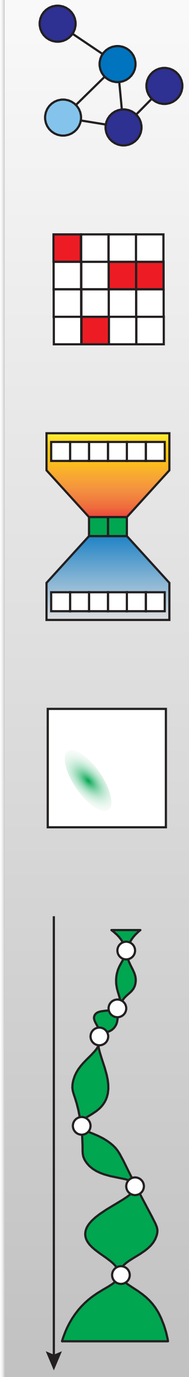
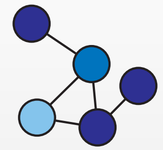
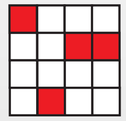
Deep Learning Methods for Learning Phenotype from Genotype

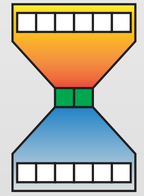
Eric J. Ma
Dept. Biological Engineering, MIT

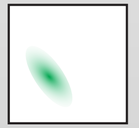


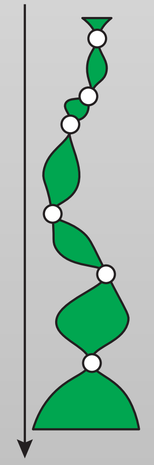
Automatic discovery of structural features predictive of phenotype











Sequence regression ignores positional interactions

Sequence	DR
PQVTLWQKPIVTIKIGG	2.4
PQVTLWQRPIVTIKIGG	3.8
PQVTLWQRPLVTIKIGG	9.4
PQVTLWQRPIVTIKIGG	3.5

Sequence regression ignores positional interactions

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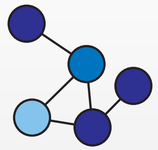

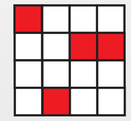

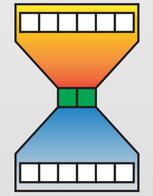

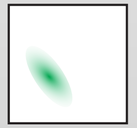

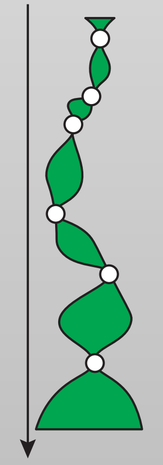

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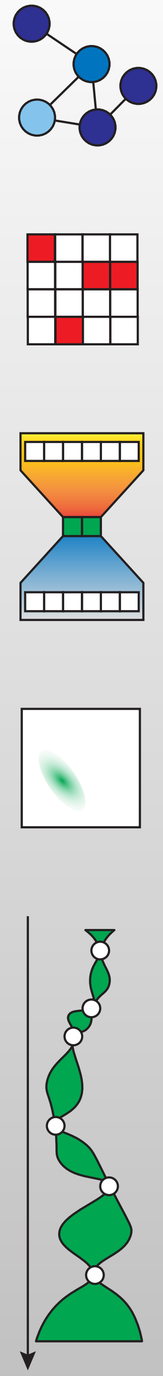

Proteins have a natural graph (network) representation

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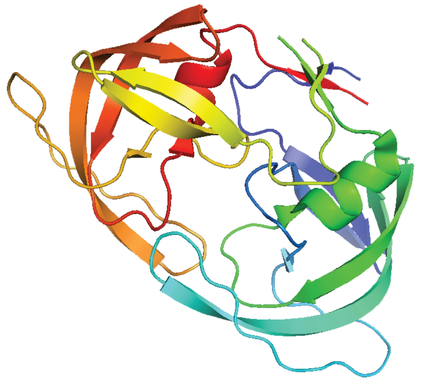
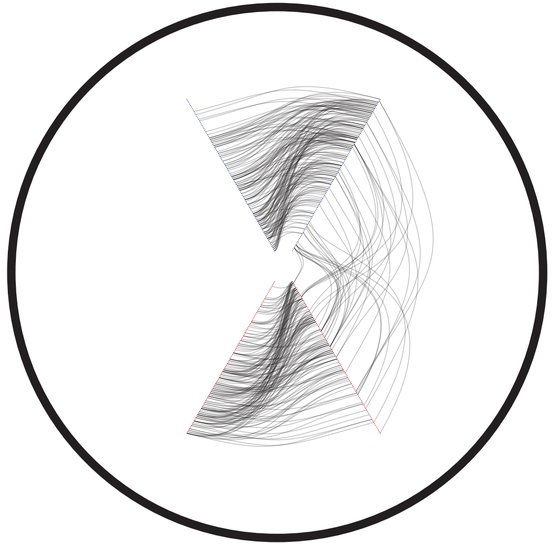
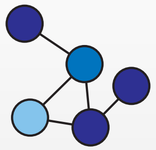
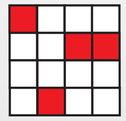
Homology Model

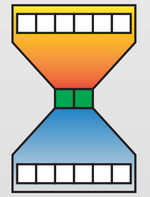


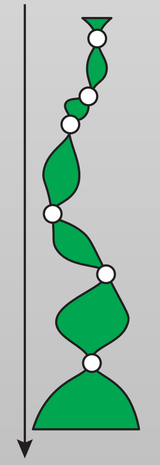
Network Representation











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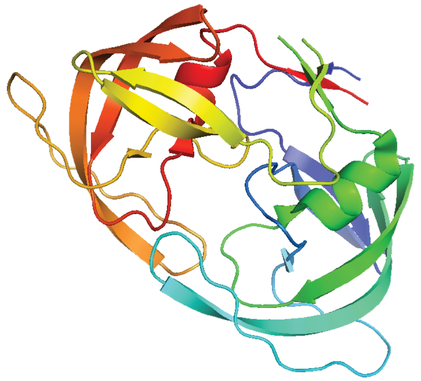
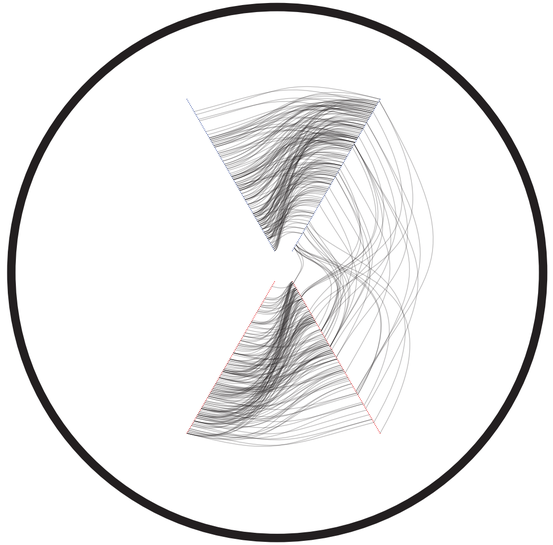
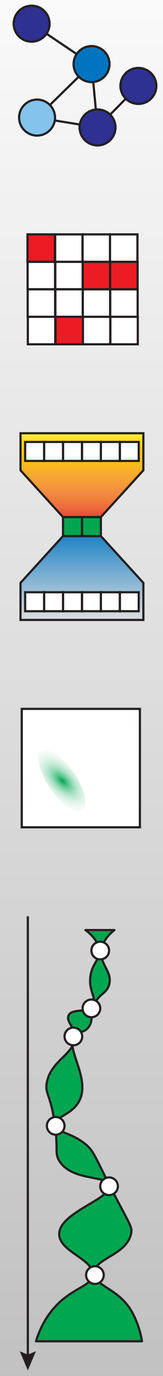


Network Representation



Nodes: Amino acids
Edges: Biochemical interactions



Can graph regression on proteins help us interpret structure better?

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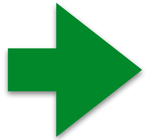
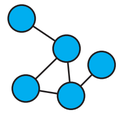
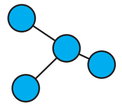
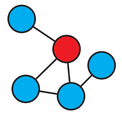
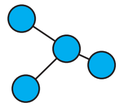
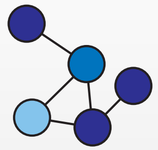
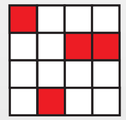
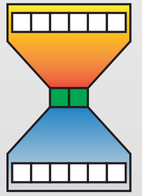
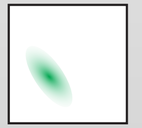


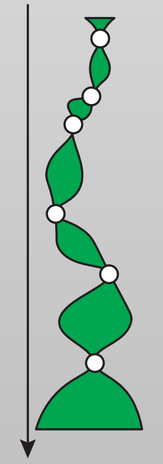
Structure Graph	DR
	2.4
	3.8
	9.4
	3.5







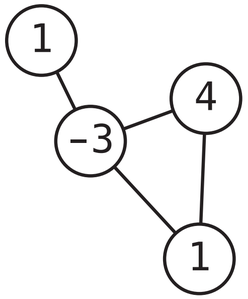


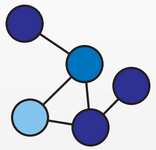


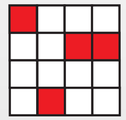
Graph convolutions let us compute unique fingerprints for distance graphs

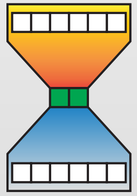
Input Convolution Non-Linearity Fingerprint

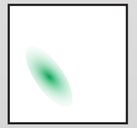
Scalars

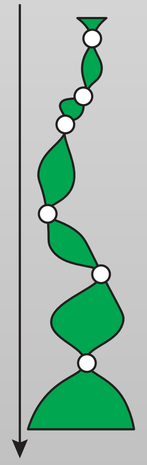












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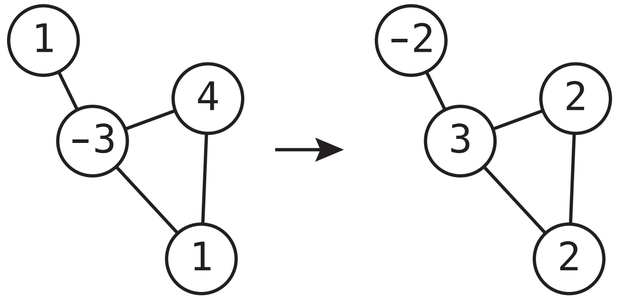

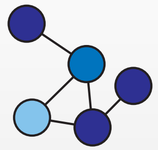

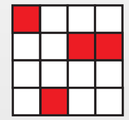

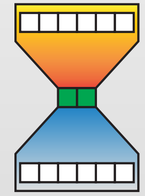

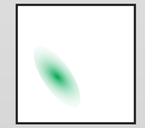

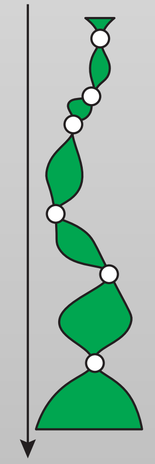

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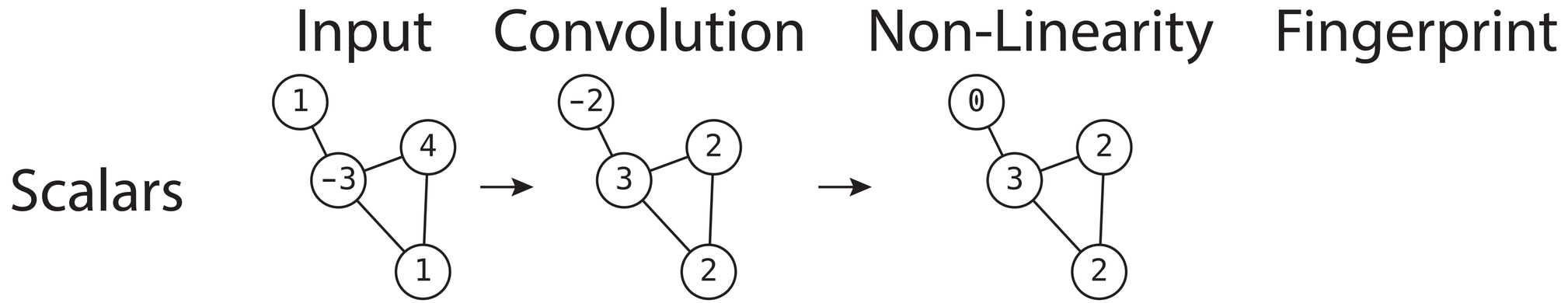

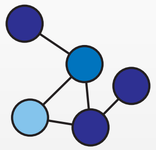

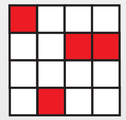

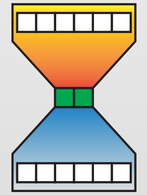

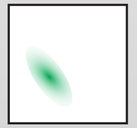

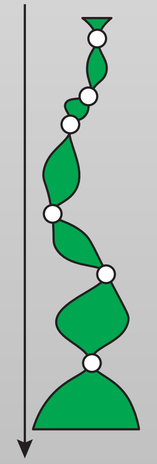

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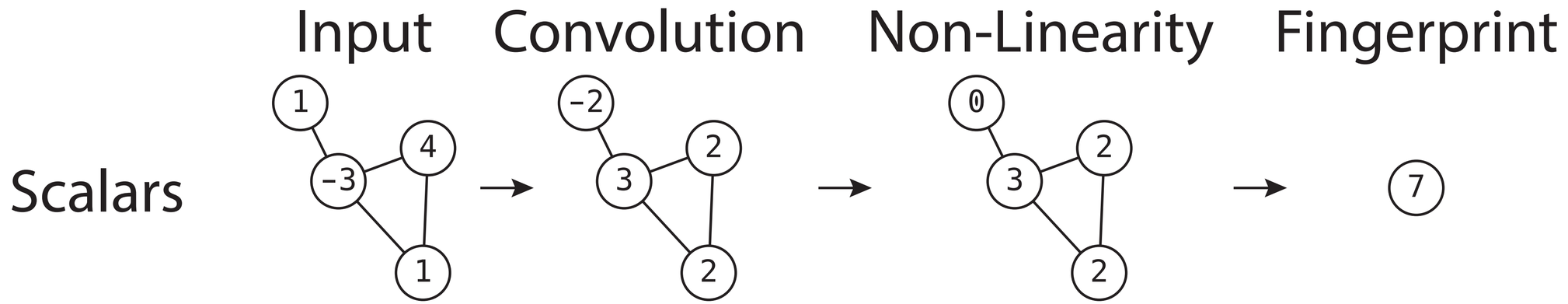
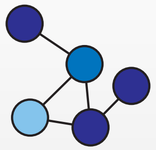
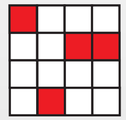
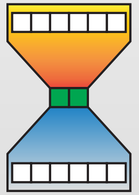
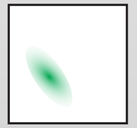
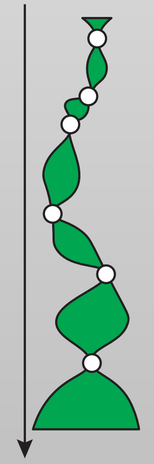




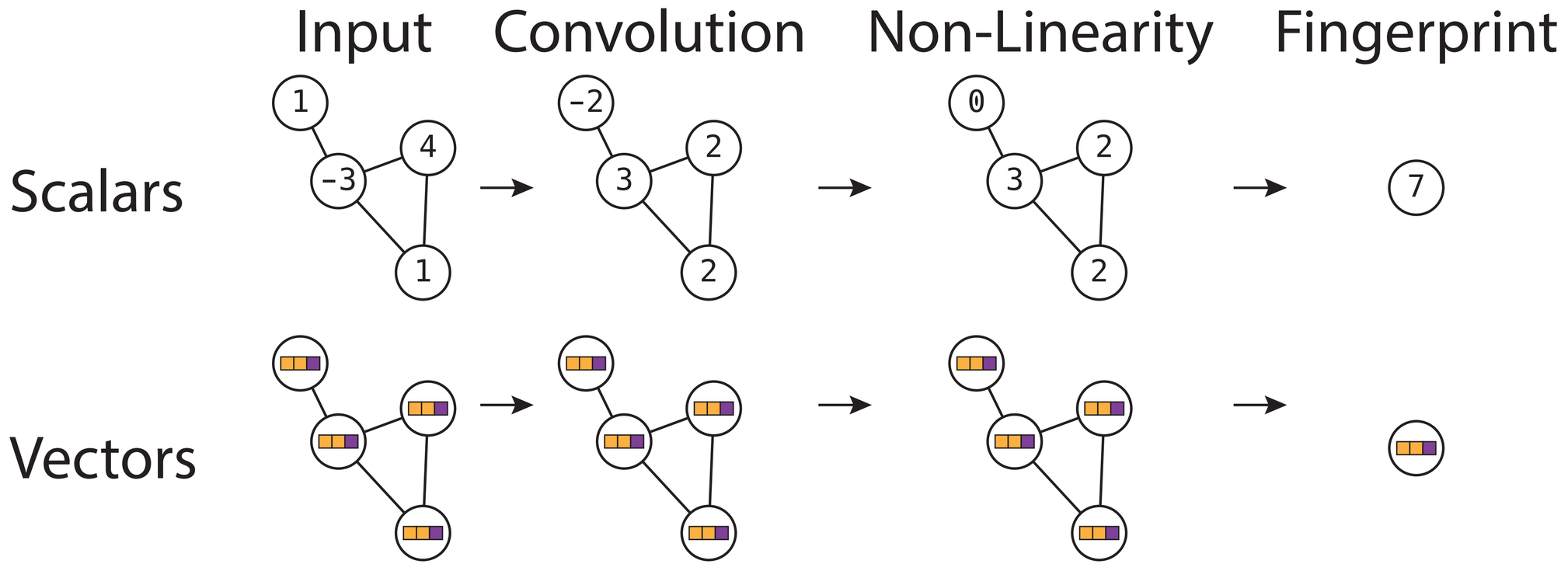


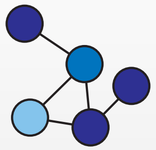
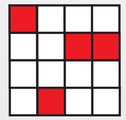
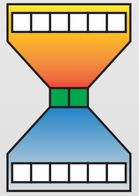
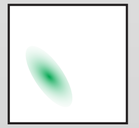
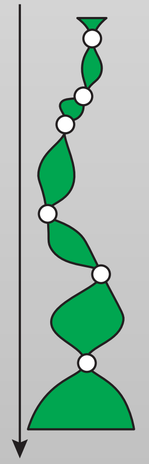




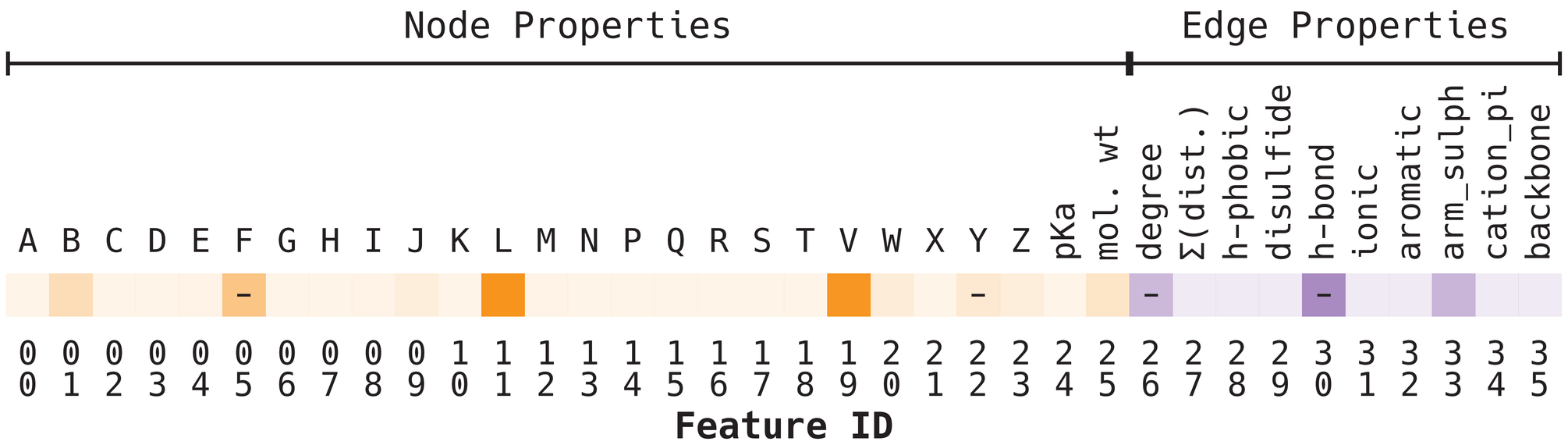


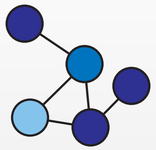
Graph convolutions let us compute unique fingerprints for distance graphs

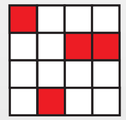


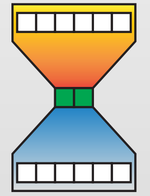






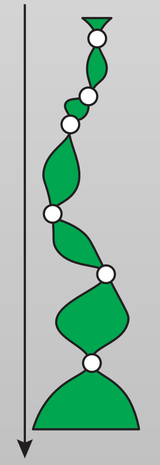
Graph convolutions let us compute unique fingerprints for distance graphs



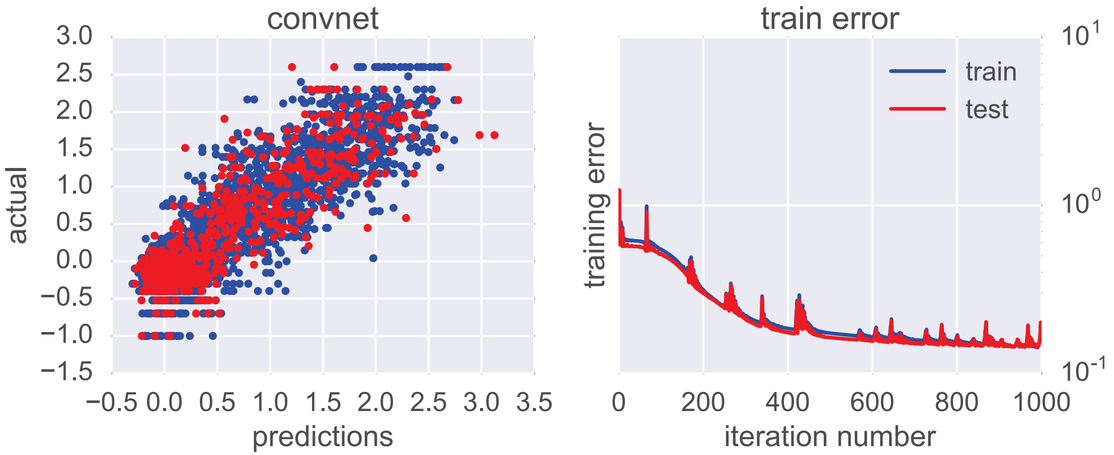


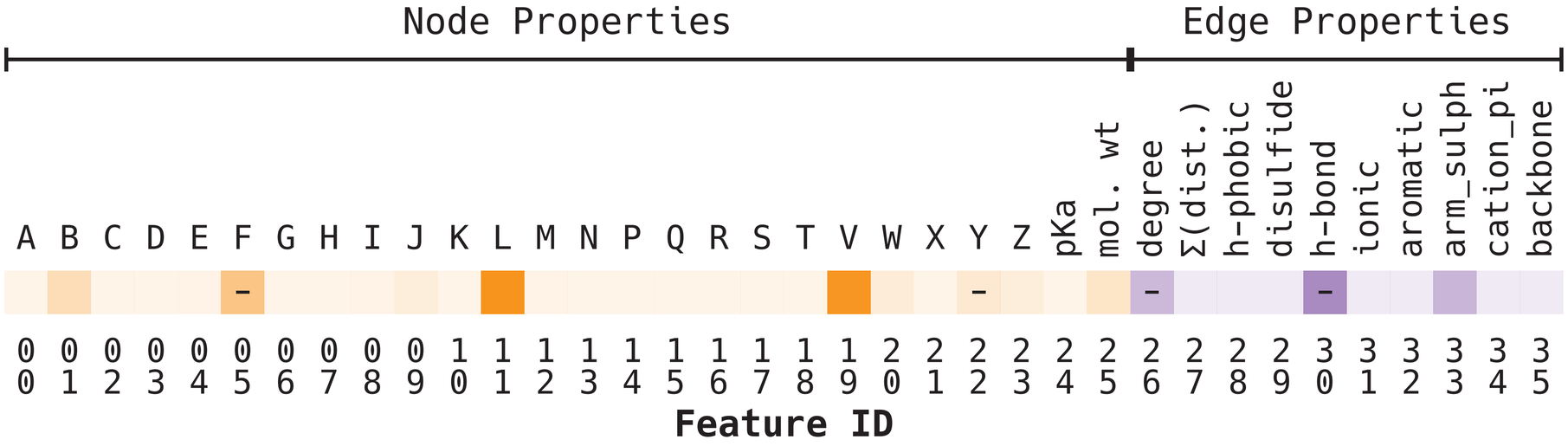




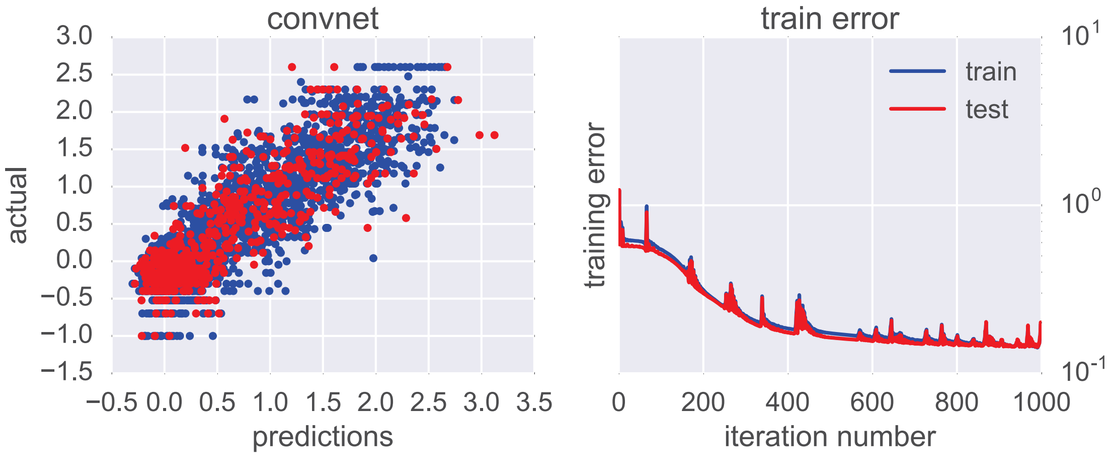


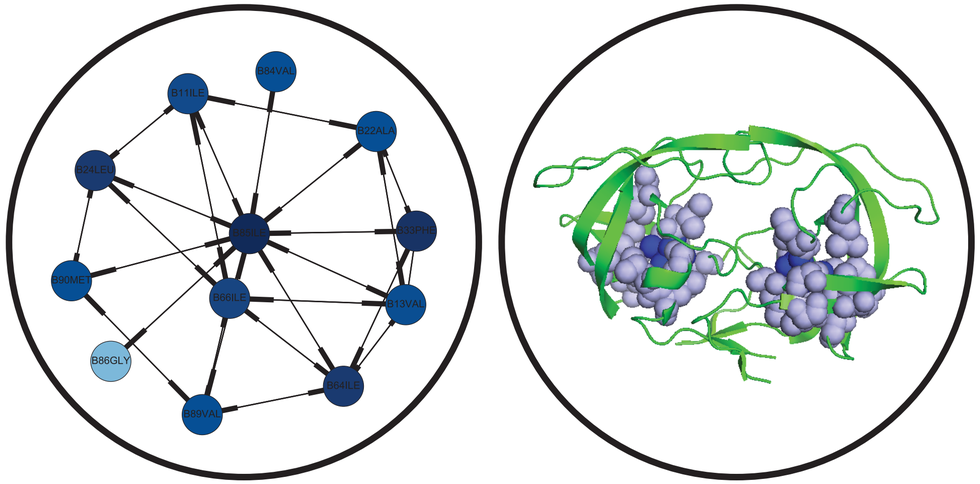
Graph convolutions automatically learn HIV protease a.a. neighbourhoods responsible for drug resistance

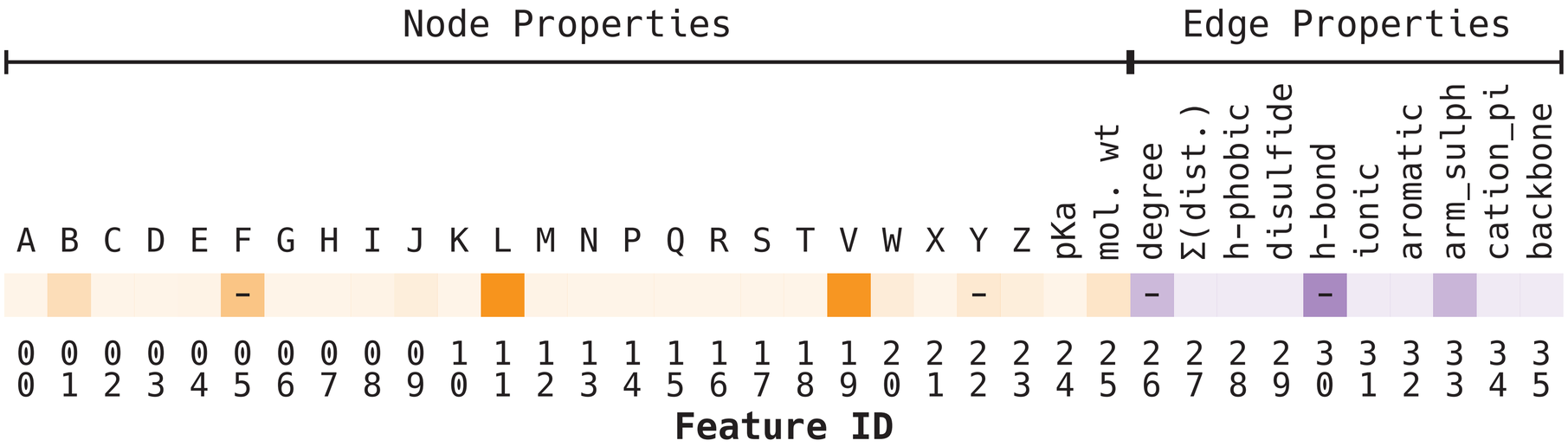


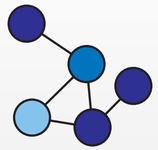


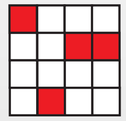
Graph convolutions automatically learn HIV protease a.a. neighbourhoods responsible for drug resistance

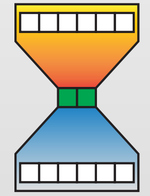


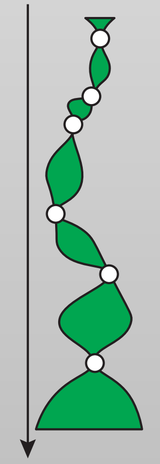




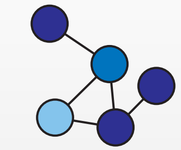
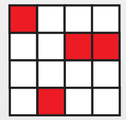
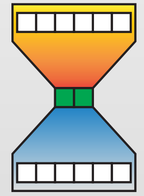
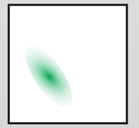
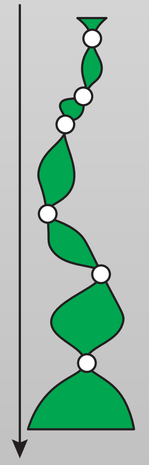




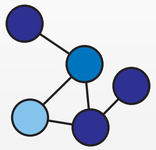


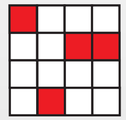


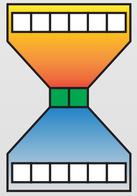
Forecasting fast-evolving pathogen sequence trajectory

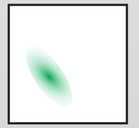






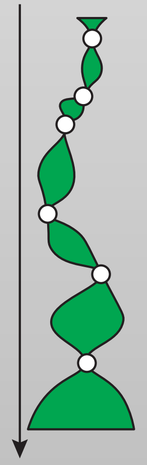
Forecasting sequence evolution is difficult because sequence space is discrete





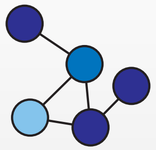


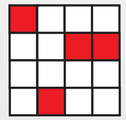


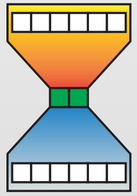


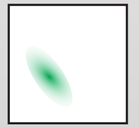
Forecasting sequence evolution is difficult because sequence space is discrete

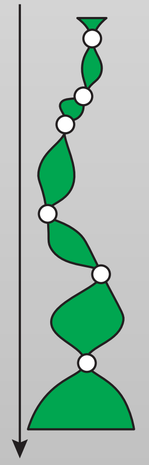
Combinatorics problem











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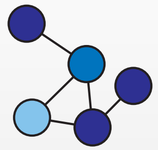
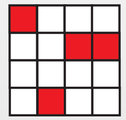
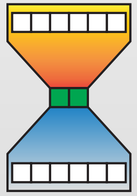
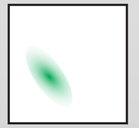
Combinatorics problem

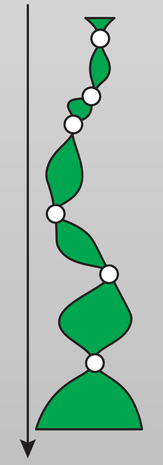
10 a.a.: 20^{10} theoretical space









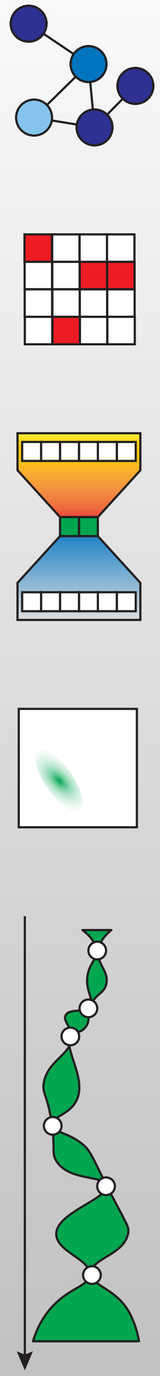


Forecasting sequence evolution is difficult because sequence space is discrete

Combinatorics problem

10 a.a.: 20^{10} theoretical space

Deep mutational scans: 10^{5} empirical space



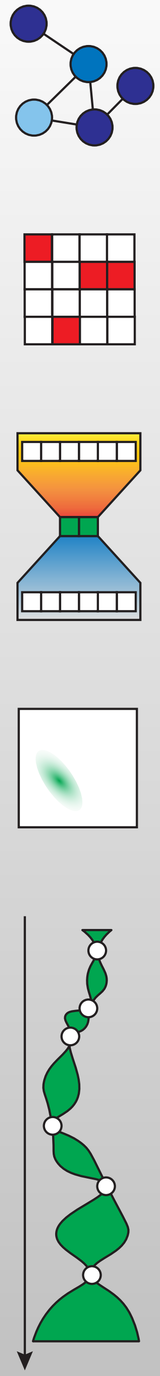
Forecasting sequence evolution is difficult because sequence space is discrete

Combinatorics problem

10 a.a.: 20^{10} theoretical space

Deep mutational scans: 10^5 empirical space

Mutational **direction** cannot be predicted easily



Variational auto-encoders provide a path towards continuous space

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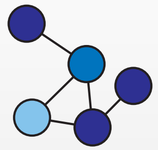
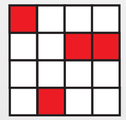
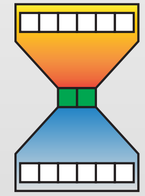
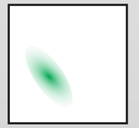
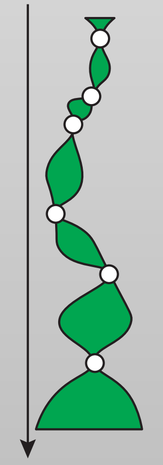
SQQAVIPNIGSRPRIRD
SQQAVIPNIGSRPRIRD
SQQAVIPNIGSRPRIRD

Variational auto-encoders provide a path towards continuous space

SQQTVIPNIGSRPRVRN
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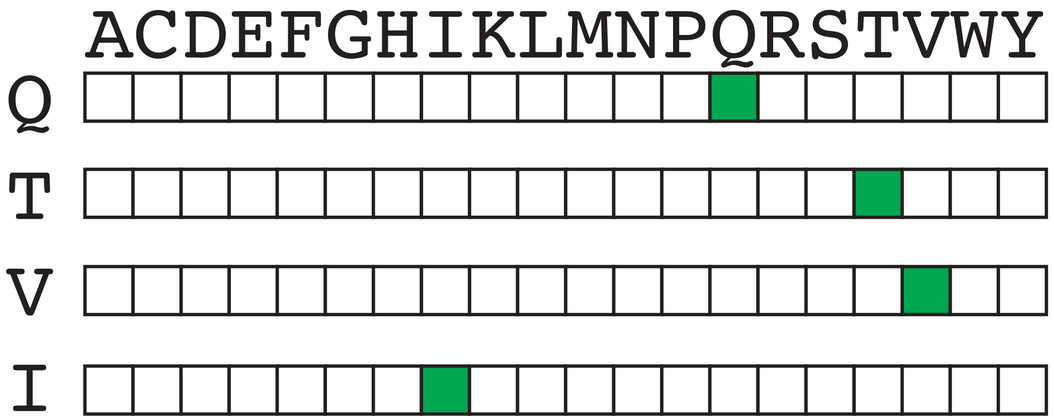

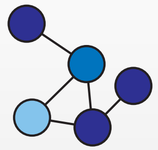

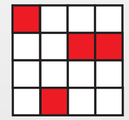

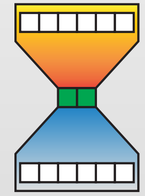

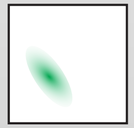

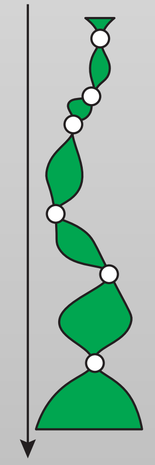

Variational auto-encoders provide a path towards continuous space

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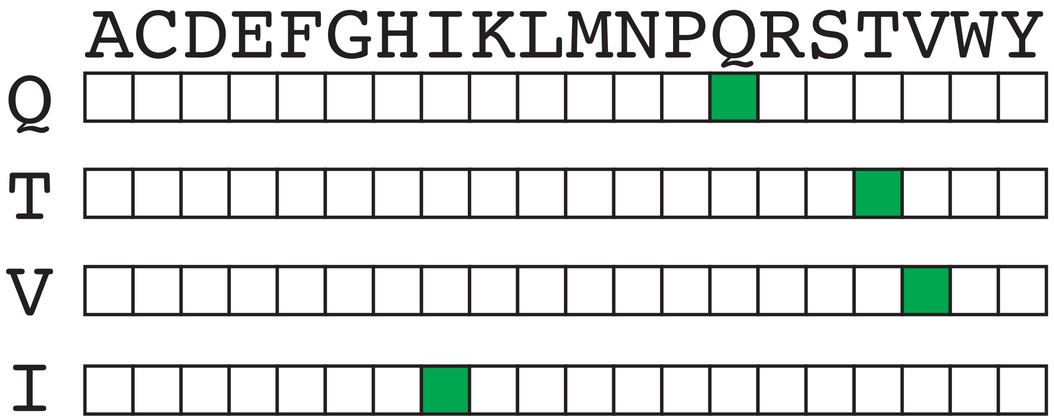
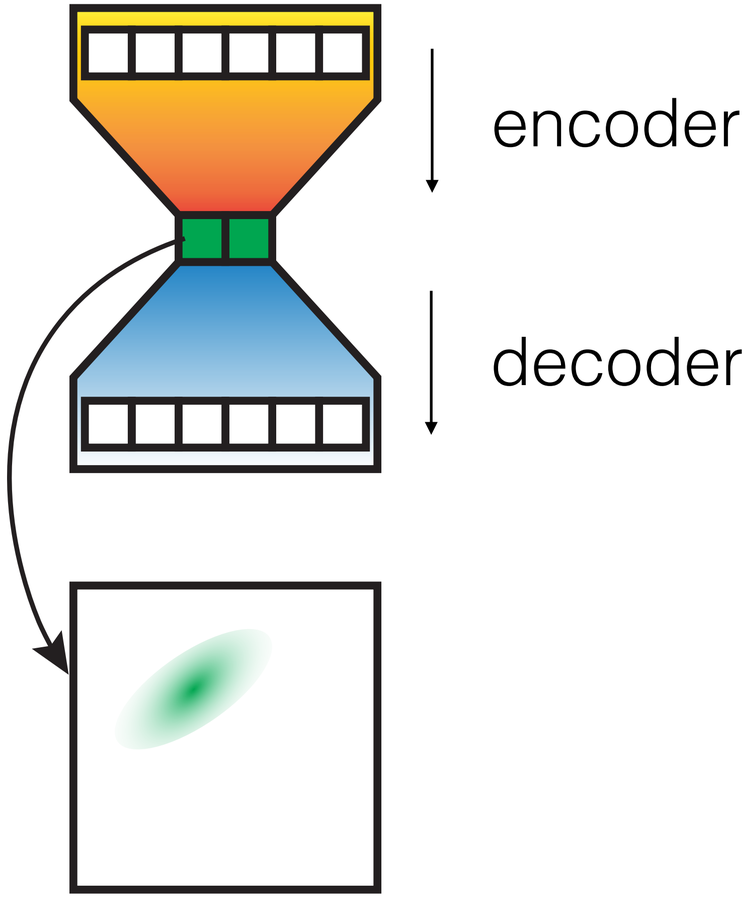
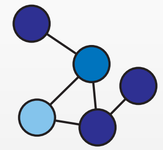
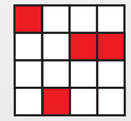
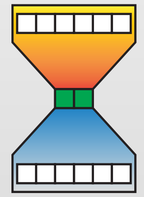
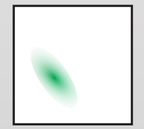


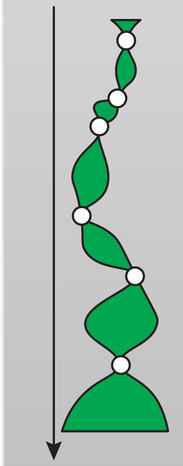




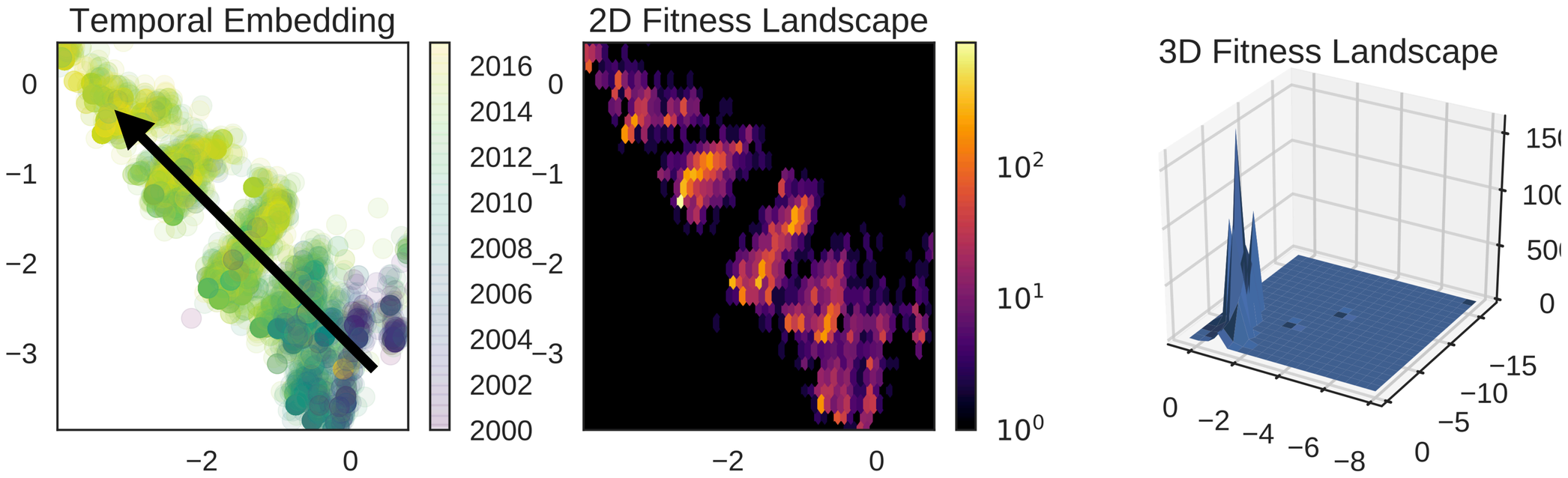




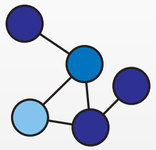


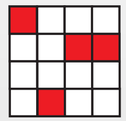


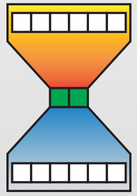
Influenza H3N2 protein evolution has direction in continuous space

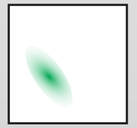


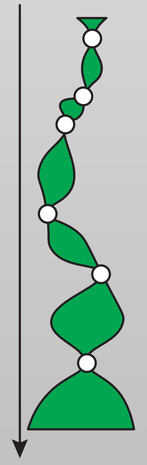
Gaussian process regression enables probabilistic forecasting & sampling of new sequence space



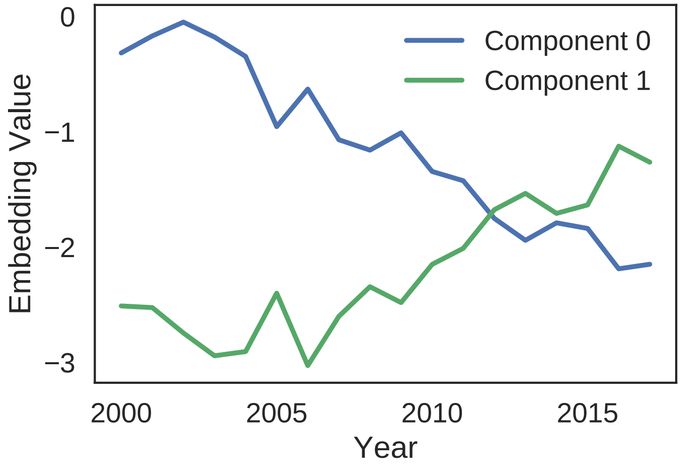


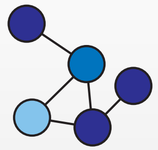


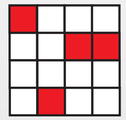


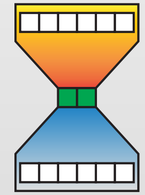


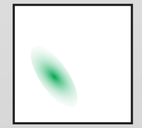
Gaussian process regression enables probabilistic forecasting & sampling of new sequence space

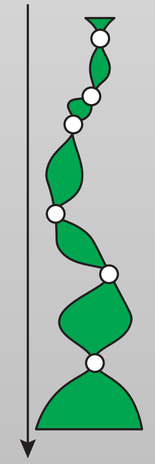




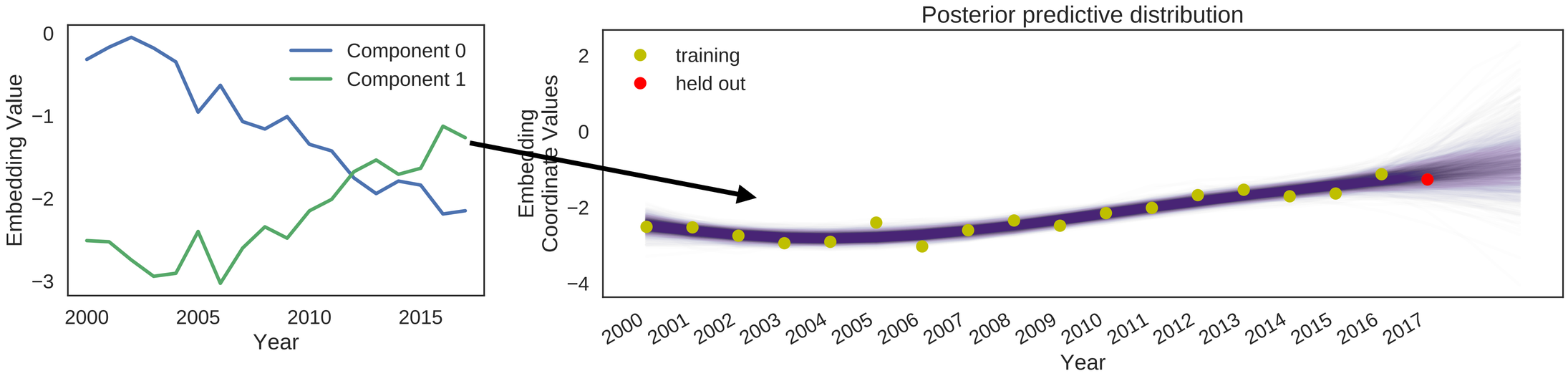


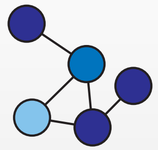


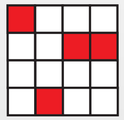


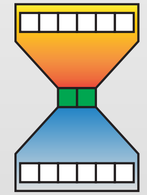


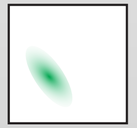
Gaussian process regression enables probabilistic forecasting & sampling of new sequence space

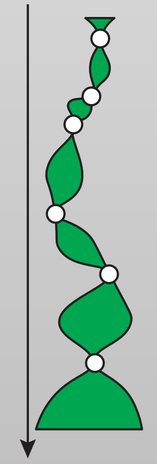




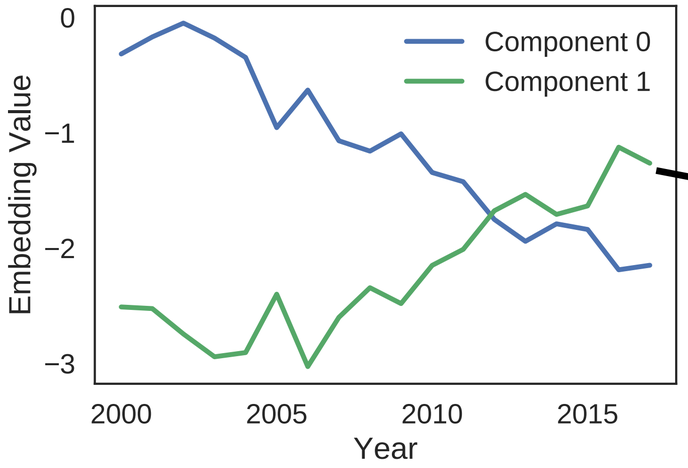


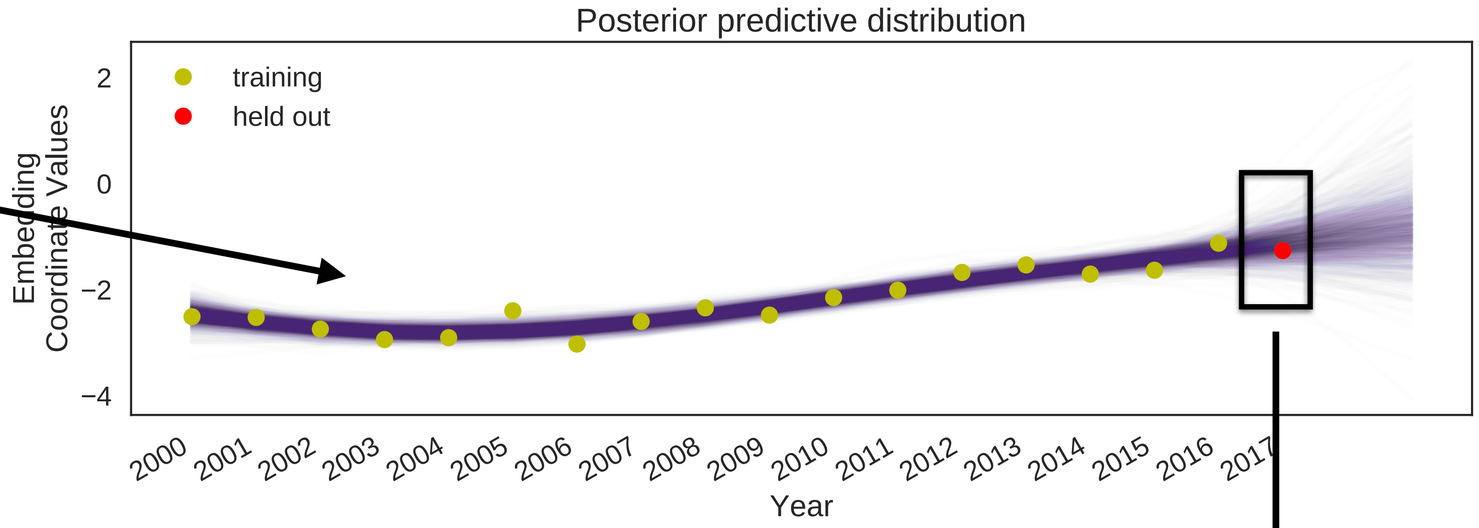


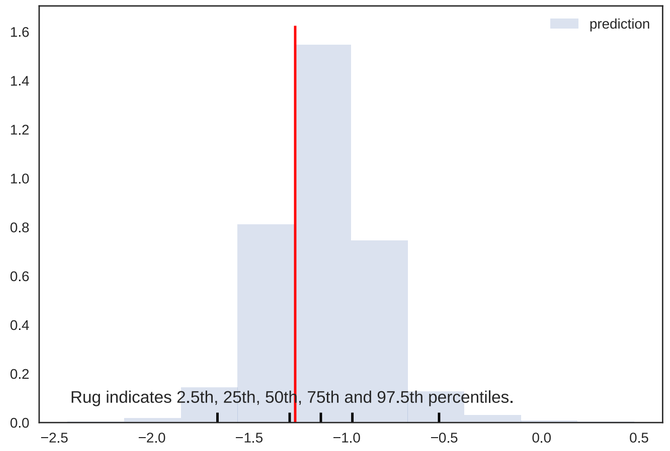


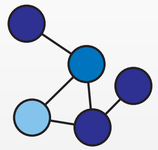


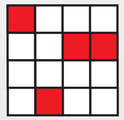
Gaussian process regression enables probabilistic forecasting & sampling of new sequence space

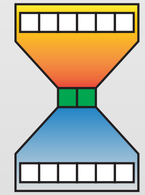


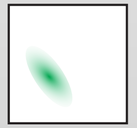


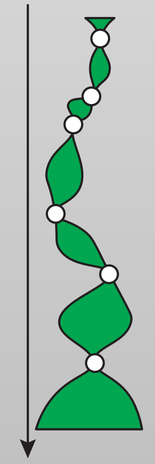




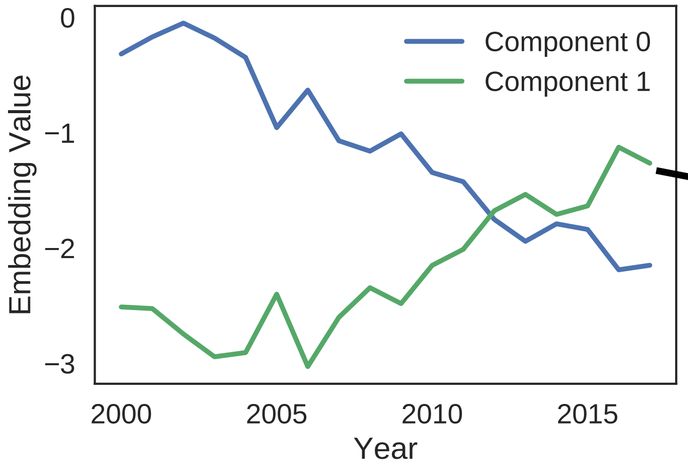


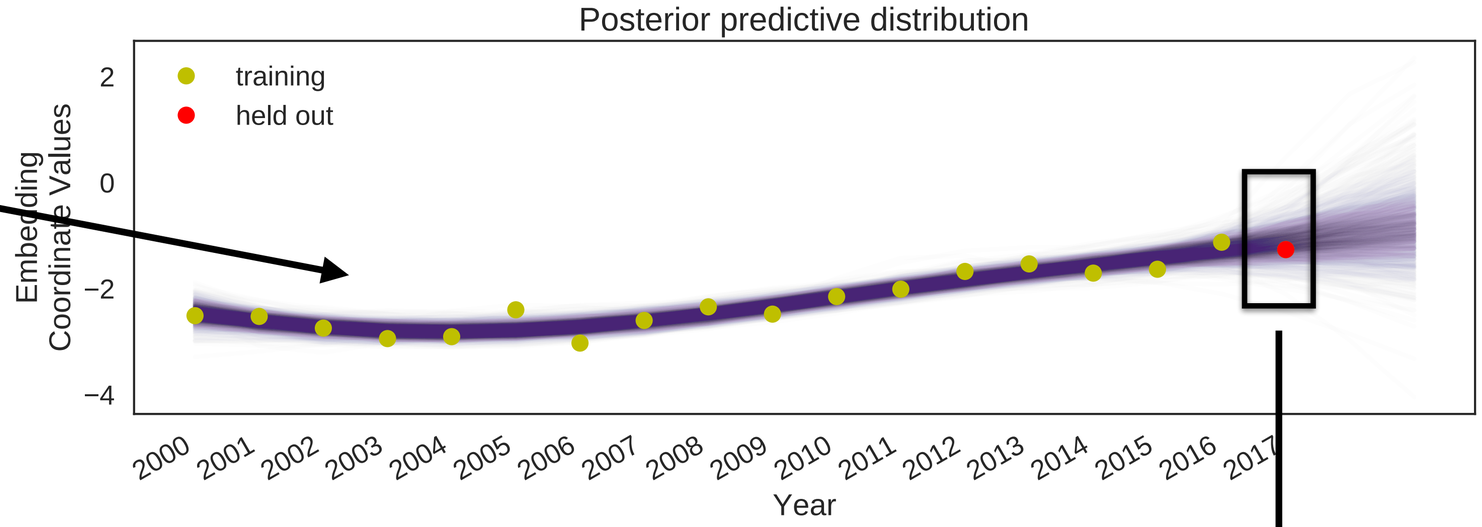


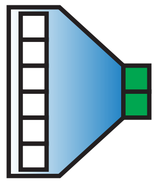


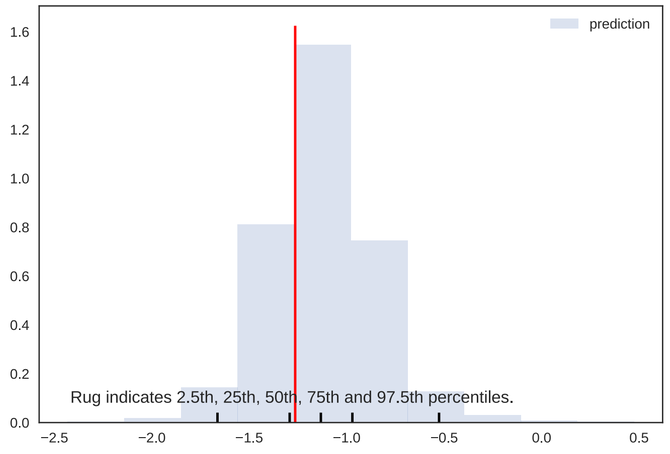


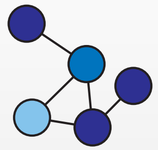
Gaussian process regression enables probabilistic forecasting & sampling of new sequence space

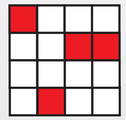


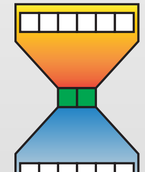


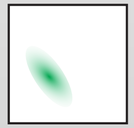


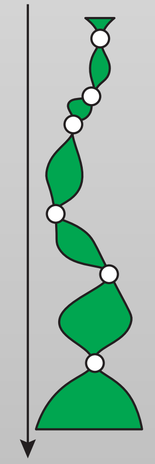




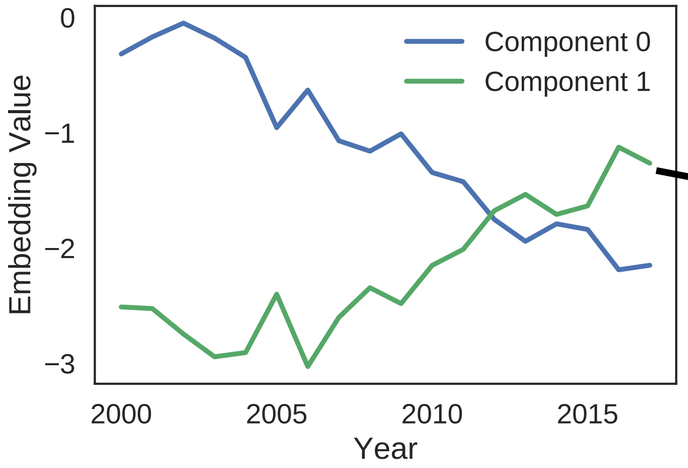


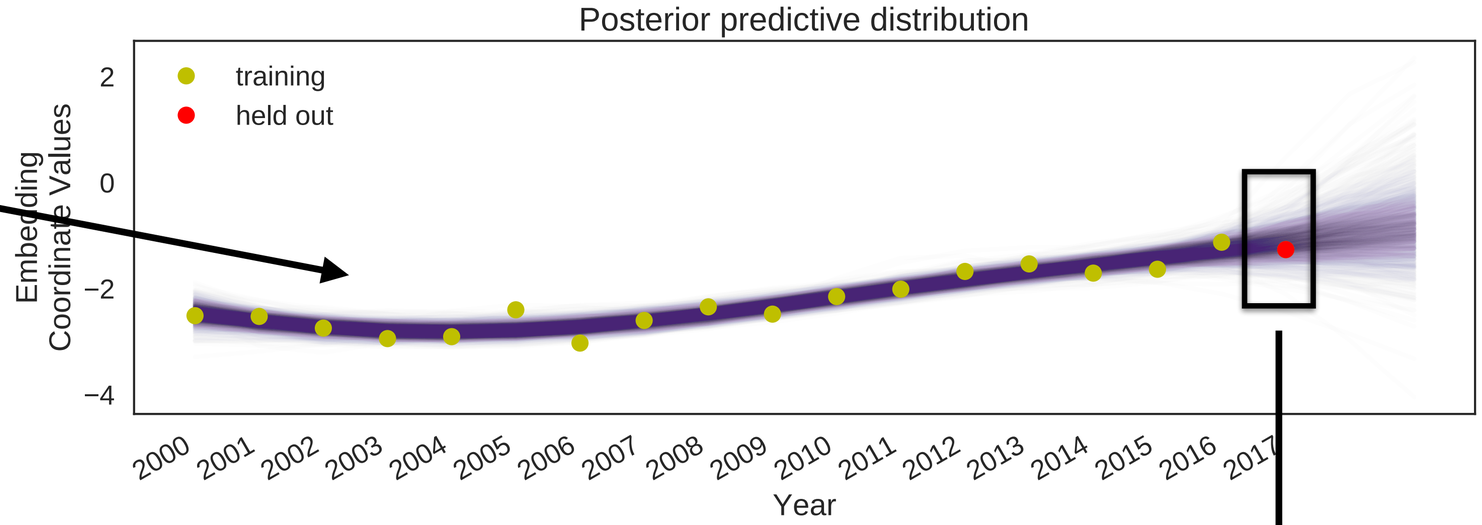






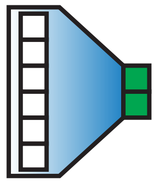
Gaussian process regression enables probabilistic forecasting & sampling of new sequence space

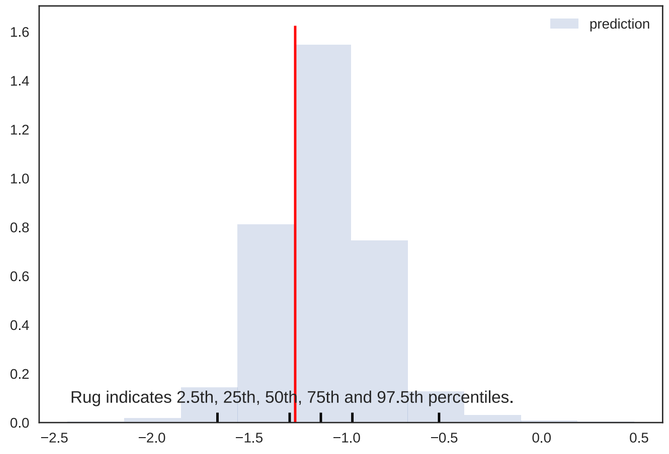




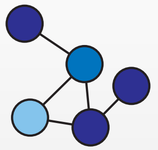
Pos. 176, 327 most likely to change.

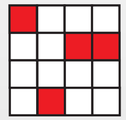
Antigenic effects moderate.

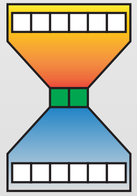


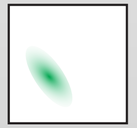


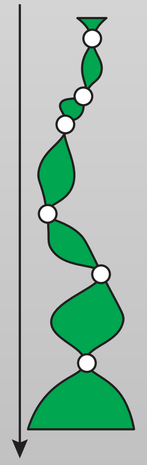
Take-Home Ideas





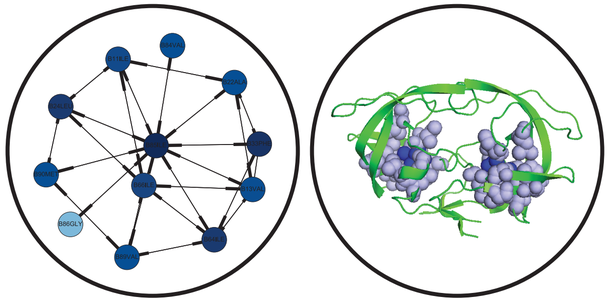


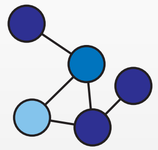


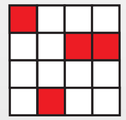


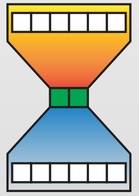
Take-Home Ideas

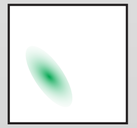
Graph convolutions: automatically learning structural determinants of phenotype

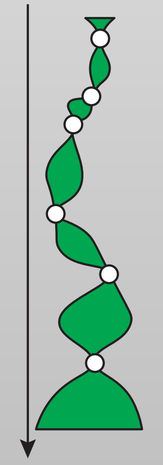






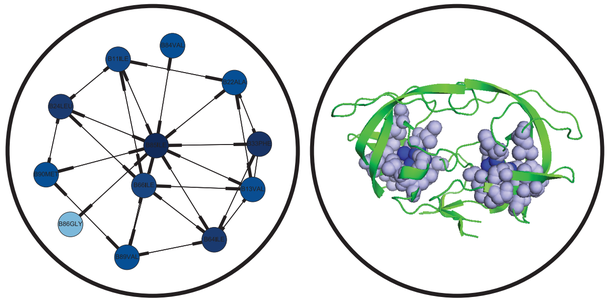




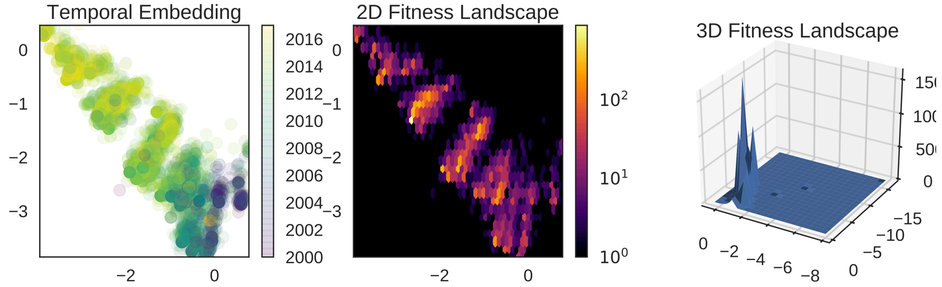


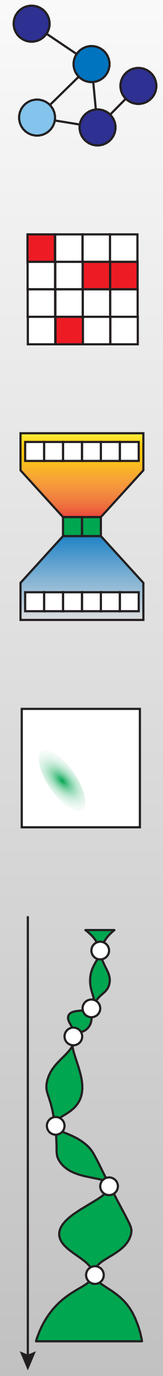
Take-Home Ideas

Graph convolutions: automatically learning structural determinants of phenotype



Variational autoencoders: forecasting fast-evolving pathogen sequence trajectory

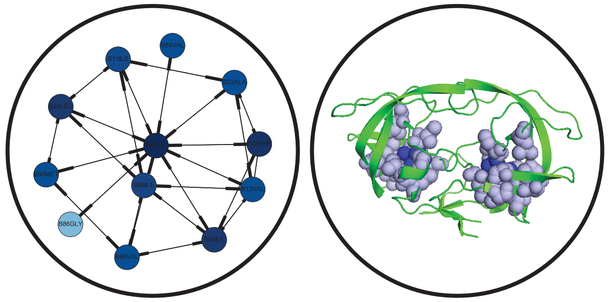


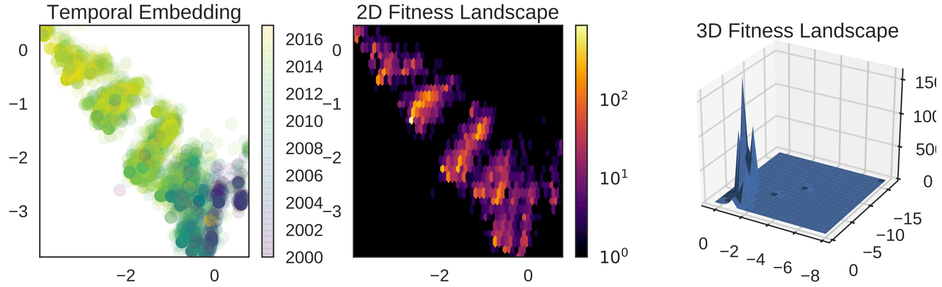


Take-Home Ideas

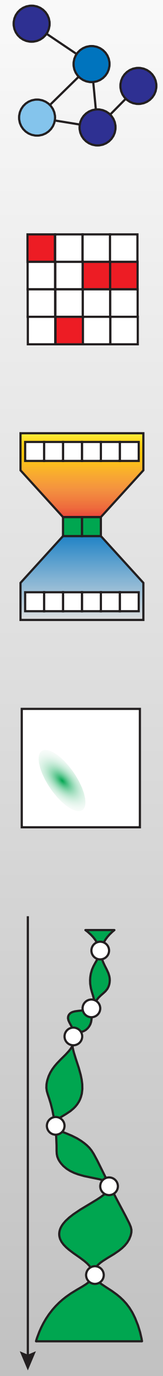
Graph convolutions: automatically learning structural determinants of phenotype

Variational autoencoders: forecasting fast-evolving pathogen sequence trajectory





Applications: CAD of biologics, pre-emptive vaccine development.



Acknowledgments

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