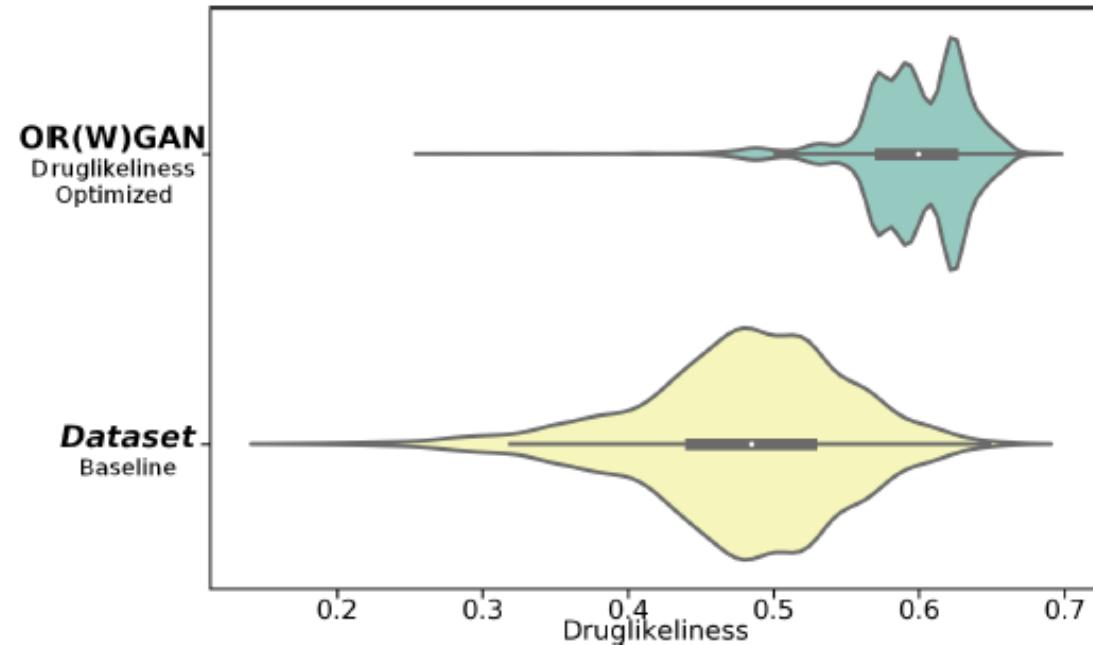


Figure 2: Violinplots of Druglikeness for molecules from the baseline *Dataset*(n=5000) and optimized OR(W)GAN (n=5440).

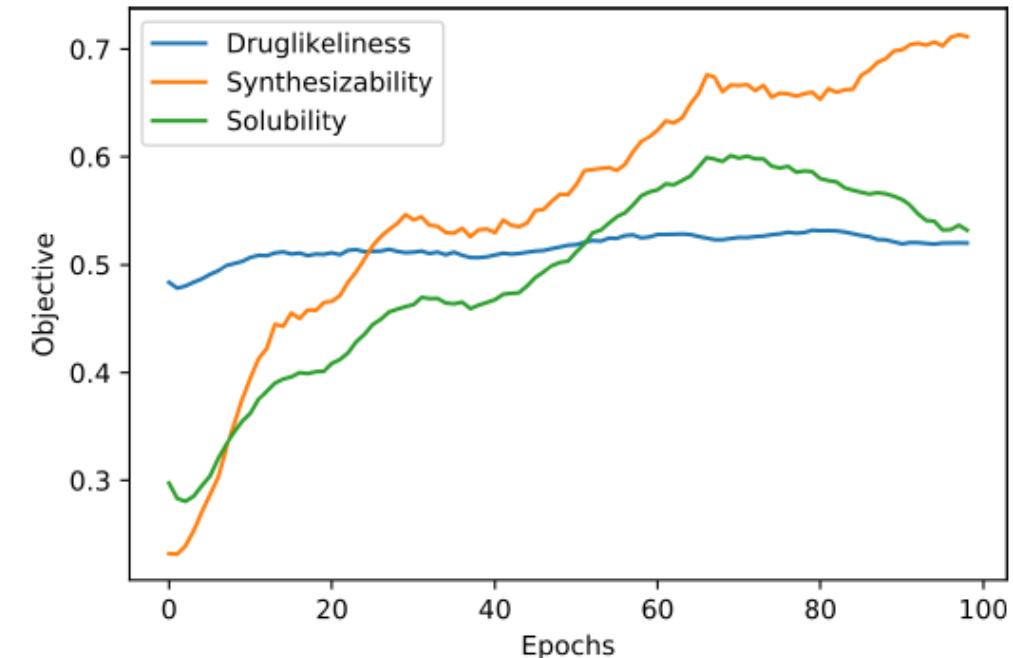


Figure 3: Plots of each objective across the training epochs. Objectives were trained for one epoch, and then switched for another.

Objective	Algorithm	Validity (%)	Diversity	Druglikeness	Synthesizability	Solubility	
	MLE	75.9	0.64	0.48 (0%)	0.23 (0%)	0.30 (0%)	
	SeqGAN	80.3	0.61	0.49 (2%)	0.25 (6%)	0.31 (3%)	
Druglikeness	ORGAN	88.2	0.55	0.52 (8%)	0.32 (38%)	0.35 (18%)	
	OR(W)GAN	85.0	<b>0.95</b>	<b>0.60</b> <b>(25%)</b>	0.54 (130%)	0.47 (57%)	
	Naive RL	97.1	0.8	0.57 (19%)	0.53 (126%)	0.50 (67%)	
Synthesizability	ORGAN	<b>96.5</b>	<b>0.92</b>	0.51 (6%)	<b>0.83</b> <b>(255%)</b>	0.45 (52%)	
	OR(W)GAN	<b>97.6</b>	<b>1.00</b>	0.20 (-59%)	0.75 (223%)	0.84 (184%)	
	Naive RL	<b>97.7</b>	<b>0.96</b>	0.52 (8%)	<b>0.83</b> <b>(256%)</b>	0.46 (54%)	
Solubility	ORGAN	<b>94.7</b>	0.76	0.50 (4%)	0.63 (171%)	0.55 (85%)	
	OR(W)GAN	94.1	<b>0.90</b>	0.42 (-12%)	0.66 (185%)	0.54 (81%)	
	Naive RL	92.7	0.75	0.49 (3%)	0.70 (200%)	<b>0.78</b> <b>(162 %)</b>	
All/Alternated	ORGAN	96.1	92.3	0.52 (9%)	0.71 (206%)	0.53 (79%)	

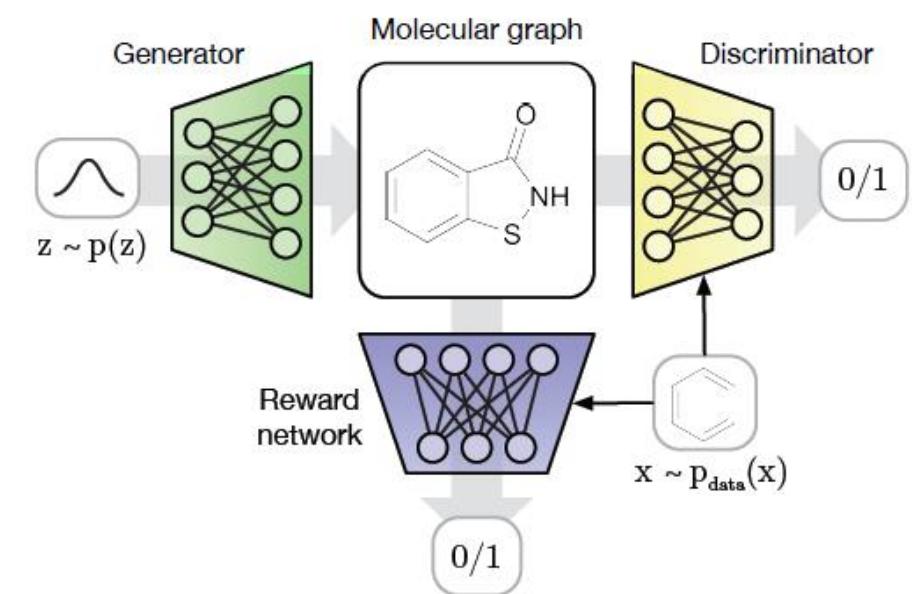
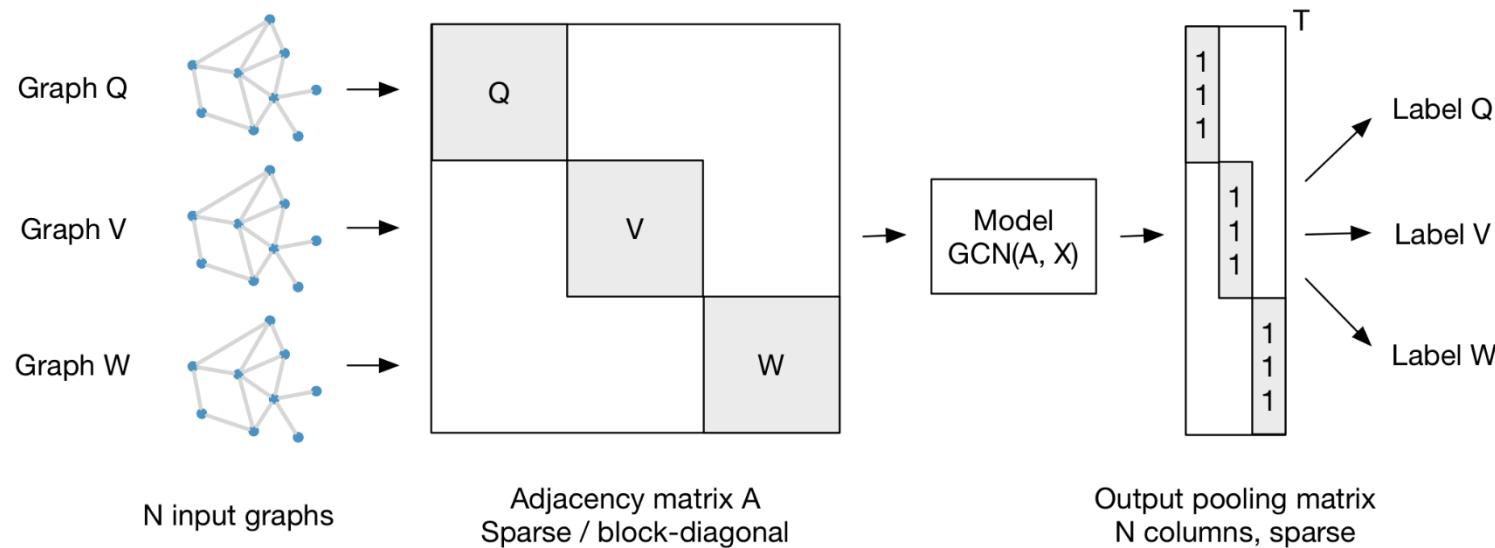
---

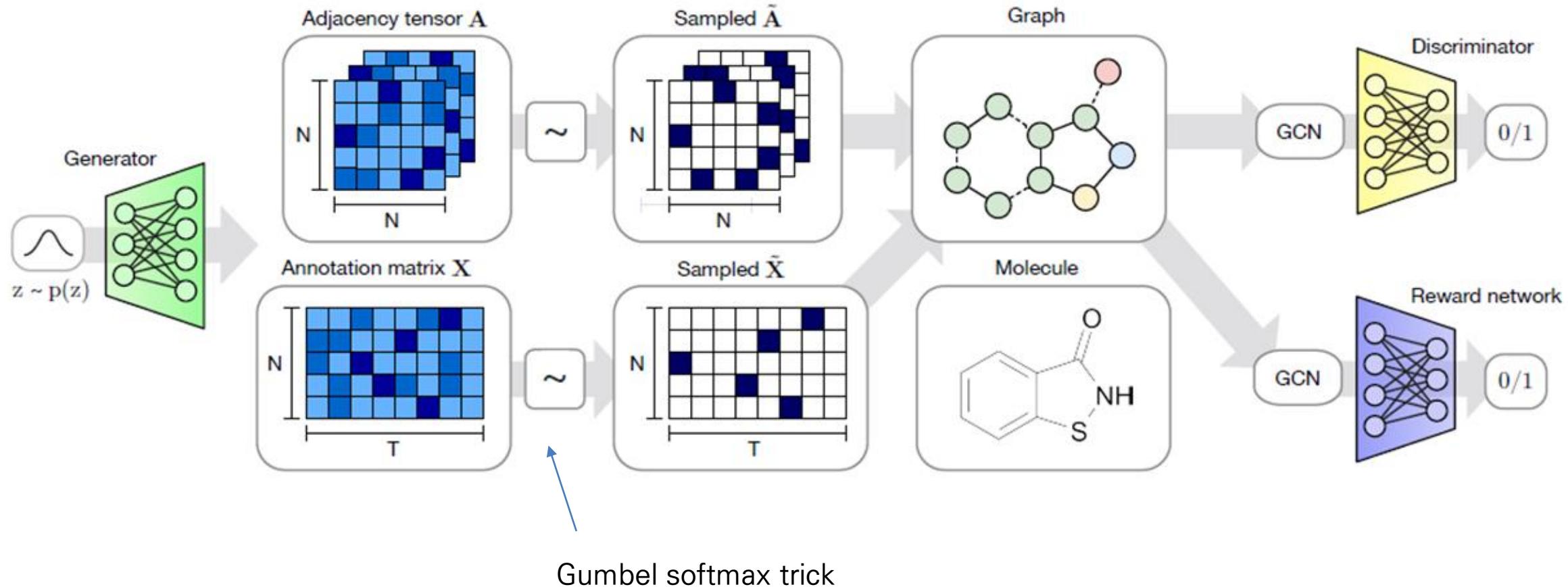
## **MolGAN: An implicit generative model for small molecular graphs**

---

**Nicola De Cao<sup>1</sup> Thomas Kipf<sup>1</sup>**

- SMILES → Learning both **syntactic rules** and the **order ambiguity** of the representation
- SMILES from graph representation: **Additional overhead**
- Directly learning on graph representations





Algorithm	Valid	Unique	Novel	Solubility
$\lambda = 0$ (full RL)	<b>99.8</b>	2.3	97.9	<b>0.86</b>
$\lambda = 0.01$	98.2	2.2	<b>98.1</b>	0.74
$\lambda = 0.05$	92.2	2.7	95.0	0.67
$\lambda = 0.1$	87.3	<b>3.2</b>	87.2	0.56
$\lambda = 0.25$	88.2	2.1	88.2	0.65
$\lambda = 0.5$	86.6	2.1	87.5	0.48
$\lambda = 0.75$	89.6	2.8	89.6	0.57
$\lambda = 1$ (no RL)	87.7	2.9	97.7	0.54

Algorithm	Valid	Unique	Novel
CharacterVAE	10.3	67.5	90.0
GrammarVAE	60.2	9.3	80.9
GraphVAE	55.7	<b>76.0</b>	61.6
GraphVAE/imp	56.2	42.0	75.8
GraphVAE NoGM	81.0	24.1	61.0
<b>MolGAN</b>	<b>98.1</b>	10.4	<b>94.2</b>

MolGAN: An implicit generative model for small molecular graphs								
Objective	Algorithm	Valid (%)	Unique (%)	Time (h)	Diversity	Druglikeness	Synthesizability	Solubility
Druglikeness	ORGAN	88.2	69.4*	9.63*	0.55	0.52	0.32	0.35
	OR(W)GAN	85.0	8.2*	10.06*	0.95	0.60	0.54	0.47
	Naive RL	97.1	54.0*	9.39*	0.80	0.57	0.53	0.50
	<i>MolGAN</i>	<b>99.9</b>	2.0	1.66	0.95	<b>0.61</b>	0.68	0.52
	<i>MolGAN (QM9)</i>	<b>100.0</b>	2.2	4.12	<b>0.97</b>	<b>0.62</b>	0.59	0.53
Synthesizability	ORGAN	96.5	45.9*	8.66*	0.92	0.51	0.83	0.45
	OR(W)GAN	97.6	30.7*	9.60*	<b>1.00</b>	0.20	0.75	0.84
	Naive RL	97.7	13.6*	10.60*	0.96	0.52	0.83	0.46
	<i>MolGAN</i>	<b>99.4</b>	2.1	1.04	0.75	0.52	<b>0.90</b>	0.67
	<i>MolGAN (QM9)</i>	<b>100.0</b>	2.1	2.49	0.95	0.53	<b>0.95</b>	0.68
Solubility	ORGAN	94.7	54.3*	8.65*	0.76	0.50	0.63	0.55
	OR(W)GAN	94.1	20.8*	9.21*	0.90	0.42	0.66	0.54
	Naive RL	92.7	100.0*	10.51*	0.75	0.49	0.70	0.78
	<i>MolGAN</i>	<b>99.8</b>	2.3	0.58	<b>0.97</b>	0.45	0.42	<b>0.86</b>
	<i>MolGAN (QM9)</i>	<b>99.8</b>	2.0	1.62	<b>0.99</b>	0.44	0.22	<b>0.89</b>
All/Alternated	ORGAN	96.1	97.2*	10.2*	0.92	<b>0.52</b>	0.71	0.53
All/Simultaneously	<i>MolGAN</i>	<b>97.4</b>	2.4	2.12	0.91	0.47	<b>0.84</b>	<b>0.65</b>
All/Simultaneously	<i>MolGAN (QM9)</i>	<b>98.0</b>	2.3	5.83	<b>0.93</b>	0.51	<b>0.82</b>	<b>0.69</b>



ARTICLE

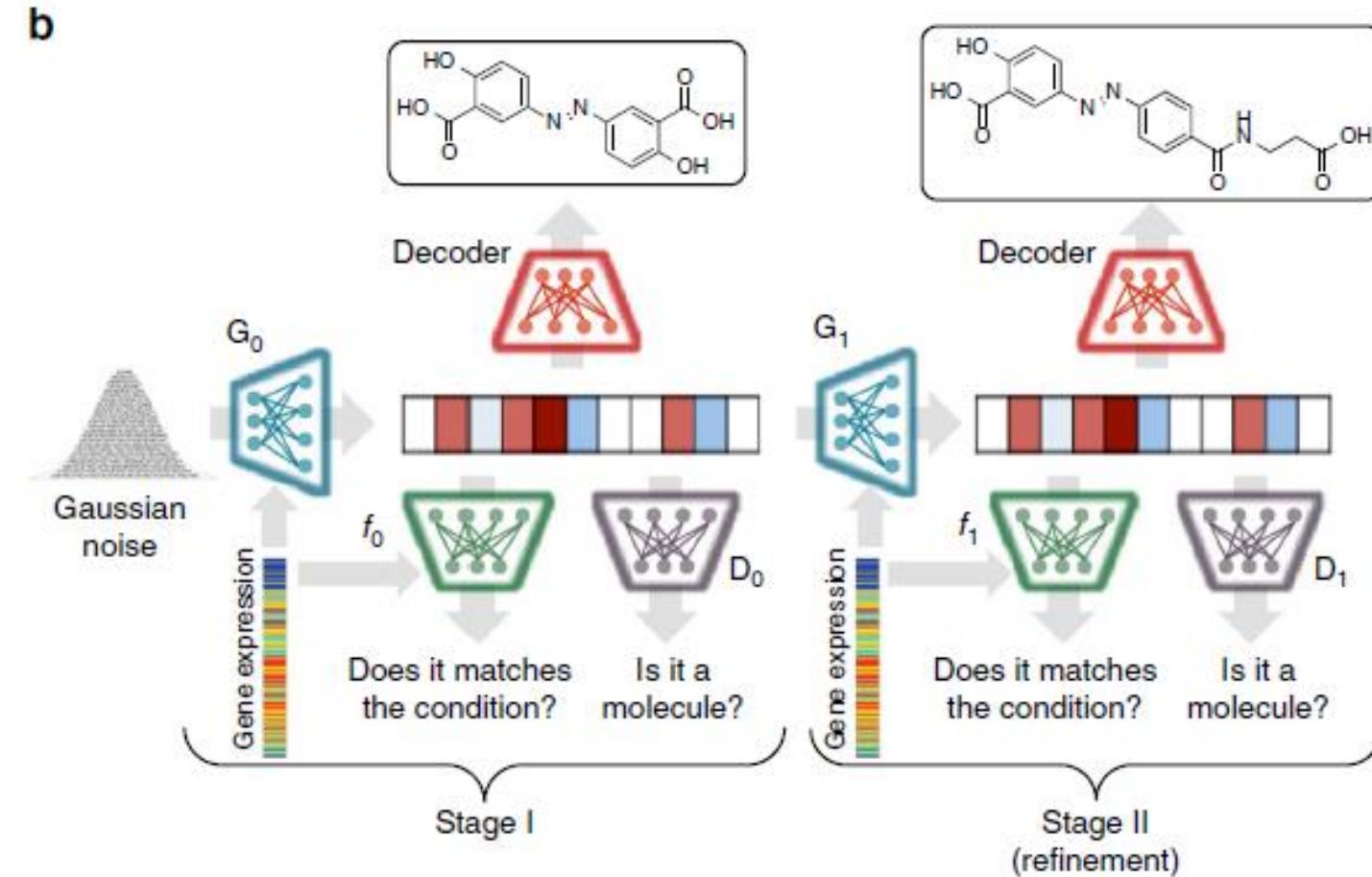
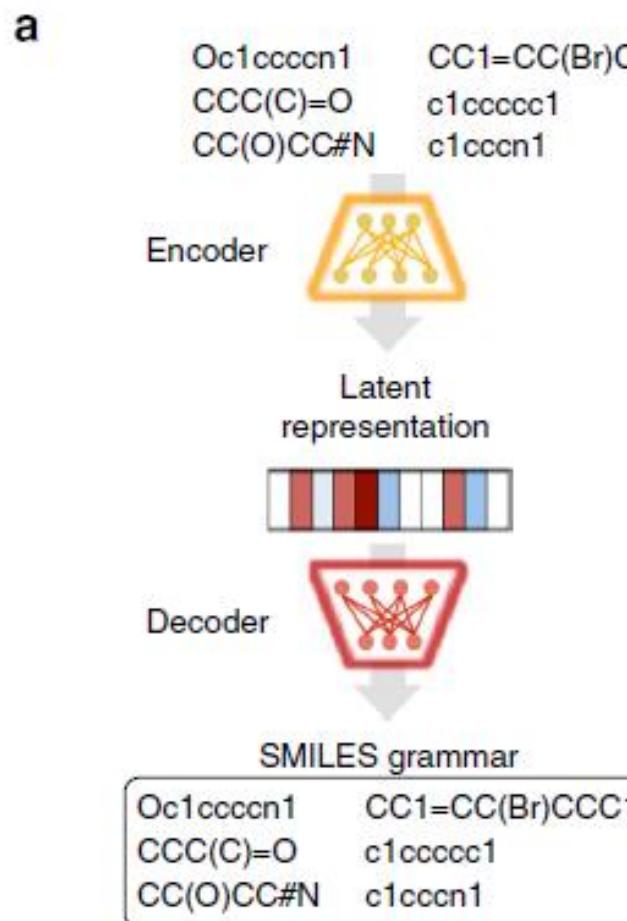
<https://doi.org/10.1038/s41467-019-13807-w>

OPEN

## De novo generation of hit-like molecules from gene expression signatures using artificial intelligence

Oscar Méndez-Lucio<sup>1,2\*</sup>, Benoit Baillif<sup>1</sup>, Djork-Arné Clevert<sup>3</sup>, David Rouquier<sup>1,5\*</sup> & Joerg Wichard<sup>4,5\*</sup>

# Conditional GAN for Drug Discovery (Latent GAN) (2/3)



- **GuacaMol:** Benchmarking Models for de Novo Molecular Design
  - Based on ChEMBL24 dataset
  - <https://www.benevolent.com/guacamol>
- **Molecular Sets (MOSES):** A Benchmarking Platform for Molecular Generation Models
  - Based on ZINC dataset
  - <https://github.com/molecularsets/moses>

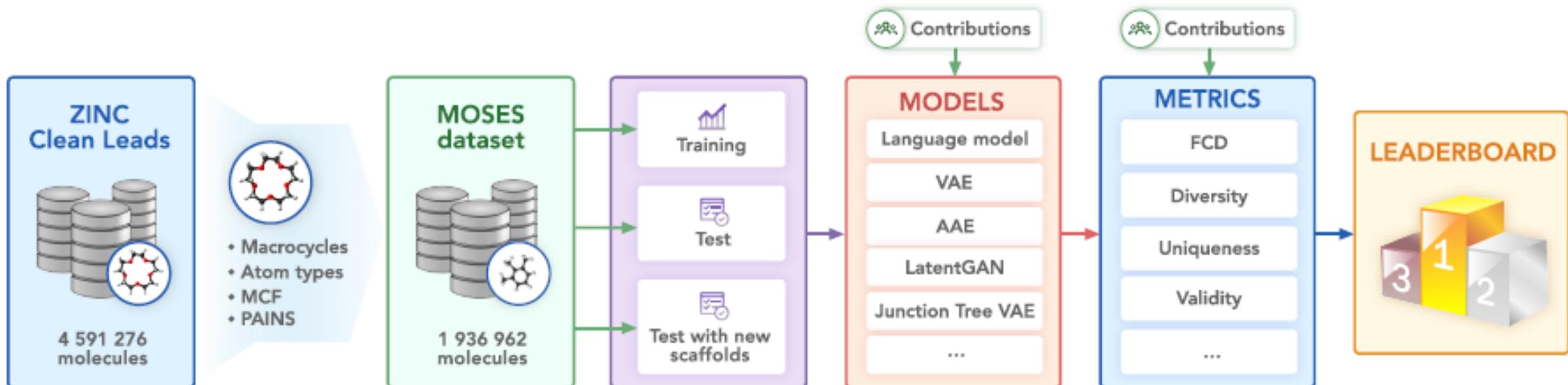
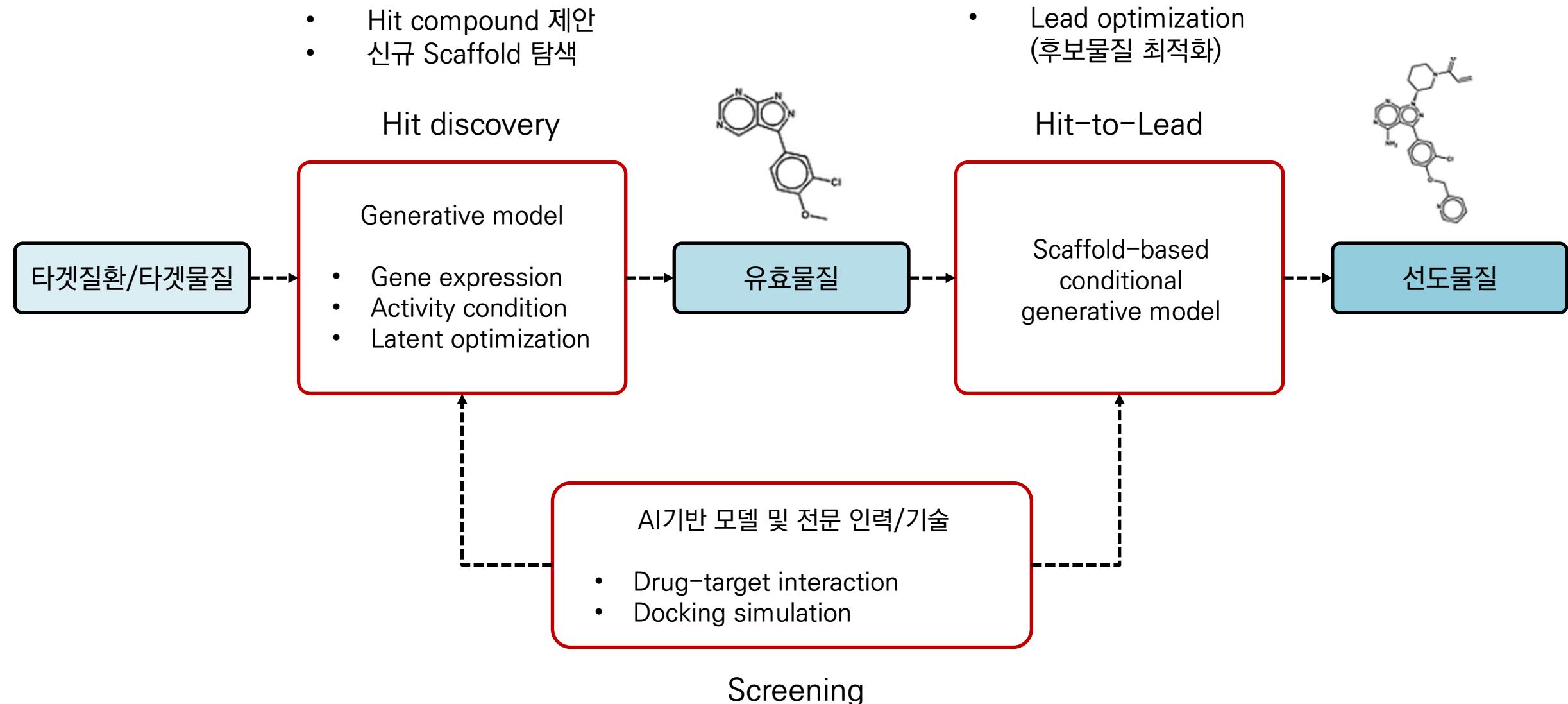


Table 2: Performance metrics for baseline models: fraction of valid molecules, fraction of unique molecules from 1,000 and 10,000 molecules, internal diversity, fraction of molecules passing filters (MCF, PAINS, ring sizes, charges, atom types).

Model	Valid (↑)	Unique@1k (↑)	Unique@10k (↑)	IntDiv (↑)	IntDiv2 (↑)	Filters (↑)
<i>Train</i>	<i>1.0</i>	<i>1.0</i>	<i>1.0</i>	0.857	0.851	<i>1.0</i>
AAE	0.937 (± 0.034)	<b>1.0</b> (± 0.0)	0.997 (± 0.002)	<b>0.856</b> (± 0.003)	<b>0.85</b> (± 0.003)	0.996 (± 0.001)
CharRNN	0.975 (± 0.026)	<b>1.0</b> (± 0.0)	<b>0.999</b> (± 0.0)	<b>0.856</b> (± 0.0)	<b>0.85</b> (± 0.0)	0.994 (± 0.003)
JTN-VAE	<b>1.0</b>	<b>1.0</b>	<b>0.999</b>	0.851	0.845	0.978
LatentGAN	0.899	<b>1.0</b>	0.998	<b>0.856</b>	<b>0.85</b>	0.969
VAE	0.977 (± 0.001)	<b>1.0</b> (± 0.0)	0.998 (± 0.001)	<b>0.856</b> (± 0.0)	<b>0.85</b> (± 0.0)	<b>0.997</b> (± 0.0)

Table 3: Scaffold split metrics for baseline models: Fréchet ChemNet Distance (FCD), Similarity to the nearest neighbour (SNN), Fragment similarity (Frag), Scaffold similarity (Scaff), Novelty.

Model	FCD (↓)		SNN (↑)		Frag (↑)		Scaf (↑)		Novelty (↑)
	Test	TestSF	Test	TestSF	Test	TestSF	Test	TestSF	
<i>Train</i>	<b>0.008</b>	<b>0.476</b>	<b>0.642</b>	<b>0.586</b>	<b>1.0</b>	<b>0.999</b>	<b>0.991</b>	<b>0.0</b>	<b>0.0</b>
AAE	0.556 (± 0.203)	<b>1.057</b> (± 0.237)	0.608 (± 0.004)	0.568 (± 0.005)	0.991 (± 0.005)	0.99 (± 0.004)	0.902 (± 0.037)	0.079 (± 0.009)	0.793 (± 0.028)
CharRNN	<b>0.073</b> (± 0.025)	0.52 (± 0.038)	<b>0.601</b> (± 0.021)	<b>0.565</b> (± 0.014)	<b>1.0</b> (± 0.0)	<b>0.998</b> (± 0.0)	0.924 (± 0.006)	<b>0.11</b> (± 0.008)	0.842 (± 0.051)
JTN-VAE	0.422	0.996	0.556	0.527	0.996	0.995	0.892	0.1	0.915
LatentGAN	0.275	0.777	0.54	0.514	0.999	0.997	0.889	0.107	<b>0.952</b>
VAE	0.099 (± 0.013)	0.567 (± 0.034)	<b>0.626</b> (± 0.0)	<b>0.578</b> (± 0.001)	0.999 (± 0.0)	<b>0.998</b> (± 0.0)	<b>0.939</b> (± 0.002)	0.059 (± 0.01)	0.695 (± 0.007)



# Thank you



Daeryung Techno Town 18-cha, 20th floor, 19,  
Gasan digital 1-ro, Geumcheon-gu, Seoul, Republic of Korea  
**T.** +82-2-6190-7500 **F.** +82-2-2629-4586 **H.** [www.selvasai.com](http://www.selvasai.com)