機械学習を用いた
機能分子の自動設計

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Deep Learning: 予測から生成へ

Art

Can Google's Deep Dream become an art machine?

The company's neural network has created a slew of beautiful and at times terrifying images, and is being harnessed to create unique artwork

1754 207

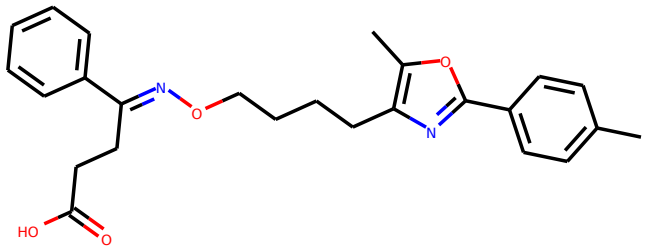
Alex Rayner

Monday 28 March 2016
22.51 BST

Moonage Daydream: art created by Deep Dream. Photograph: Deep Dream

新規化合物生成

機械学習(予測)



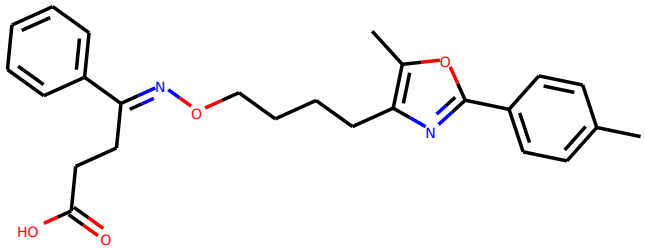
Properties:

Binding Score
Bio Activity
ADMET
…

望ましい性質&
正しい(存在可能な)化合物の生成

SMILES

- SMILESの例



Cc3ccc(c2nc(CCCCO/N=C(CCC(O)=O)c1ccccc1)c(C)o2)cc3

- SMILESの要素

Atom: {C, c, o, O, N, F, [C@@H], n, -, S,Cl, [O-],[C@H], [NH+],[C@], s, Br, [nH], [NH3+], [NH2+], [C@@], [N+], [nH+], [S@], [N-], [n+],[S@@], [S-], I, [n-], P, [OH+],[NH-], [P@@H], [P@@], [PH2], [P@], [P+], [S+],[o+], [CH2-], [CH-], [SH+], [O+], [s+], [PH+], [PH], [S@@+] }
Bonds: {/,=, ¥# }
Ring: {1,2,3,4,5,6,7,8,9}
Branch: {(,)}

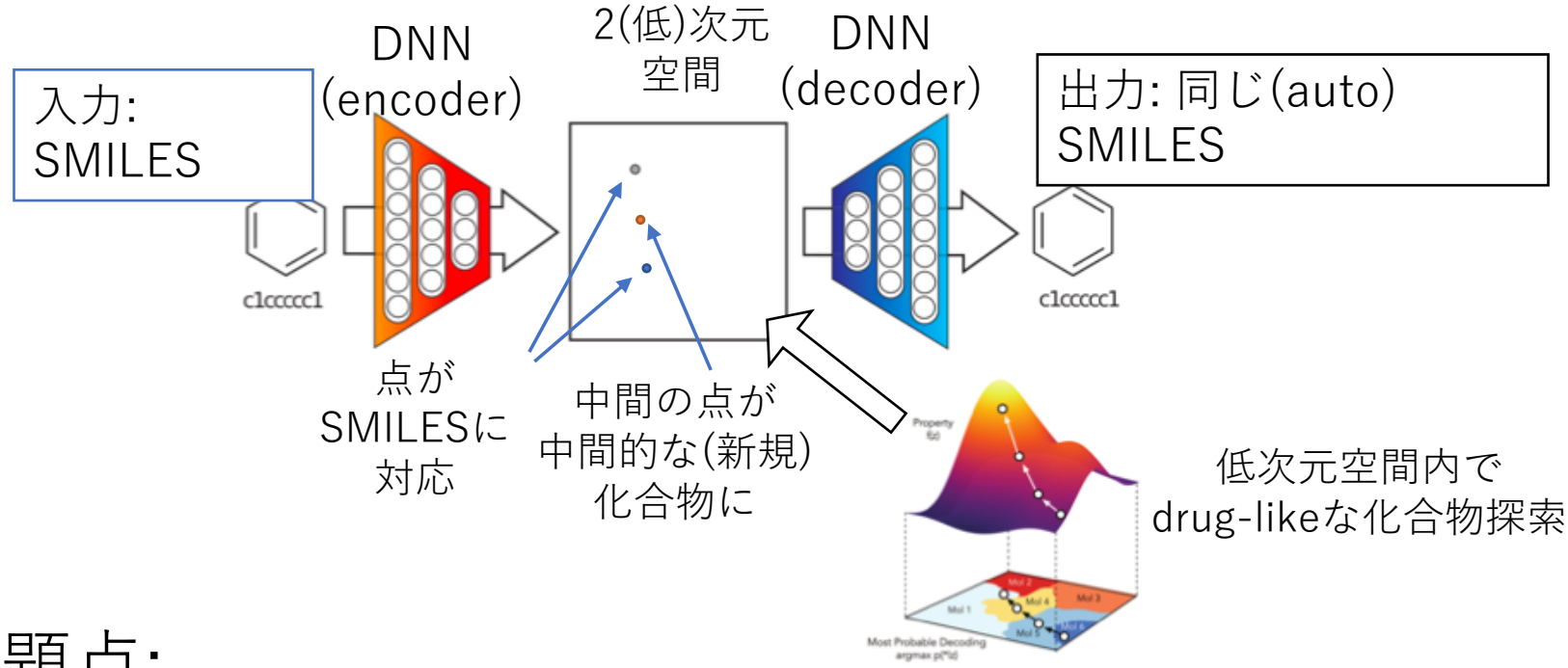
De novo 化合物生成

- これまでの化合物自動生成法は、あらかじめ定義されたFragmentを組み合わせるものが多かった
- 深層学習によるde novo生成
  - Variational autoencoder (Kusner et al., ICML 2017)
  - Recurrent neural network (Segler et al., Arxiv, 2017)

- ChemTS (https://github.com/tsudalab/ChemTS)
  - モンテカルロ木探索 + Recurrent Neural Network

VAEに基づく化合物生成

- Variational Auto Encoder (VAE).

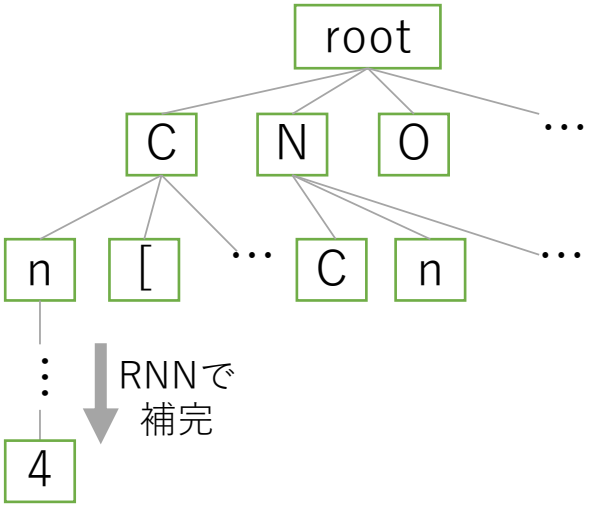


- 問題点:
  - 正しいSMILESの生成確率が低い (0.4%→5%程度)
  - 遅い

Gómez-Bombarelli et al., “Automatic chemical design using a data-driven continuous representation of molecules,” Arxiv, 2016.
Kusner et al., "Grammar Variational Autoencoder," ICML, 2017.

ChemTS: MCTS and RNN

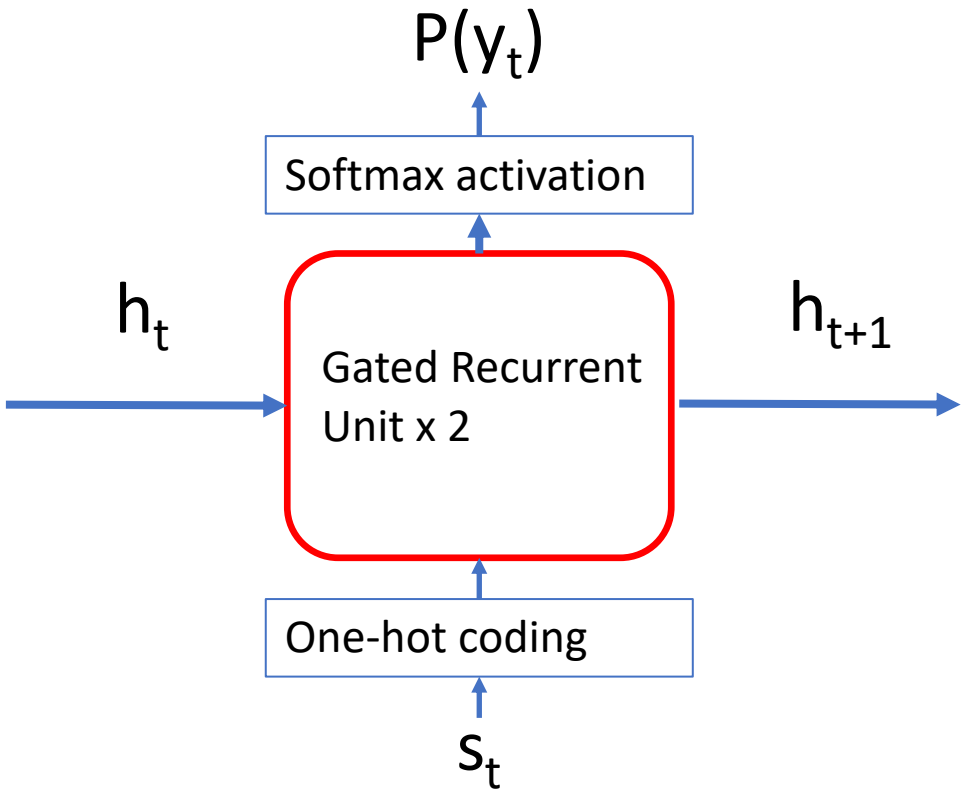
- SMILES文字列の探索木
- 最初はRootのみ
- MCTSを用いて探索木を徐々に伸ばす
- 中間ノードは、SMILESのprefixに対応
- RNNを用いて完全なSMILESに補完する



有効なSMILES生成の確率が高い(40%超)
高速な生成が可能

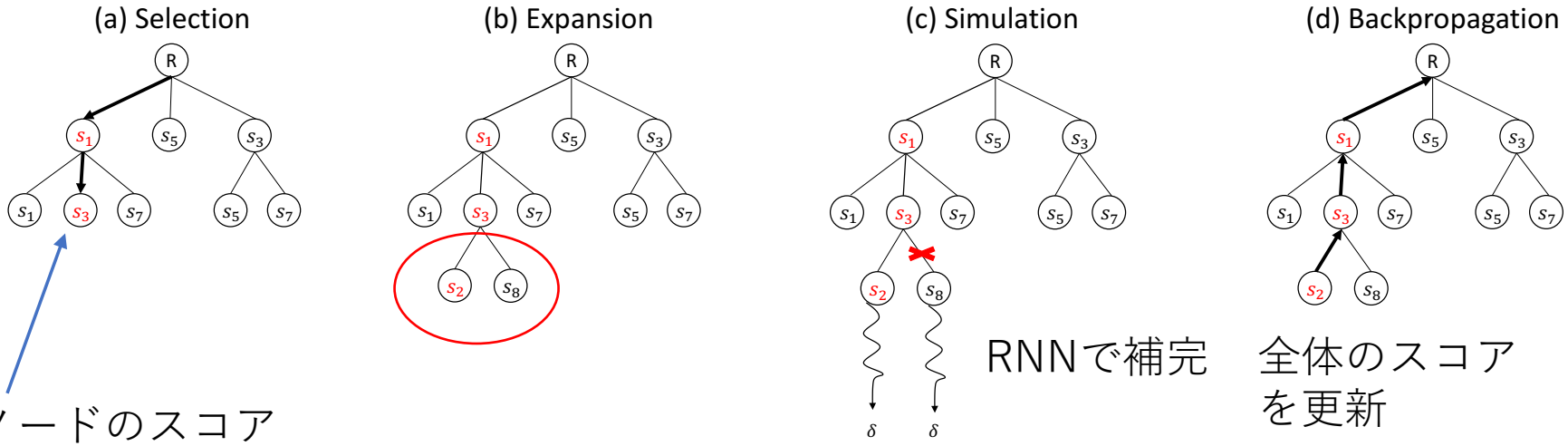
RNN：25万化合物で訓練

- 入力：文字列$s_1,\ldots,s_T$
- 出力：文字列の確率分布 $P(y_1),\ldots,P(y_T)$
- 出力は、入力を右に一文字シフトしたもの



Keras & Tensorflow

MCTSによる探索



各ノードのスコア

$$u_i = \frac{w_i}{v_i} + C\frac{\sqrt{2\ln V_{parent}}}{v_i}$$

子ノードのスコアの平均

“伸びしろ”

有効なSMILESのみ以下のdrug-likenessの値を評価

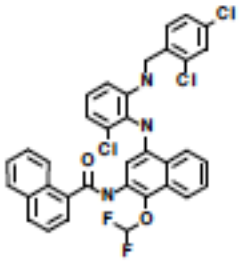
$$J(m) = logP(m) - SA(m) - RingPenalty(m)$$

(Gómez-Bombarelli et al. ICML2016)

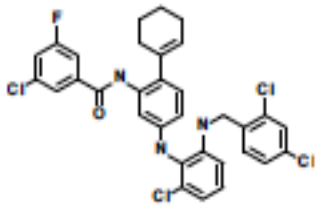
Table 1. Maximum score J at time points 2,4,6 and 8 hours achieved by different molecular generation methods. The rightmost column shows the number of generated molecules per minute. The average values and standard deviations over 10 trials are shown.

Method	2h	4h	6h	8h	Molecules/Min
ChemTS	4.91 ± 0.38	5.41 ± 0.51	5.49 ± 0.44	5.58 ± 0.50	40.89 ± 1.57
RNN+BO	3.54 ± 0.27	4.46 ± 0.24	4.46 ± 0.24	4.46 ± 0.24	8.33 ± 0.00
Only RNN	4.51 ± 0.27	4.62 ± 0.26	4.79 ± 0.25	4.79 ± 0.25	41.33 ± 1.42
CVAE+BO	-30.18 ± 26.91	-1.39 ± 2.24	-0.61 ± 1.08	-0.006 ± 0.92	0.14 ± 0.08
GVAE+BO	-4.34 ± 3.14	-1.29 ± 1.67	-0.17 ± 0.96	0.25 ± 1.31	1.38 ± 0.91

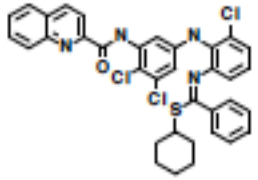
SMILES representation	J
O=C(Nc1cc(Nc2c(Cl)cccc2NCc2ccc(Cl)cc2Cl)c2ccccc2c1OC(F)F)c1cccc2ccccc12	6.56
O=C(Nc1cc(Nc2c(Cl)cccc2NCc2ccc(Cl)cc2Cl)ccc1C1=CCCCC1)c1cc(F)cc(Cl)c1	6.43
O=C(Nc1cc(Nc2c(Cl)cccc2N=C(SC2CCCCC2)c2ccccc2)cc(Cl)c1Cl)c1ccc2ccccc2n1	6.34
O=C(Nc1cc(Oc2ccc(Cl)cc2Cl)ccc1Nc1cc(Cl)ccc1Cl)c1ccc(Cl)cc1	6.33
O=C(Nc1cc(Nc2c(Cl)cccc2Cl)c(Cl)cc1Br)N(c1ccccc1)c1ccc(Cl)cc1	6.26
O=C(Nc1cc(Oc2c(Cl)cccc2Oc2ccc(-c3ccccc3)cc2)ccc1Cl)c1ccccc1	6.19
O=C(Nc1cc(Nc2c(Cl)cccc2Cl)c(Cl)c(C(=O)N(Cc2ccccc2)c2ccccc2)c1Cl)c1ccccc1F	6.08
O=C(Nc1cc(Oc2ccc(Cl)cc2Cl)cc(Cl)c1Cl)c1ncoc1-c1ccc(Sc2ccccc2)cc1	6.007
O=C(Nc1cc(Nc2c(Cl)cccc2NCc2ccc(Cl)cc2Cl)c2nccccc2c1Cl)c1ccc(Cl)cc1	6.0067
O=C(Nc1cc(Nc2c(Cl)cccc2NCc2ccc(Cl)cc2)c(Cl)cc1Cl)c1cc(F)ccc1Cl	6.0062



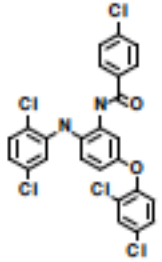
$J = 6.56$



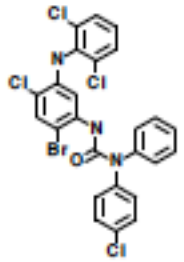
$J = 6.43$



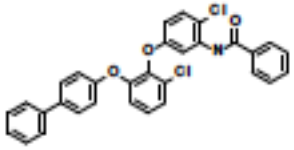
$J = 6.34$



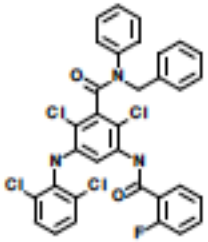
$J = 6.33$



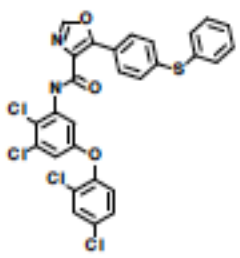
$J = 6.26$



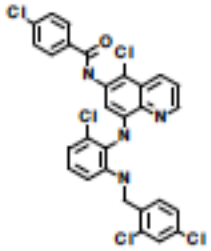
$J = 6.19$



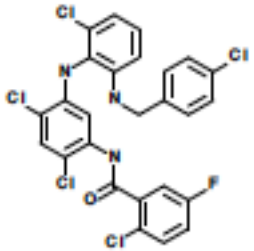
$J = 6.08$



$J = 6.007$



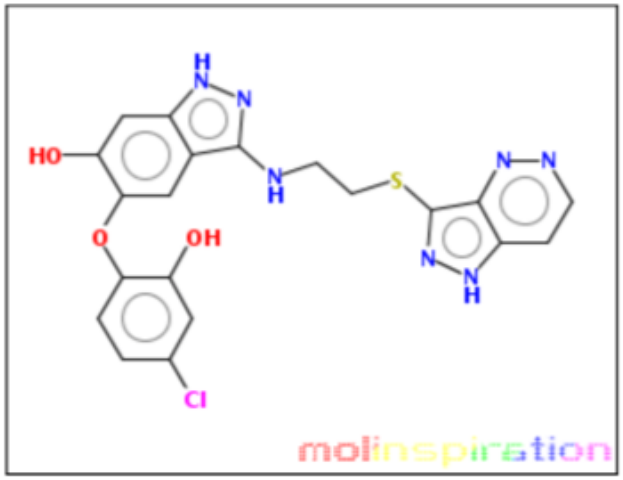
$J = 6.0067$



$J = 6.0062$

Docking to CDK2 (ChemTS + rDock)

originalSMILES Oc1cc(Cl)ccc1Oc1cc2c(NCCSc3n[nH]c4ccnnc34)n[nH]c2cc1O
miSMILES: Oc1cc(Cl)ccc1Oc1cc2c(NCCSc3n[nH]c4ccnnc34)n[nH]c2cc1O



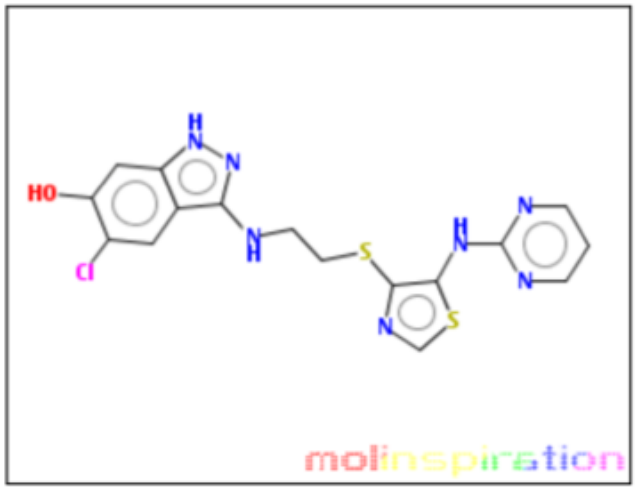
Molinspiration bioactivity score v2016.03

GPCR ligand	0.29
Ion channel modulator	0.13
Kinase inhibitor	0.64
Nuclear receptor ligand	-0.15
Protease inhibitor	0.05
Enzyme inhibitor	0.15

Get data as text (for copy / paste).

Get 3D geometry BETA

originalSMILES Oc1cc2[nH]nc(NCCSc3ncsc3Nc3ncccn3)c2cc1Cl
miSMILES: Oc1cc2[nH]nc(NCCSc3ncsc3Nc3ncccn3)c2cc1Cl



Molinspiration bioactivity score v2016.03

GPCR ligand	0.20
Ion channel modulator	-0.01
Kinase inhibitor	0.93
Nuclear receptor ligand	-0.43
Protease inhibitor	0.13
Enzyme inhibitor	0.19

Get data as text (for copy / paste).

Get 3D geometry BETA

おわりに

- Clever but slow (BO)　対 Stupid but fast (MCTS)
- Wanted: 合成ルート自動生成