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RDKit UGM 2017

SMILES enumeration as Data Augmentation for Neural Network Modeling of Molecules

Outline

- Short intro to presenter
- Neural Nets 0 to 120 mph
- LSTM Recurrent Neural Networks
- Data Augmentation
- SMILES enumeration
- DHFR example
- Tox21 shootout
- Conclusion

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- Ph.D (Computational Chemistry), University of Copenhagen (DK)
- Industry experience:
  - Drug Discovery IT Support and Databases, LEO Pharma A/S (DK)
- Postdoc #1
  - Protein NMR, Department of Biology, Copenhagen University (DK)
- Postdoc #2
  - Chemometrics and automatic PLS model tuning, Department of Food, Copenhagen University (DK)
- Wildcard Pharmaceutical Consulting

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Molecular data science and machine learning

Computational Chemistry

Molecular Machine Learning

Research and Laboratory IT services

Are Neural Networks the future?

- My Previous experience:
  - Slow to train
  - Prone to over fitting
  - Complex (many hyper parameters)
  - Not as good and robust predictions as simpler models
- But recently they gained momentum (again-again)
  - GPU computing
    - Theano and Tensorflow
  - Better weight initialization
  - Activation functions (Relu)
  - Regularization (Dropout, noise, weight regularization)
  - Advances in network architectures: CNN's, RNN's (LSTM, GRU)
  - Larger amounts of data

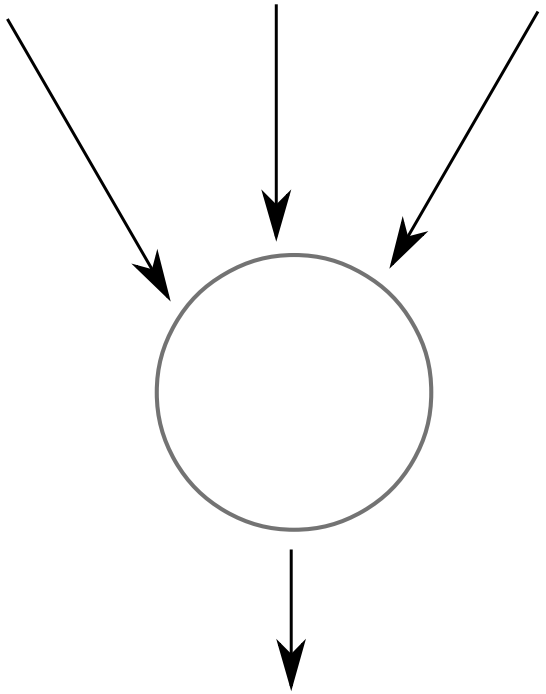
A spectrum of Machine Learning Tasks

- Statistical End
  - Low number of samples
  - "Simple" model can capture variation
  - Main problem is to separate noise from signal
- MLR, PLS, SVM

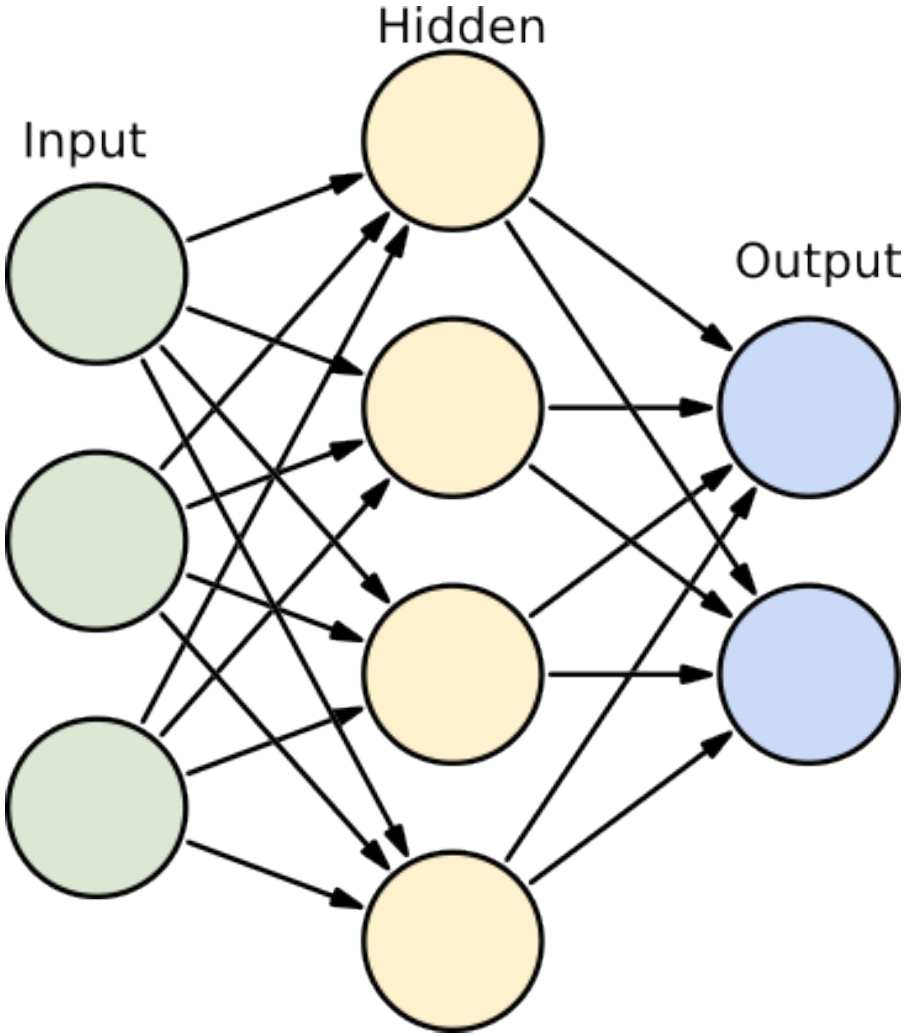
- AI End
  - High dimensional data
  - Complicated model: Example Link picture to label
  - Main problem: How to represent and model data
- Use Neural nets and let back propagation figure it out.

Artificial Neurons

Input	0.1	1	-0.9
weights	20	-1	-2
Weighted sum	20*0.1 + -1*1 + -2*-0.9 = 2.8		
Activation Function	tanh(6) = 0.992		
Output	0.992		

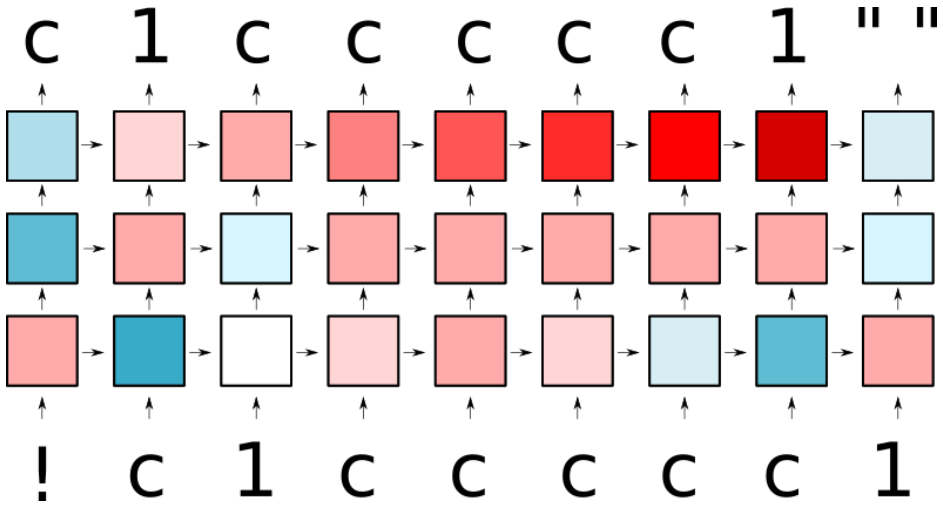


Feed Forward Neural Networks



- Fixed size input
- One or more hidden layers

Recurrent Neural Networks



- Sequences of features as inputs
- The same task for every element of a sequence, with the output being affected by the previous computations
- Modeling of sequences such as text, tweets, time series etc.

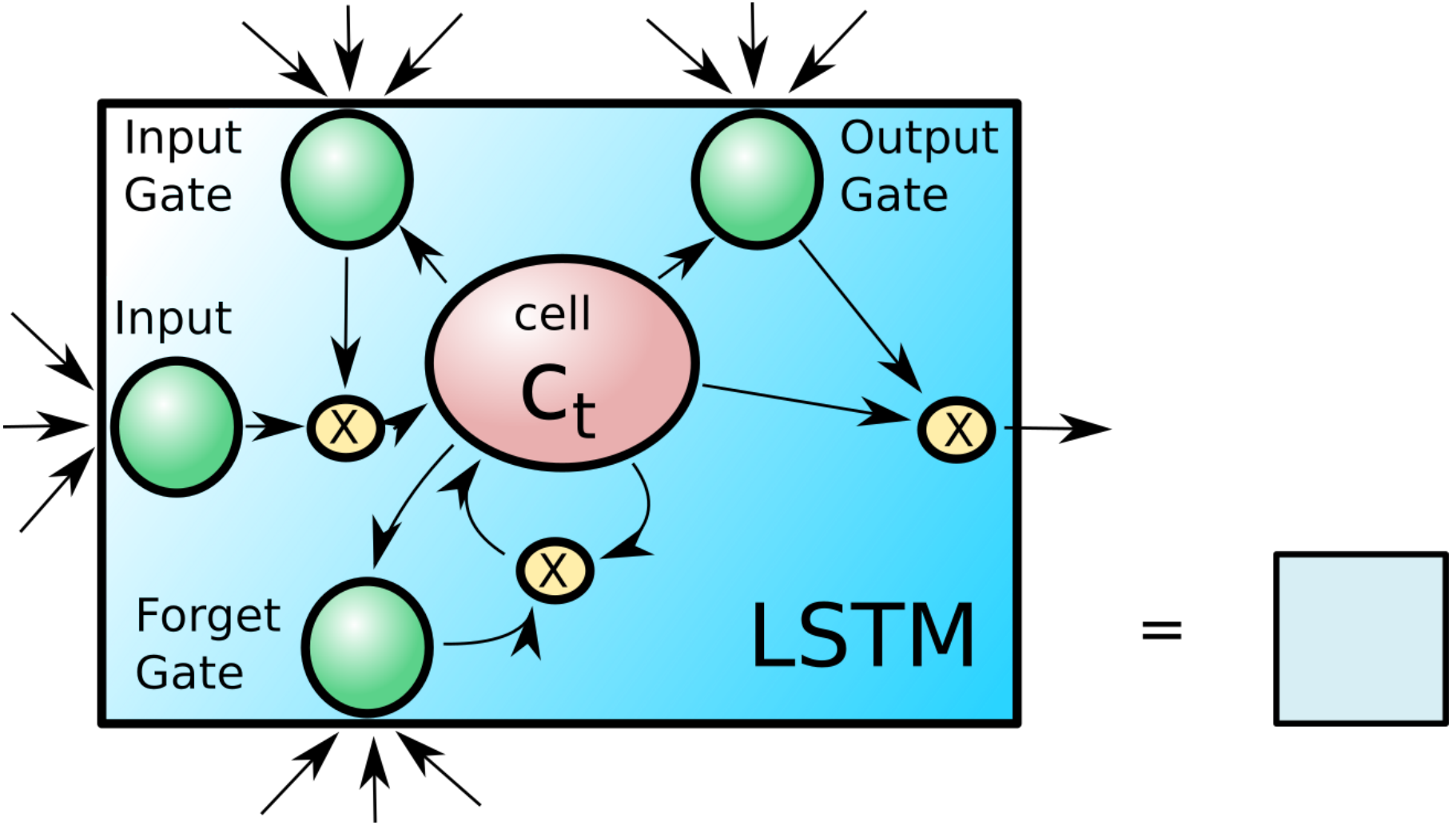
SMILES Notation

- **S**implified **M**olecular **I**nput **L**ine **E**ntry **S**pecification
- Linear molecular notation format
- Atoms as Letters (lowercase aromatics)
- Special bonds = # : -
- Branching ( )
- Rings via numbering: c1ccccc1
- [Hydrogenation and charge]
- cis-trans isomery / \
- R/S Stereochemistry @ @@

Idea

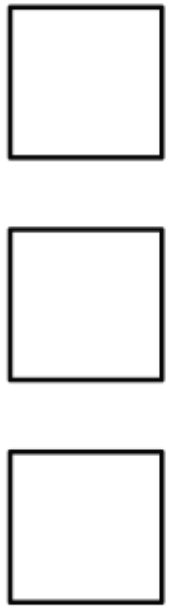
- Recurrent neural networks are good at modeling sequences such as text
- SMILES is a linear text molecular representation
- ….
- ….
- Must … try … to … combine!

LSTM-architecture



LSTM RNN in Action

LSTM RNN in Action



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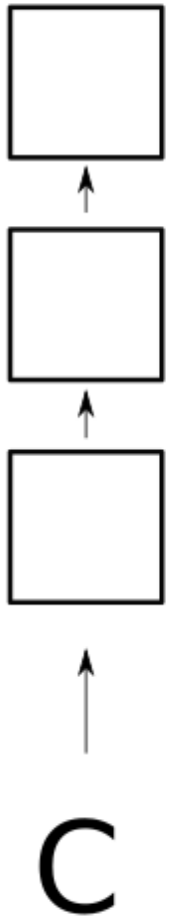
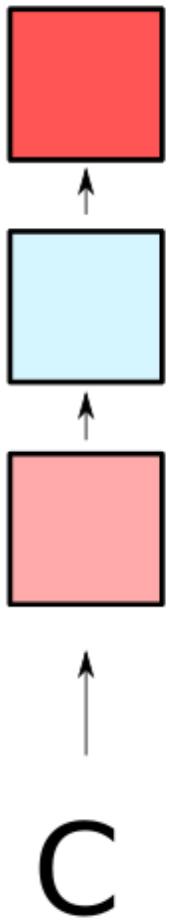
LSTM RNN in Action

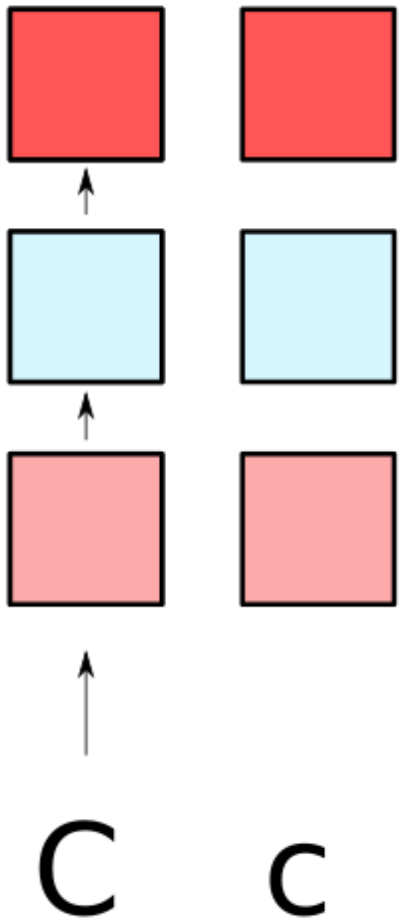
LSTM RNN in Action



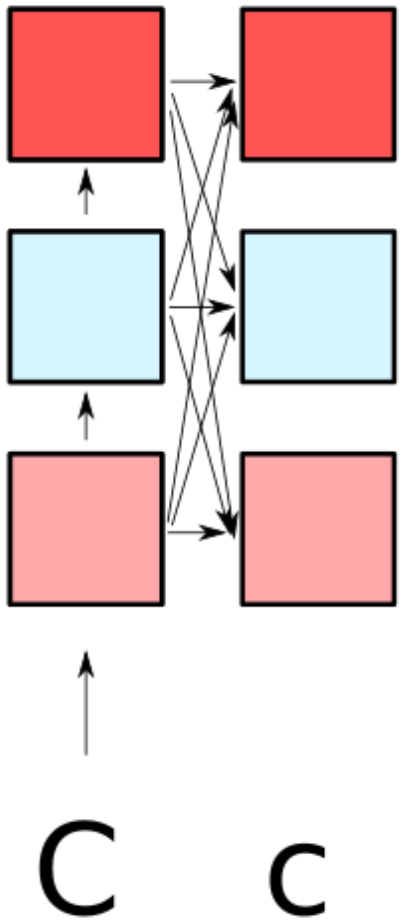
LSTM RNN in Action



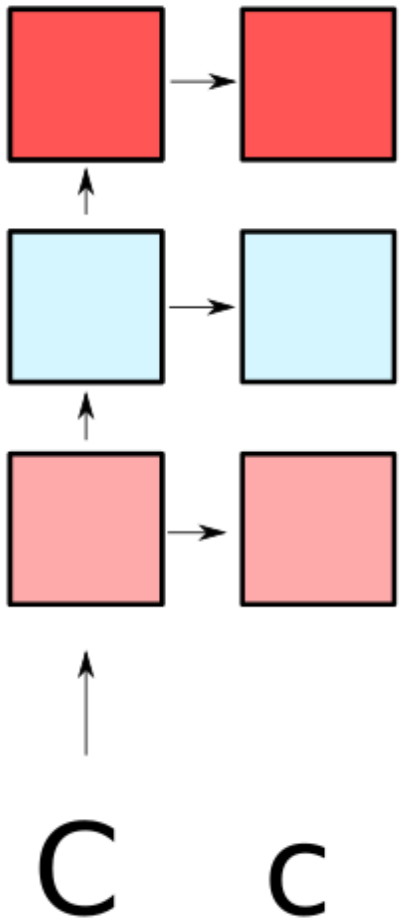
LSTM RNN in Action



LSTM RNN in Action



LSTM RNN in Action



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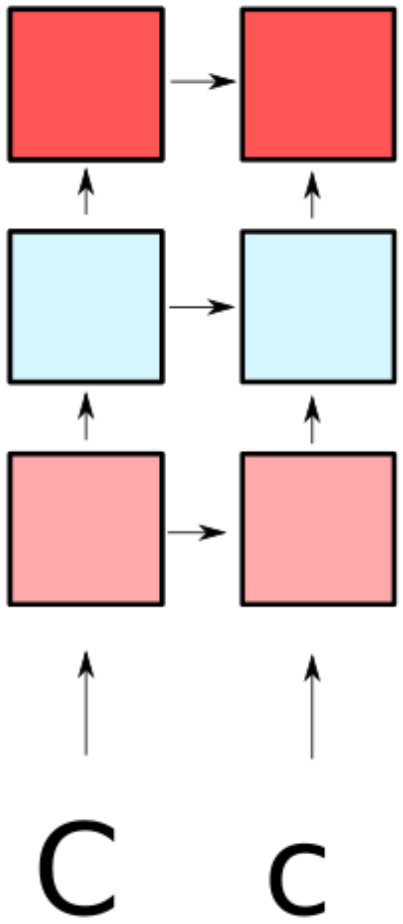

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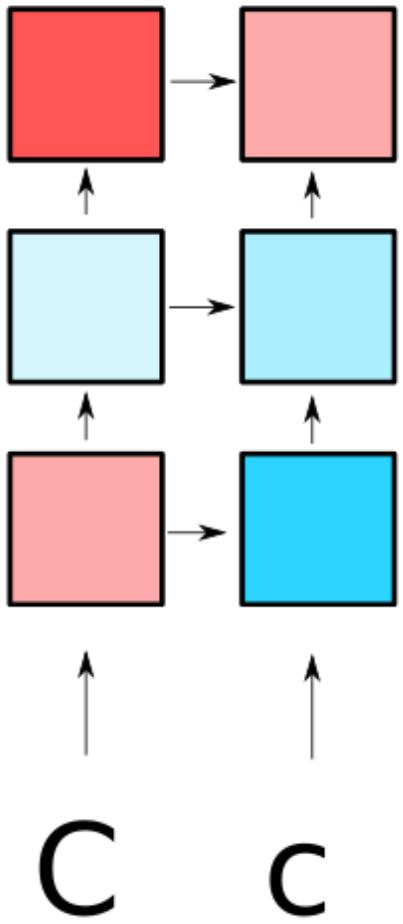
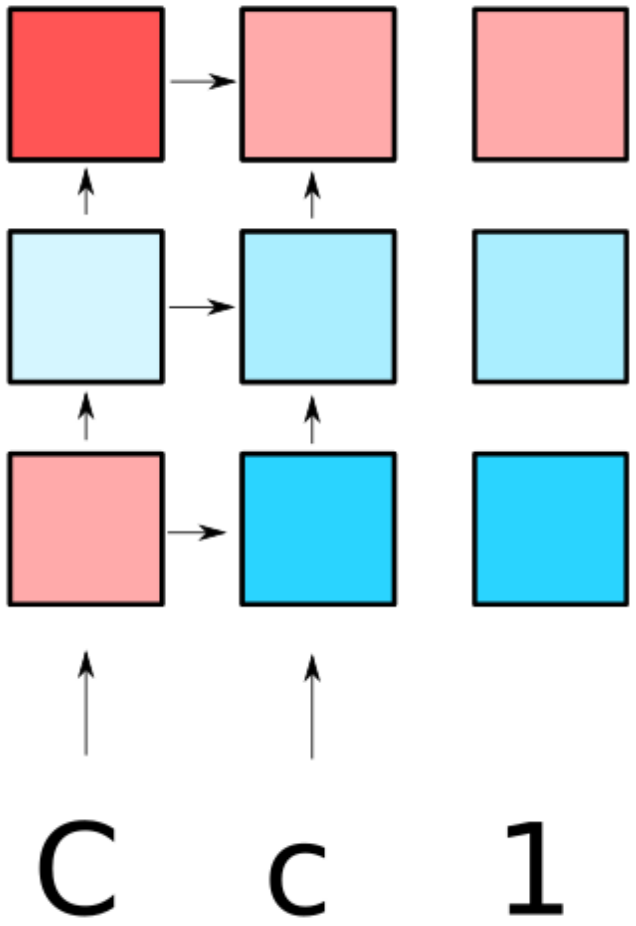
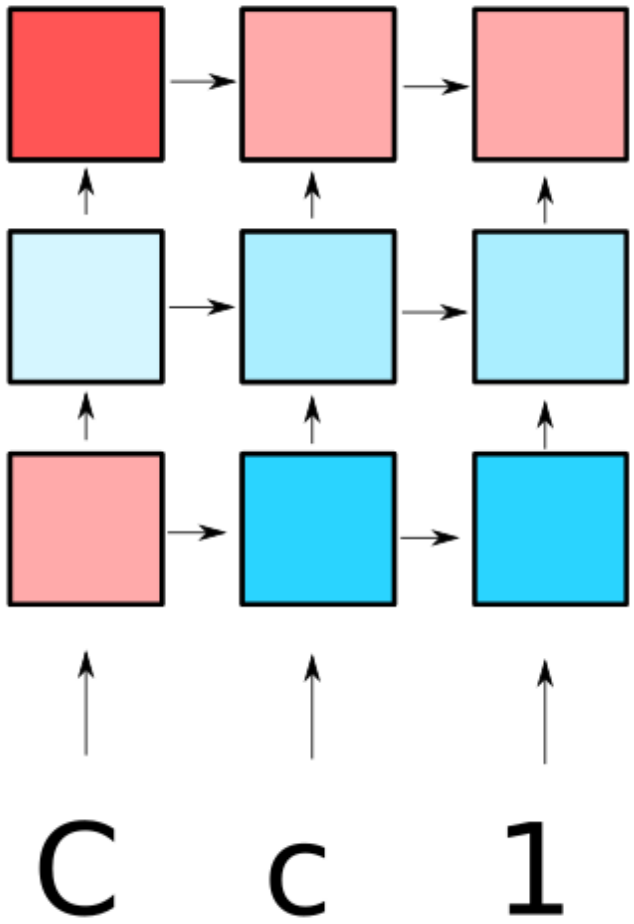


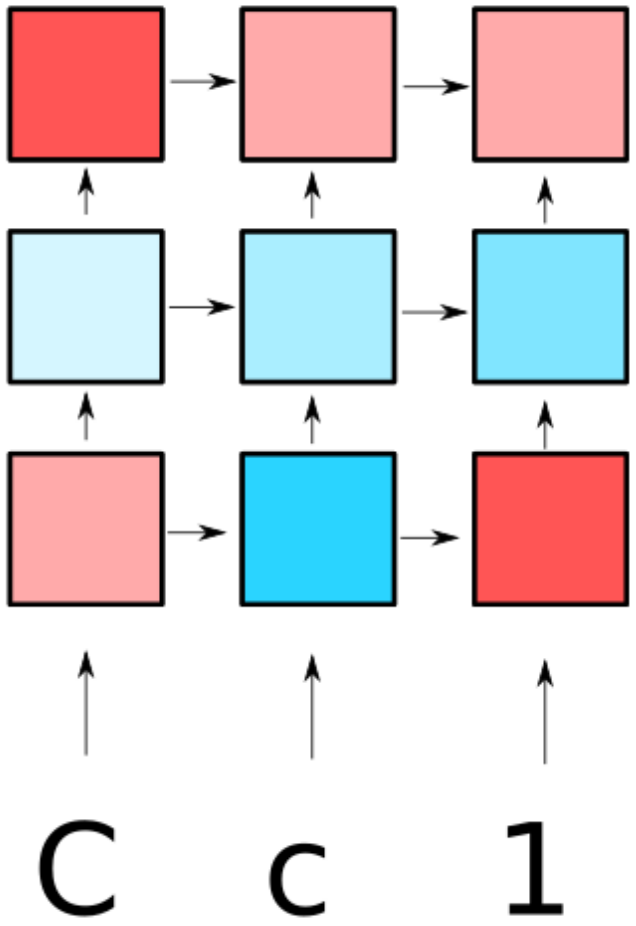
LSTM RNN in Action



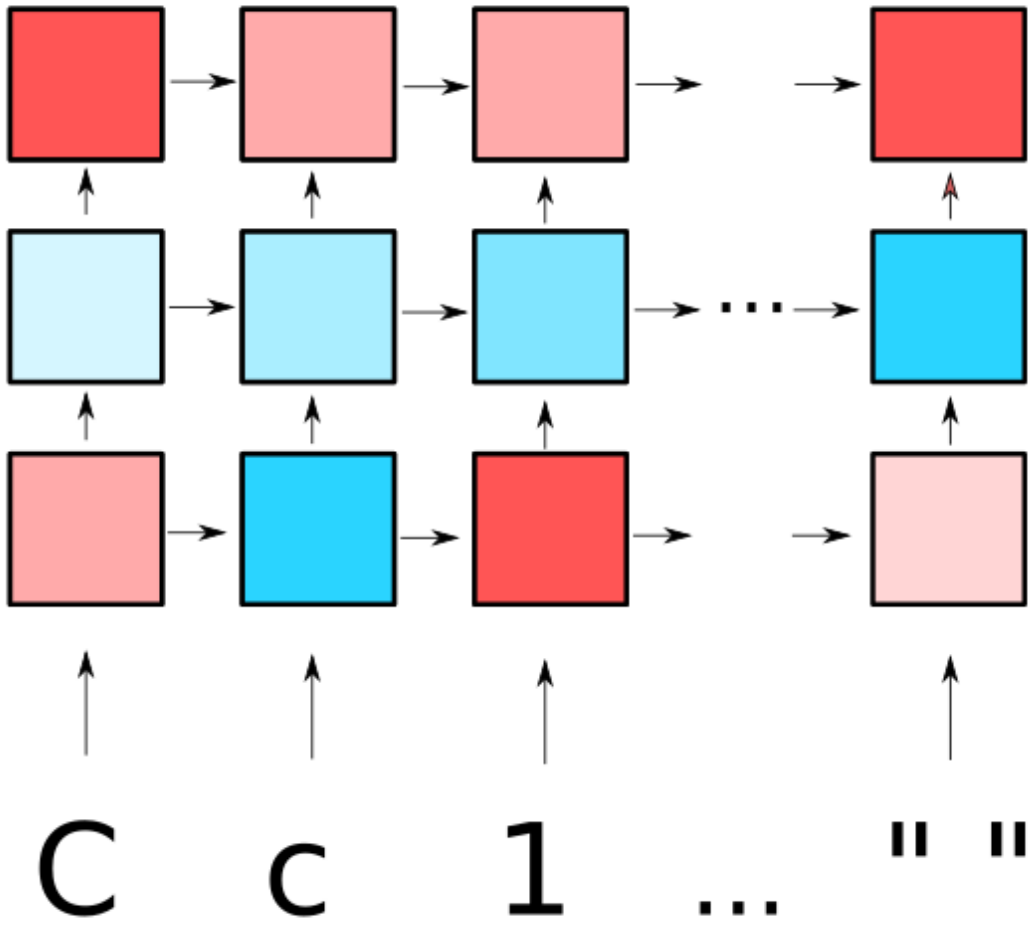
LSTM RNN in Action



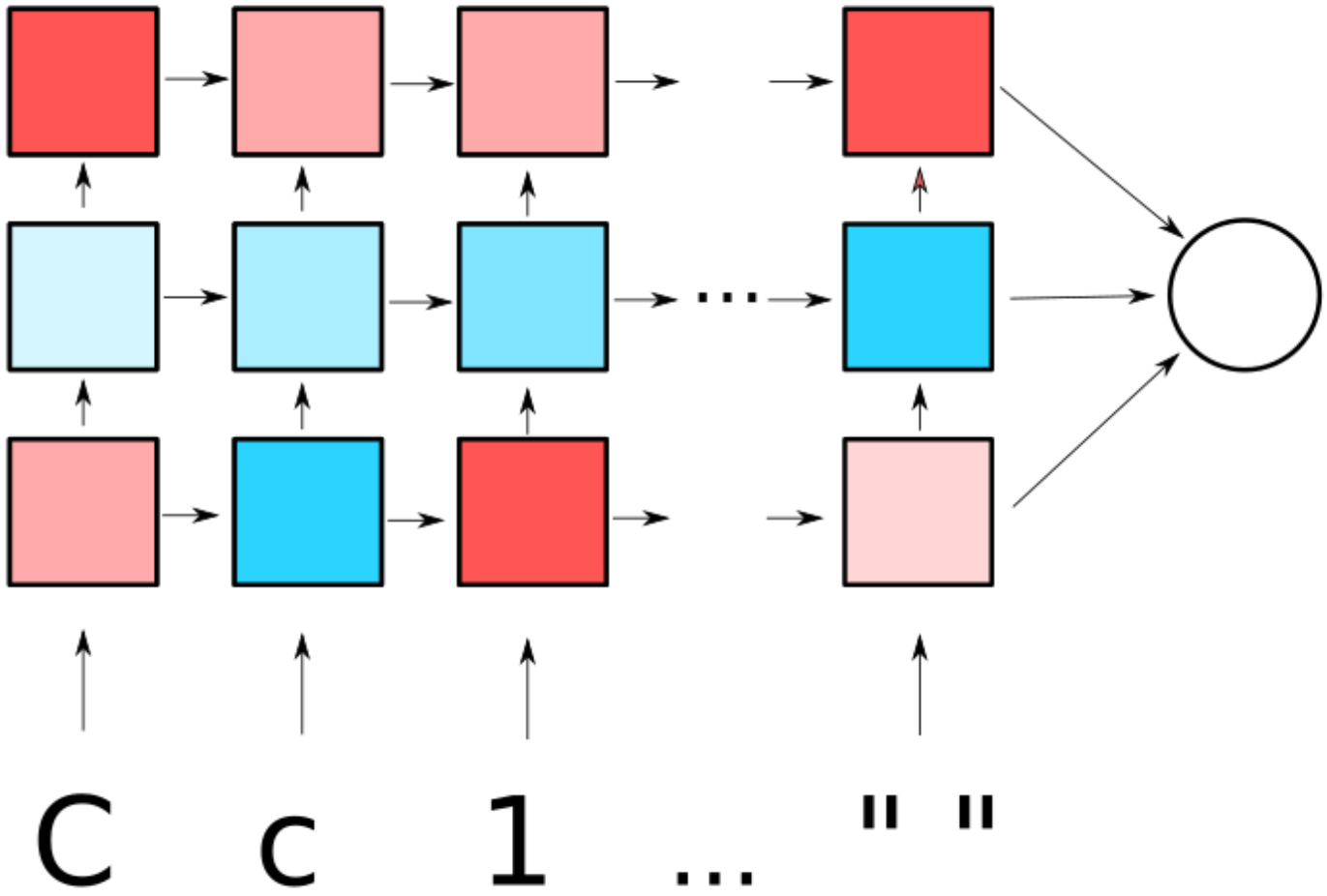
LSTM RNN in Action



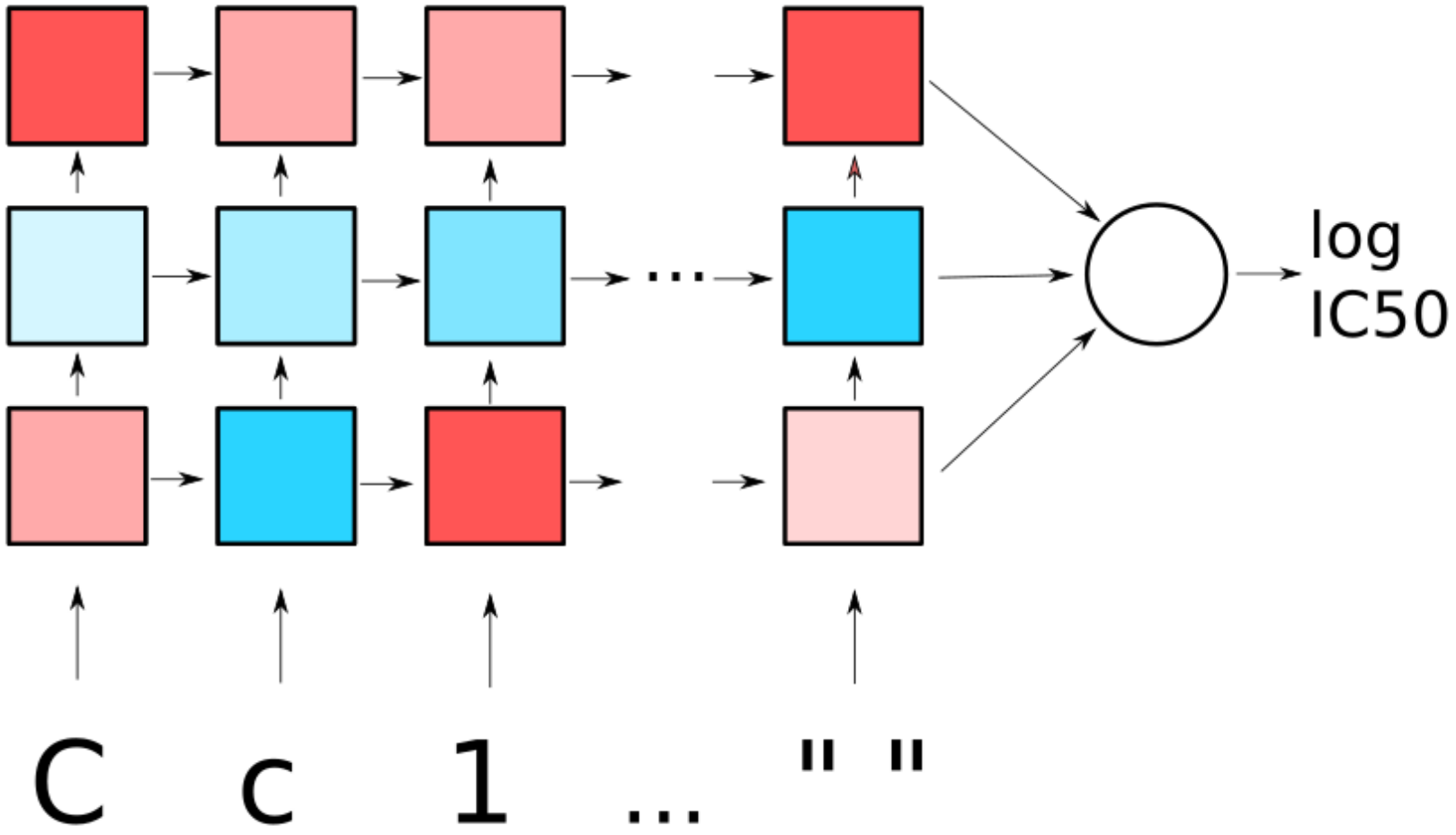
LSTM RNN in Action



LSTM RNN in Action



LSTM RNN in Action



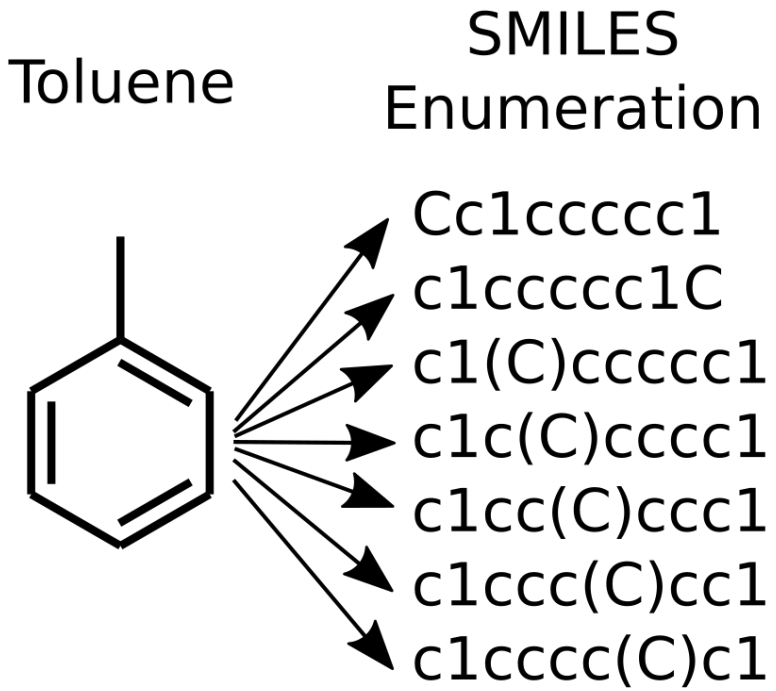
But we need a lot of DATA!

Data Augmentation

- A cat is a cat is a cat...
- Modified pictures with a recognizable cat
- Zooming, cropping, mirroring, flipping, rotation, hue, color, contrast, etc. + combinations
- => Neural network gets more training examples from same number of labeled pictures

SMILES Enumeration

- The serialization of molecules is ambiguous
- Canonical SMILES ensures a 1:1 relationship between molecule and SMILES
- I go the other way and generate multiple SMILES for the same molecule
- Works as data augmentation?



RDKit Code 1

```
from rdkit import Chem
from randomizemolblock import RandomizeMolBlock

def RandomizeMol(mol):
    """Function that randomizes an RDKit mol by round tripping a molblock"""
    mb = Chem.MolToMolBlock(mol)
    mb = RandomizeMolBlock(mb)
    return Chem.MolFromMolBlock(mb)

def randomize_smile(smile):
    """randomize a SMILES"""
    mol = RandomizeMol(Chem.MolFromSmiles(smile))
    return Chem.MolToSmiles(mol, canonical=False)
```

RDKit Code 2

```
def get_mol_set(smile, tries=10000, split=True):
    """Make a set of unique randomized SMILES"""
    s = set()
    canonical = Chem.MolToSmiles(Chem.MolFromSmiles(smile))
    s.add(canonical)
    for i in range(tries):
        s.add(randomize_smile(smile))
    print "total %s found"%(len(s))
    if split:
        s.remove(canonical)
        return canonical, s
    else:
        return s
```

Free NN Tools and High level API's

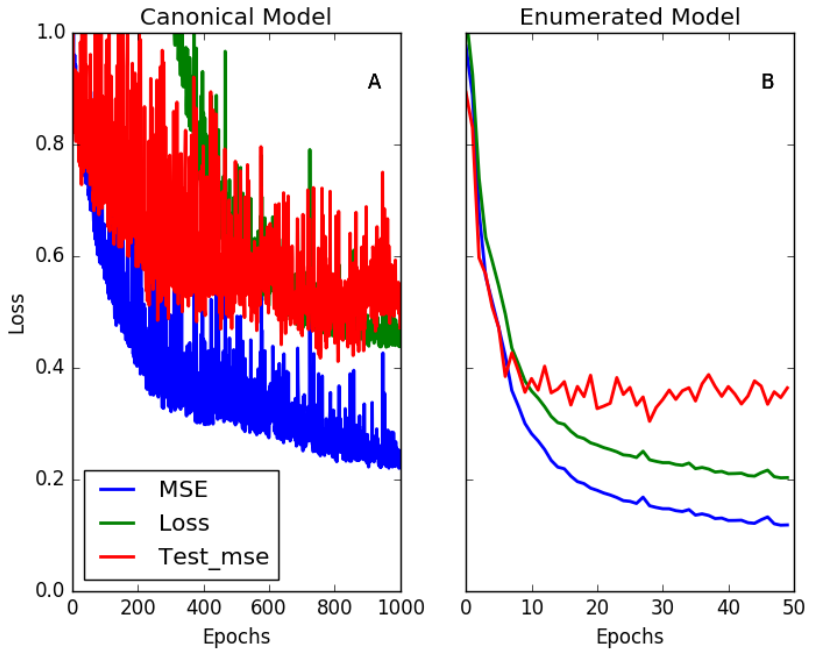
- Python Tensor libraries for GPU computing
  - Theano
  - TensorFlow (Google)
- High Level Python Api's
  - Keras (Now part of TensorFlow)

Example Keras Code

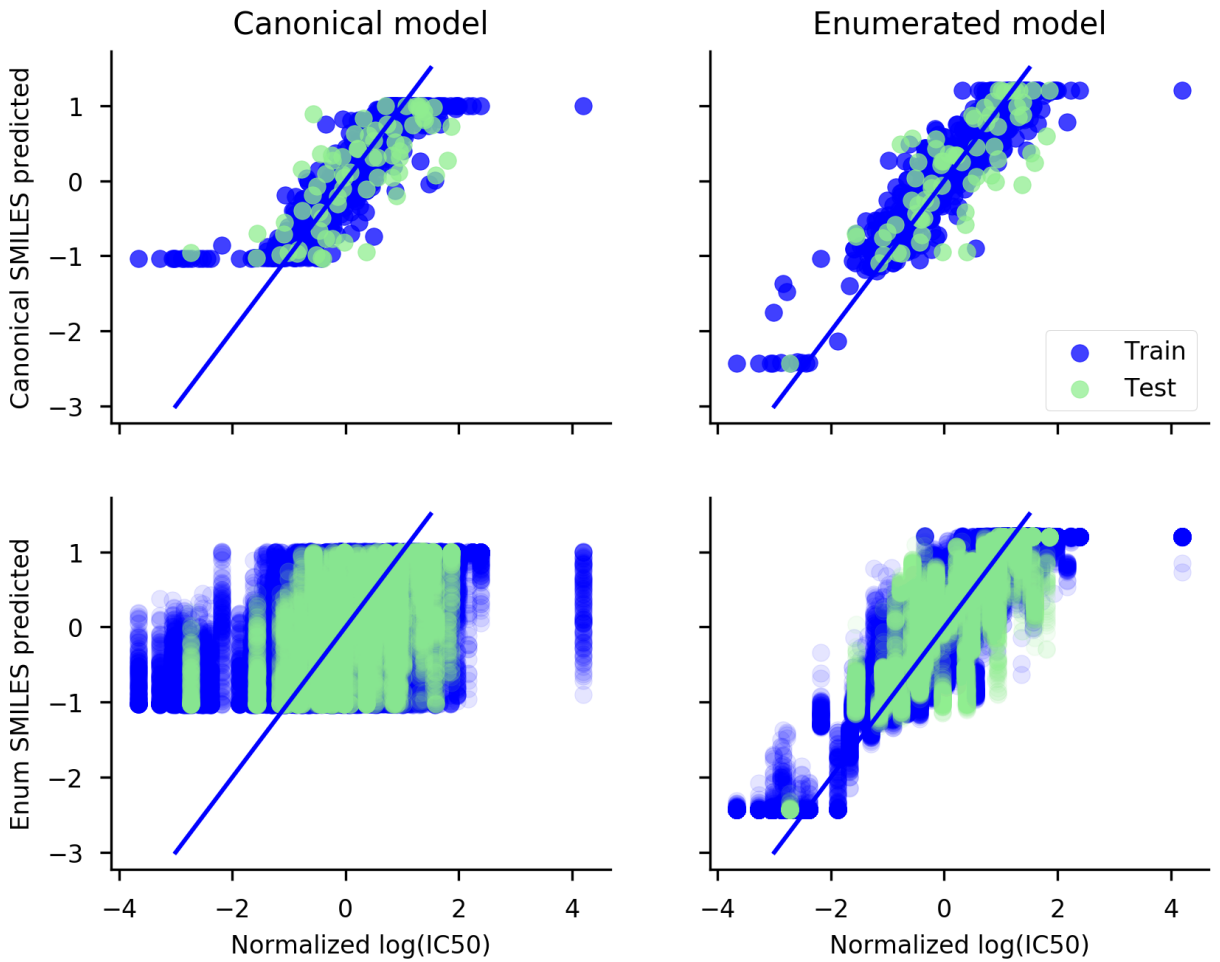
```
#Define model

model = Sequential()

model.add(LSTM(64, input_shape=(X.shape[1], X.shape[2]), dropout_W =
0.19))

wr2 = WeightRegularizer(l2 = 0.01, l1 = 0.005)

model.add(Dense(y.shape[0], activation = "linear",W_regularizer=wr2))


#Compile model to GPU/CPU code

model.compile(loss='mse', optimizer='RMSprop')


#Train

train_history= model.fit(X_train,y_train, nb_epoch=50, batch_size=800,
validation_data=(X_test,y_test))
```

DHFR Test of SMILES Enumeration

- 756 dihydrofolate inhibitors with *P. carinii* DHFR inhibition data.
- Canonical dataset: **602** train and **71** test molecules
- Enumerated dataset: **79143** and **9412** SMILES
- Enumeration made tuning and training easier
- Enumeration gave lower loss and R^2 on test set

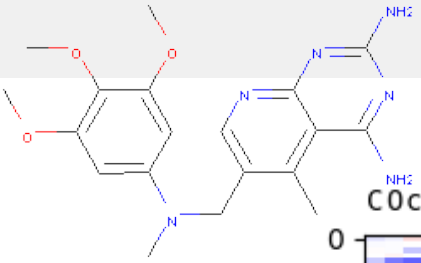


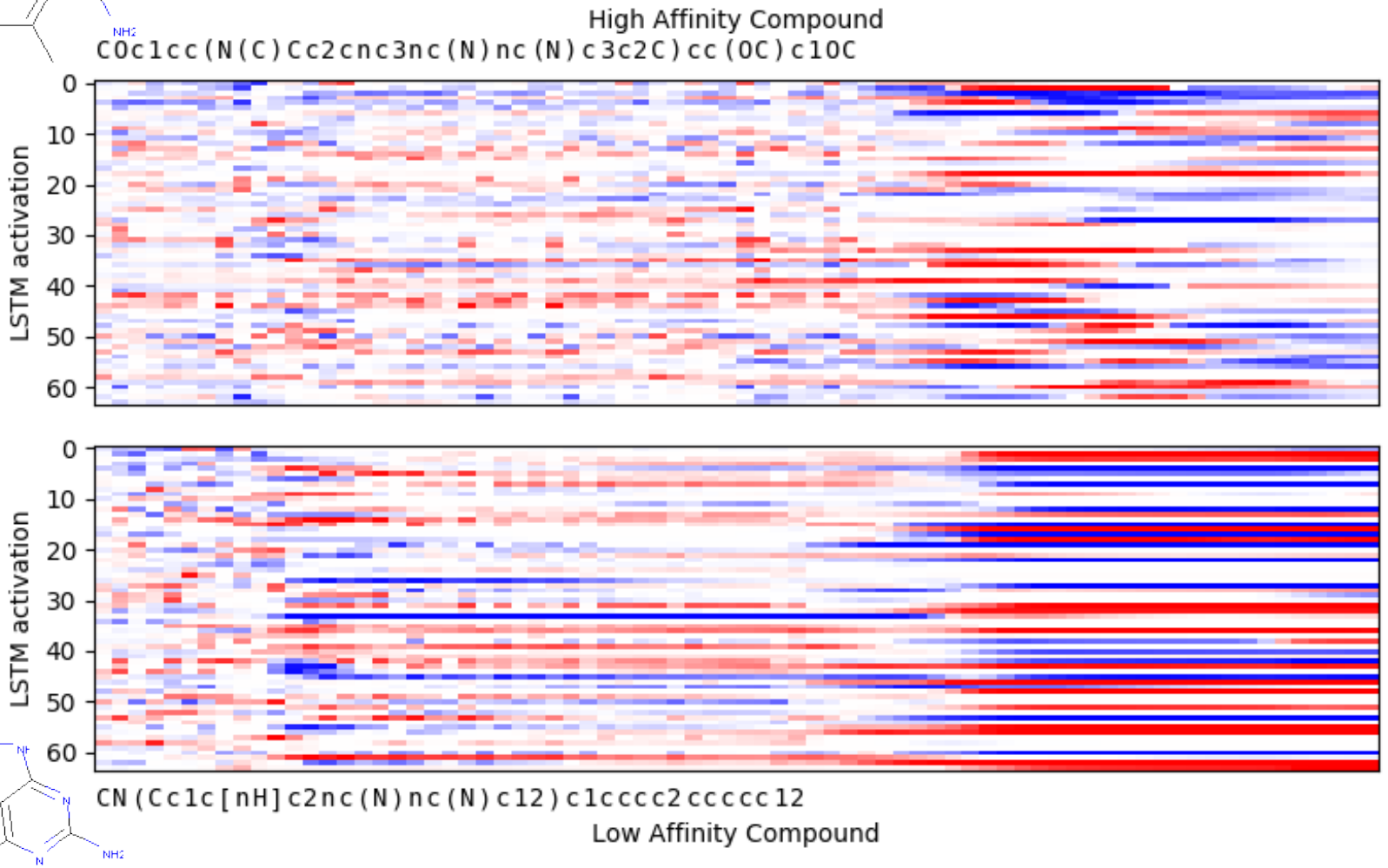
Comparison of Models

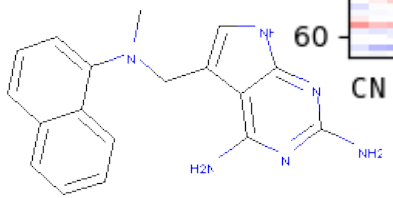


- E. J. Bjerrum. “SMILES Enumeration as Data Augmentation for Neural Network Modeling of Molecules” https://arxiv.org/abs/1703.07076

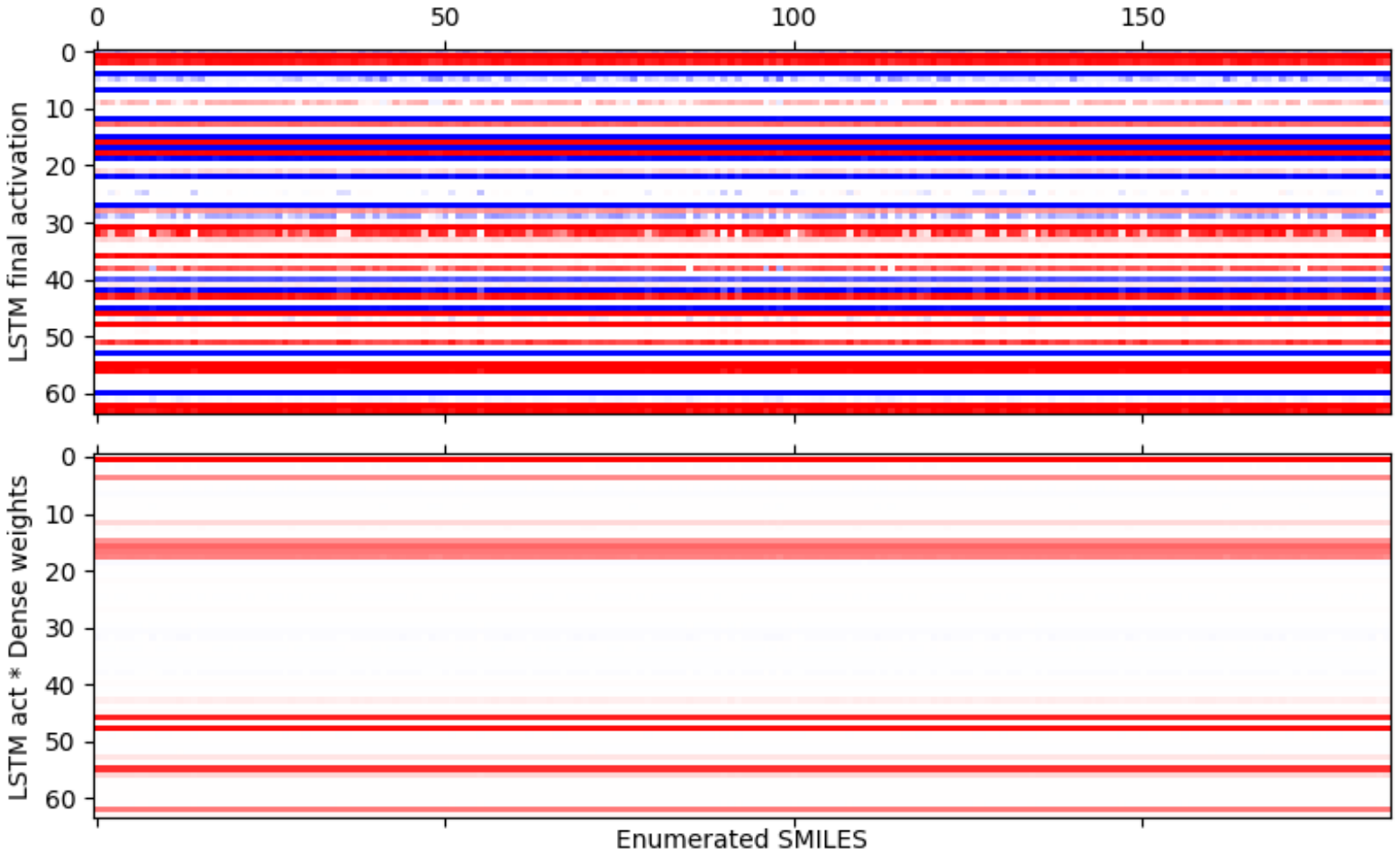
LSTM Activation







Final Vector Variability



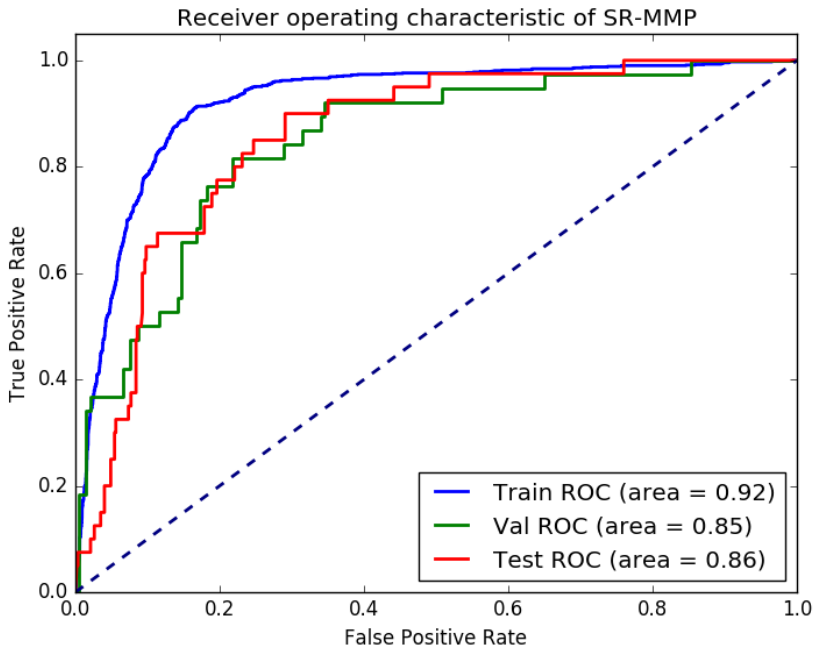
TOX21 Dataset Shootout

- LSTM-NN trained on Tox21 dataset
- 11 thousand compounds, 12 assays
- Co-modeling of assay results: 98295 data points
- Over 700.000 augmented samples

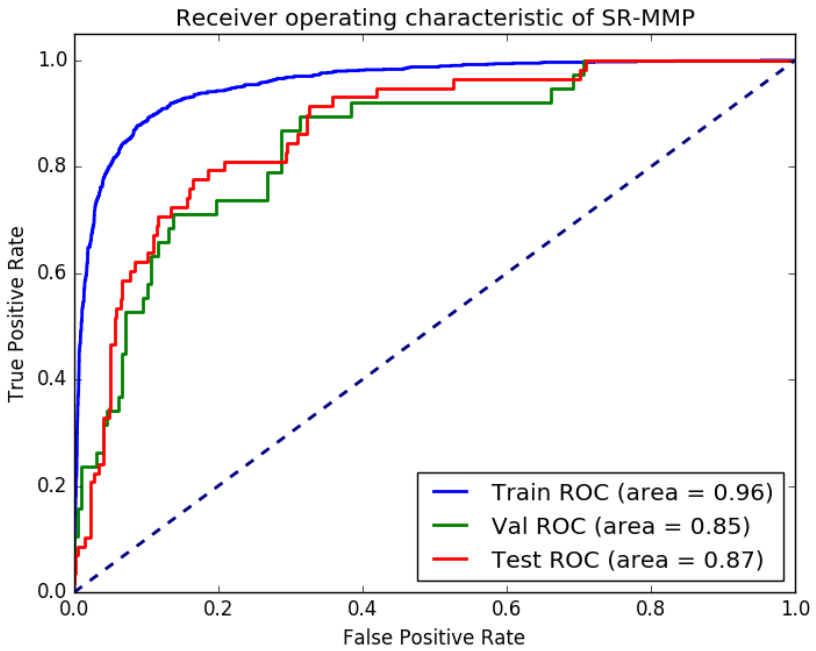
- Feed forward neural network
- Morgan Fingerprints as molecular representation
- Both models hyper parameters were optimized with Gaussian processes

Performance is on par

Smiles LSTM-DNN



FP DNN



Auc Val 0.85, single DNN with MT learning
DeepTox: Toxicity Prediction using
Deep Learning: doi: 10.3389/fenvs.2015.00080

LSTM in QSAR

- Enables input of smiles strings directly to QSAR model
- Slow to train
- Needs “large” datasets
- Data augmentation helps
- On par with optimized FFNN models with FP/descriptors as input

- Future investigation
  - Test more datasets
  - How to best co-model data types
  - Could be merged with other types of input (e.g. FP, descriptors, Assay results)
  - Can final vector be used for other purposes?

Conclusions

- Neural Networks can be used to handle unusual tasks
- Spill over effects from research in other areas
- Good, free, high level API's are available
- LSTM/GRU suitable for SMILES input and output
- Flexible Integration
  - Co-modeling of outputs
  - Merging of inputs
  - Feedback to/from work flows
- Consider the nature of the problem (dataset size, complexity, wanted outcome), NN's may not be the optimal choice
- Many hyper parameters to tune as well as architecture choice
  - Gaussian Process Optimization
- I'm quite enthusiastic :-)

Thank you

- Looking for research collaborations
- Questions/Contact: esben@wildcardconsulting.dk
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- Science blog and more:

www.wildcardconsulting.dk/ useful-information