ConfuseNN: Interpreting convolutional neural network inferences in population genomics with data shuffling

Linh Tran

Genetics Graduate Interdisciplinary Program

University of Arizona

David Castellano

Ryan Gutenkunst

THE

GENETICAL THEORY OF NATURAL SELECTION

BY

R. A. FISHER, Sc.D., F.R.S.

OXFORD
AT THE CLARENDON PRESS
1930

THE DISTRIBUTION OF GENE FREQUENCIES UNDER IRREVERSIBLE MUTATION

By Sewall Wright

Department of Zoölogy, The University of Chicago

Linkage Disequilibrium in Finite Populations

W. G. Hill and Alan Robertson*

Institute of Animal Genetics, Edinburgh, 9.

THE
GENETICAL THEORY OF
NATURAL SELECTION

BY

R. A. FISHER, Sc.D., F.R.S.

OXFORD

AT THE CLARENDON PRESS

1930

PROCEEDINGS
OF THE
NATIONAL ACADEMY OF SCIENCES

Volume 24   July 15, 1938   Number 7

Copyright 1938 by The National Academy of Sciences

THE DISTRIBUTION OF GENE FREQUENCIES UNDER
IRREVERSIBLE MUTATION

By SEWALL WRIGHT

DEPARTMENT OF ZOÖLOGY, THE UNIVERSITY OF CHICAGO

Communicated June 13, 1938

Theoretical and Applied Genetics 38, 226—231 (1968)

Linkage Disequilibrium in Finite Populations

W. G. HILL and ALAN ROBERTSON*

Institute of Animal Genetics, Edinburgh, 9.

JOURNAL ARTICLE

The Unreasonable Effectiveness of Convolutional Neural Networks in Population Genetic Inference

Lex Flagel, Yaniv Brandvain, Daniel R Schrider   (2019)

ImaGene: a convolutional neural network to quantify natural selection from data

Luis Torada[1†], Lucrezia Lorenzon[1,2†], Alice Beddis[1†], Ulas Isildak[3], Linda Pattini[2], Sara Mathieson[4] and Matteo Fumagalli[1*]   (2019)

Automatic inference of demographic parameters using generative adversarial networks

Zhanpeng Wang, Jiaping Wang, Michael Kourakos, Nhung Hoang, Hyong Hark Lee, Iain Mathieson, Sara Mathieson   (2021)

Interpreting generative adversarial networks to infer natural selection from genetic data

Rebecca Riley,[1] Iain Mathieson,[2] Sara Mathieson[1,*]   (2024)

ConfuseNN

THE
GENETICAL THEORY OF
NATURAL SELECTION

BY
R. A. FISHER, Sc.D., F.R.S.
OXFORD
AT THE CLARENDON PRESS
1930

PROCEEDINGS
OF THE
NATIONAL ACADEMY OF SCI
Volume 24   July 15, 1938
Copyright 1938 by The National Academy of Sciences

THE DISTRIBUTION OF GENE FREQ
IRREVERSIBLE MUTAT

BY SEWALL WRIGHT
DEPARTMENT OF ZOÖLOGY, THE UNIVERSITY OF CHICAGO
Communicated June 13, 1938

Theoretical and Applied Genetics 38, 226—231 (1968)

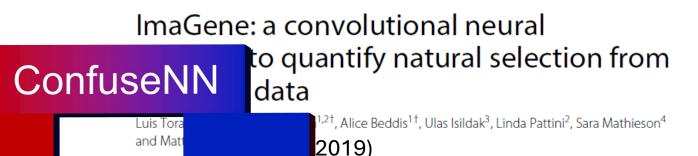Linkage Disequilibrium in Finite Populations

W. G. HILL and ALAN ROBERTSON*

Institute of Animal Genetics, Edinburgh, 9.

JOURNAL ARTICLE

The Unreasonable Effectiveness of Convolutional
Neural Networks in Population Genetic Inference

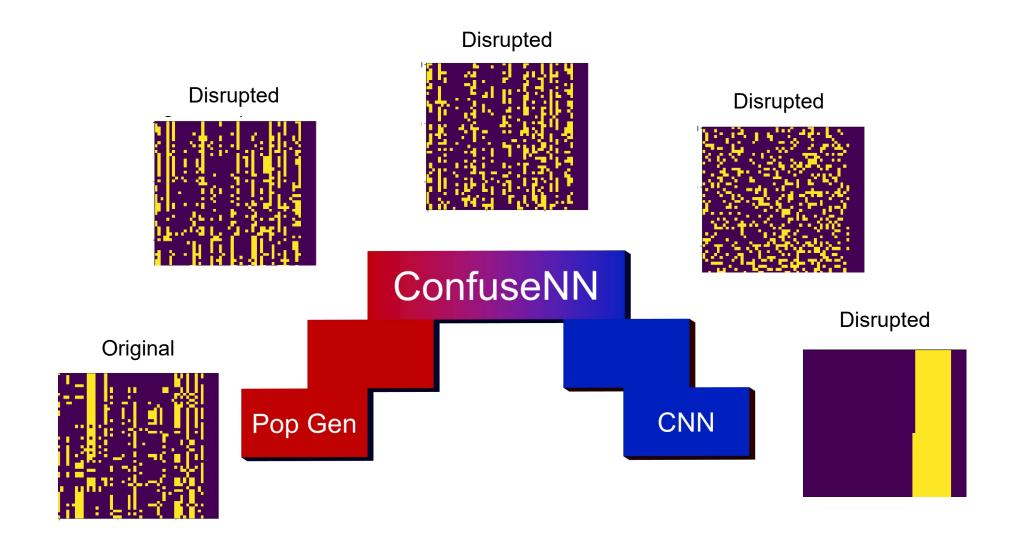Lex Flagel, Yaniv Brandvain, Daniel R Schrider ✉   (2019)

ImaGene: a convolutional neural
to quantify natural selection from
data

Luis Tora   1,2†, Alice Beddis1†, Ulas Isildak3, Linda Pattini2, Sara Mathieson4
and Matt   2019)

Pop Gen

ConfuseNN

CNN

Automatic   f demographic parameters using
generative   networks

Zhanpeng Wang, Jiaping Wang, Michael Kourakos, Nhung Hoang, Hyong Hark Lee, Iain Mathieson,
Sara Mathieson ✉   (2021)

**Interpreting generative adversarial networks to infer
natural selection from genetic data**

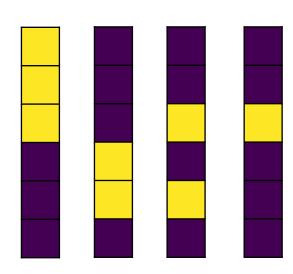Rebecca Riley,[1] Iain Mathieson [iD],[2] Sara Mathieson [iD][1,*]   (2024)

Data (SNP)

TGGTCACTCTTATCATTATGT
TGGTCACTCTTATCATTATGT

TGGTCACTCTTAACATTCTGT
TGCTCATTCTTATCATTATGT

TGCTCATTCTTATCATTATGT
TGCTCACTCTTAACATTATGT

Data (SNP)

TGGTCACTCTTATCATTATGT
TGGTCACTCTTATCATTATGT

TGGTCACTCTTAACATTCTGT
TGCTCATTCTTATCATTATGT

TGCTCATTCTTATCATTATGT
TGCTCACTCTTAACATTATGT

Haplotypes
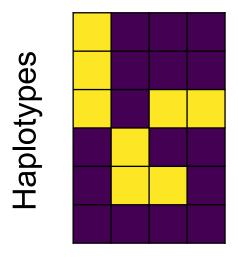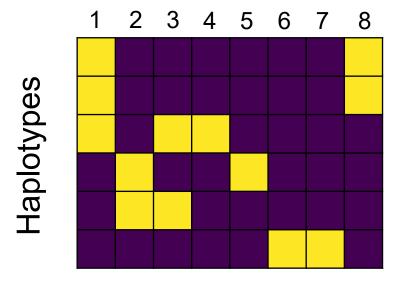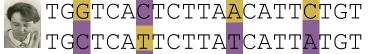
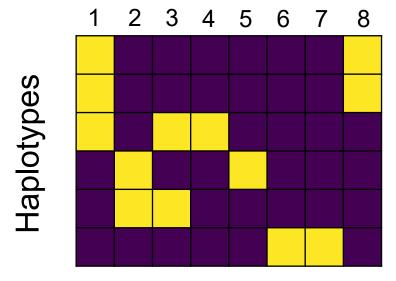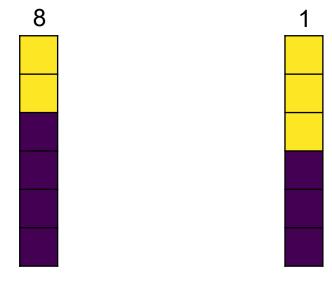Segregating sites

Data (SNP)

TG**G**TCA**C**TCTTA**T**CATTA**T**GT
TG**G**TCA**C**TCTTA**T**CATTA**T**GT

TG**G**TCA**C**TCTTA**A**CATT**C**GT
TG**C**TCA**T**TCTTA**T**CATTA**T**GT

TG**C**TCA**T**TCTTA**T**CATTA**T**GT
TG**C**TCA**C**TCTTA**A**CATTA**T**GT

Haplotypes / Segregating sites

Data (SNP)

TGGTCACTCTTATCATTATGT
TGGTCACTCTTATCATTATGT
TGGTCACTCTTAACATTCTGT
TGCTCATTCTTATCATTATGT
TGCTCATTCTTATCATTATGT
TGCTCACTCTTAACATTATGT

ConfuseNN

Disrupt spatial pattern

Segregating sites

Segregating sites

Haplotypes

Data (SNP)

TGGTCACTCTTATCATTATGT
TGGTCACTCTTATCATTATGT
TGGTCACTCTTAACATTCTGT
TGCTCATTCTTATCATTATGT
TGCTCATTCTTATCATTATGT
TGCTCACTCTTAACATTATGT

ConfuseNN

Disrupt spatial pattern

Haplotypes

1 2 3 4 5 6 7 8

Segregating sites

8 4   2   1

Segregating sites

Data (SNP)

TGGTCACTCTTATCATTATGT
TGGTCACTCTTATCATTATGT

TGGTCACTCTTAACATTCTGT
TGCTCATTCTTATCATTATGT

TGCTCATTCTTATCATTATGT
TGCTCACTCTTAACATTATGT

ConfuseNN

Disrupt spatial pattern

Haplotypes

1 2 3 4 5 6 7 8

Segregating sites

8 4   2 7   5 1

Segregating sites

Data (SNP)

TGGTCACTCTTATCATTATGT
TGGTCACTCTTATCATTATGT
TGGTCACTCTTAACATTCTGT
TGCTCATTCTTATCATTATGT
TGCTCATTCTTATCATTATGT
TGCTCACTCTTAACATTATGT

ConfuseNN

Disrupt spatial pattern

Disrupt linkage disequilibrium (LD)

Haplotypes

1 2 3 4 5 6 7 8

Segregating sites

8 4 3 2 7 6 5 1

Segregating sites

Kawakami et al. (2014)
Mol. Ecol. Resour.

Data (SNP)

ConfuseNN

Disrupt spatial pattern

Disrupt linkage disequilibrium (LD)

Haplotypes

Segregating sites

Segregating sites

Segregating sites

Data (SNP)

```
TGGTCACTCTTATCATTATGT
TGGTCACTCTTATCATTATGT
TGGTCACTCTTAACATTCTGT
TGCTCATTCTTATCATTATGT
TGCTCATTCTTATCATTATGT
TGCTCACTCTTAACATTATGT
```

ConfuseNN

Disrupt spatial pattern

Disrupt linkage disequilibrium (LD)

Haplotypes

Segregating sites

Segregating sites

Segregating sites

Data (SNP)

TGGTCACTCTTATCATTATGT
TGGTCACTCTTATCATTATGT
TGGTCACTCTTAACATTCTGT
TGCTCATTCTTATCATTATGT
TGCTCATTCTTATCATTATGT
TGCTCACTCTTAACATTATGT

ConfuseNN

Disrupt spatial pattern

Disrupt linkage disequilibrium (LD)

Haplotypes

Segregating sites

Segregating sites

Segregating sites

Data (SNP)

TGGTCACTCTTATCATTATGT
TGGTCACTCTTATCATTATGT
TGGTCACTCTTAACATTCTGT
TGCTCATTCTTATCATTATGT
TGCTCATTCTTATCATTATGT
TGCTCACTCTTAACATTATGT

ConfuseNN

Disrupt spatial pattern

Disrupt linkage disequilibrium (LD)

Haplotypes

Segregating sites

Segregating sites

Segregating sites

Data (SNP)


```
TGGTCACTCTTATCATTATGT
TGGTCACTCTTATCATTATGT
TGGTCACTCTTAACATTCTGT
TGCTCATTCTTATCATTATGT
TGCTCATTCTTATCATTATGT
TGCTCACTCTTAACATTATGT
```

ConfuseNN

Disrupt spatial pattern

Disrupt linkage disequilibrium (LD)

Haplotypes

1 2 3 4 5 6 7 8

Segregating sites

8 4 3 2 7 6 5 1

Segregating sites

1 2 3 4 5

Segregating sites

Data (SNP)

TGGTCACTCTTATCATTATGT
TGGTCACTCTTATCATTATGT
TGGTCACTCTTAACATTCTGT
TGCTCATTCTTATCATTATGT
TGCTCATTCTTATCATTATGT
TGCTCACTCTTAACATTATGT

ConfuseNN

Haplotypes — Segregating sites

	1	2	3	4	5	6	7	8
	A					B		
	A					B		
	A					B		
						B		
						B		

Disrupt spatial pattern

Segregating sites

	8	4	3	2	7	6	5	1

Disrupt linkage disequilibrium (LD)

Segregating sites

	1	2	3	4	5	6
						B
A						B
						B
A						
						B
A						B

Data (SNP)

TGGTCACTCTTATCATTATGT
TGGTCACTCTTATCATTATGT
TGGTCACTCTTAACATTCTGT
TGCTCATTCTTATCATTATGT
TGCTCATTCTTATCATTATGT
TGCTCACTCTTAACATTATGT

ConfuseNN

Disrupt spatial pattern

Disrupt linkage disequilibrium (LD)

Haplotypes

	1	2	3	4	5	6	7	8
	A						B	
	A						B	
	A						B	
							B	
							B	

Segregating sites

	8	4	3	2	7	6	5	1

Segregating sites

	1	2	3	4	5	6	7
							B
	A						B
							B
	A						B
							B
	A						B

Segregating sites

Data (SNP)

ConfuseNN

Disrupt spatial pattern

Disrupt linkage disequilibrium (LD)

Data (SNP)

Disrupt allele frequency spectrum

Number of sites

Frequency class

ConfuseNN

Haplotypes

Segregating sites

Data (SNP)

Disrupt allele frequency spectrum

ConfuseNN

Number of sites

Frequency class

Haplotypes

Segregating sites

Data (SNP)

TGGTCACTCTTATCATTATGT
TGGTCACTCTTATCATTATGT
TGGTCACTCTTAACATTCTGT
TGCTCATTCTTATCATTATGT
TGCTCATTCTTATCATTATGT
TGCTCACTCTTAACATTATGT

Disrupt allele frequency spectrum

Number of sites

Frequency class

1/6 1/3 1/2

ConfuseNN

Haplotypes

1 2 3 4 5 6 7 8

Segregating sites

1 2 3 4 5 6 7 8

Segregating sites

Data (SNP)

```
TGGTCACTCTTATCATTATGT
TGGTCACTCTTATCATTATGT
TGGTCACTCTTAACATTCTGT
TGCTCATTCTTATCATTATGT
TGCTCATTCTTATCATTATGT
TGCTCACTCTTAACATTATGT
```

Disrupt allele frequency spectrum

ConfuseNN

Number of sites vs Frequency class ($\frac{1}{6}$, $\frac{1}{3}$, $\frac{1}{2}$)

Haplotypes — Segregating sites (1 2 3 4 5 6 7 8)

Segregating sites (1 2 3 4 5 6 7 8)

Number of sites vs Frequency class ($\frac{1}{6}$, $\frac{1}{3}$, $\frac{1}{2}$)

Data (SNP)

TG**G**TCA**C**TCTTA**T**CATTA**T**GT
TG**G**TCA**C**TCTTA**T**CATTA**T**GT
TG**G**TCA**C**TCTTA**A**CATTA**C**GT
TG**C**TCA**T**TCTTA**T**CATTA**T**GT
TG**C**TCA**T**TCTTA**T**CATTA**T**GT
TG**C**TCA**C**TCTTA**A**CATTA**T**GT

Disrupt allele
frequency spectrum

Number of sites

4
3
2
1

$1/6$ $1/3$ $1/2$

Frequency class

ConfuseNN

Non-biological

Haplotypes

1 2 3 4 5 6 7 8

Segregating sites

1 2 3 4 5 6 7 8

Segregating sites

1 2 3 4 5 6 7 8

Segregating sites

Interpreting generative adversarial networks to infer natural selection from genetic data

Rebecca Riley,[1] Iain Mathieson [iD],[2] Sara Mathieson [iD] [1,*]

Binary Classification: Neutral vs positive selection

Original   Disrupted

Haplotypes

Segregating sites

True Positive Rate / False Positive Rate

Original, AUC=0.886
Disrupt spatial patterns, AUC=0.889

Interpreting generative adversarial networks to infer natural selection from genetic data

Rebecca Riley,[1] Iain Mathieson [2], Sara Mathieson [1,*]

Binary Classification: Neutral vs positive selection

Interpreting generative adversarial networks to infer natural selection from genetic data

Rebecca Riley,[1] Iain Mathieson [2], Sara Mathieson [1,*]

Binary Classification: Neutral vs positive selection

Original

Disrupted

Haplotypes

Segregating sites

True Positive Rate

False Positive Rate

Original, AUC=0.886
Disrupt spatial patterns, AUC=0.889
Disrupt LD, AUC=0.885
Disrupt AFS, AUC=0.886

Interpreting generative adversarial networks to infer natural selection from genetic data

Rebecca Riley,[1] Iain Mathieson [2] Sara Mathieson [1,*]

Binary Classification: Neutral vs positive selection

Original   Disrupted

Haplotypes

Segregating sites

True Positive Rate / False Positive Rate

Original, AUC=0.886
Disrupt spatial patterns, AUC=0.889
Disrupt LD, AUC=0.885
Disrupt AFS, AUC=0.886
Non-biological, AUC=0.875

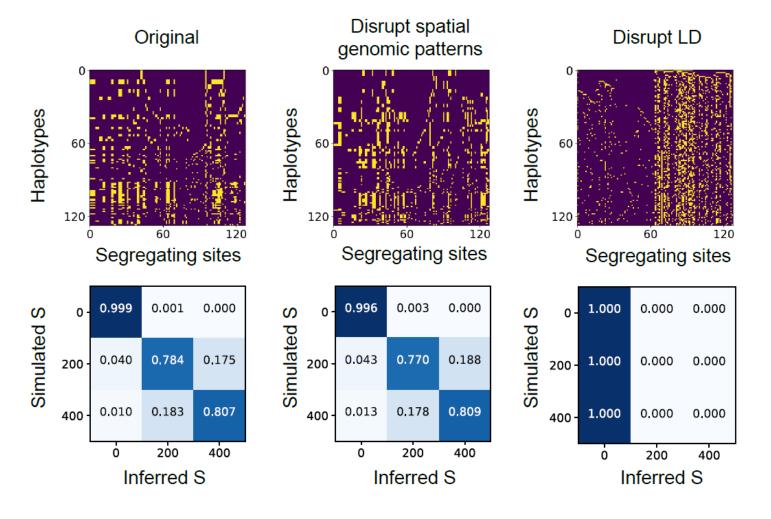# ImaGene: a convolutional neural network to quantify natural selection from genomic data

Luis Torada[1†], Lucrezia Lorenzon[1,2†], Alice Beddis[1†], Ulas Isildak[3], Linda Pattini[2], Sara Mathieson[4] and Matteo Fumagalli[1*]

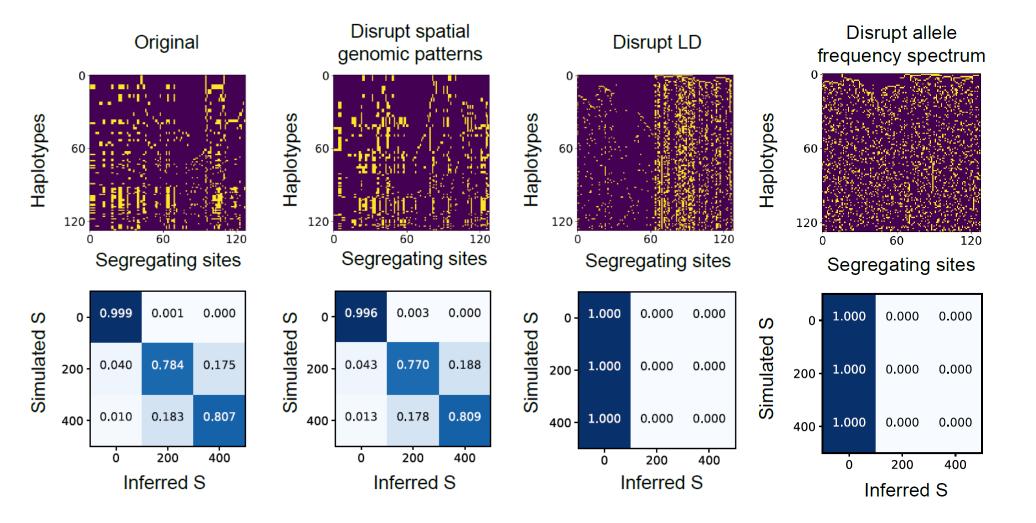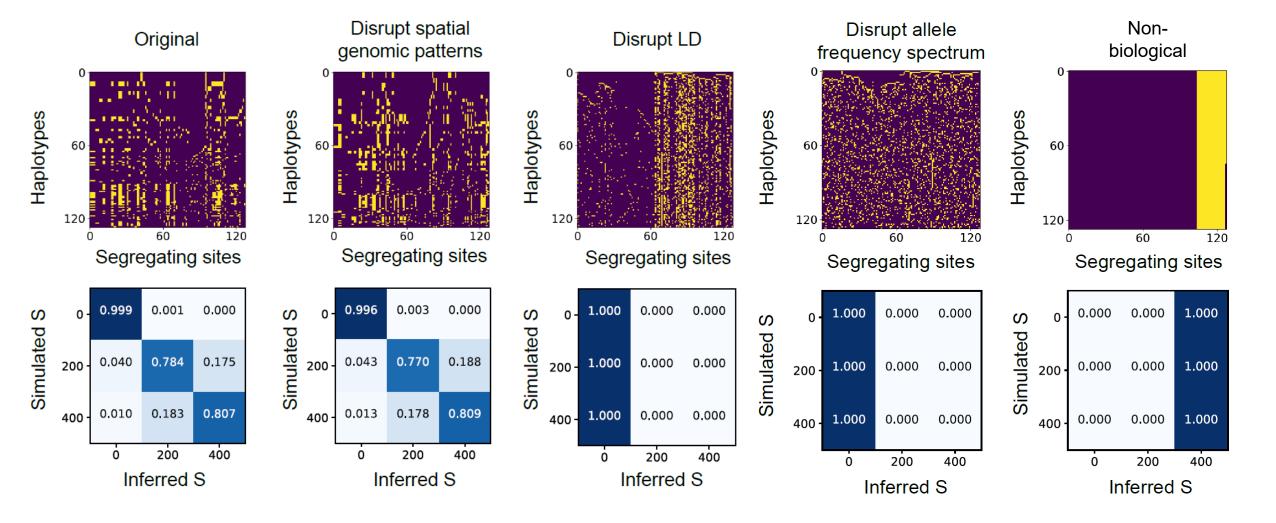Multi-class Classification: Neutral vs positive selection(s)

ImaGene: a convolutional neural network to quantify natural selection from genomic data

Luis Torada[1†], Lucrezia Lorenzon[1,2†], Alice Beddis[1†], Ulas Isildak[3], Linda Pattini[2], Sara Mathieson[4] and Matteo Fumagalli[1*]

Multi-class Classification: Neutral vs positive selection(s)

ImaGene: a convolutional neural network to quantify natural selection from genomic data

Luis Torada[1†], Lucrezia Lorenzon[1,2†], Alice Beddis[1†], Ulas Isildak[3], Linda Pattini[2], Sara Mathieson[4] and Matteo Fumagalli[1*]
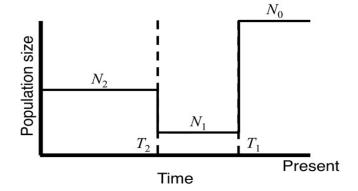
Multi-class Classification: Neutral vs positive selection(s)

ImaGene: a convolutional neural network to quantify natural selection from genomic data

Luis Torada[1†], Lucrezia Lorenzon[1,2†], Alice Beddis[1†], Ulas Isildak[3], Linda Pattini[2], Sara Mathieson[4] and Matteo Fumagalli[1*]

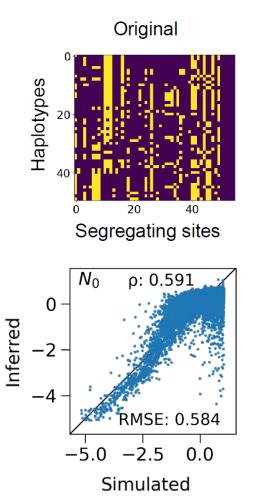Multi-class Classification: Neutral vs positive selection(s)

The Unreasonable Effectiveness of Convolutional Neural Networks in Population Genetic Inference 🔓

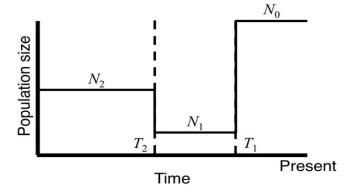Lex Flagel, Yaniv Brandvain, Daniel R Schrider ✉

Regression

Original

N_0 ρ: 0.591

RMSE: 0.584

The Unreasonable Effectiveness of Convolutional Neural Networks in Population Genetic Inference 🔓
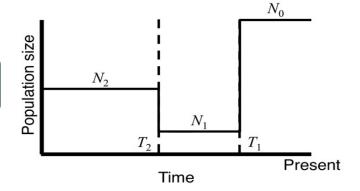
Lex Flagel, Yaniv Brandvain, Daniel R Schrider ✉

Regression

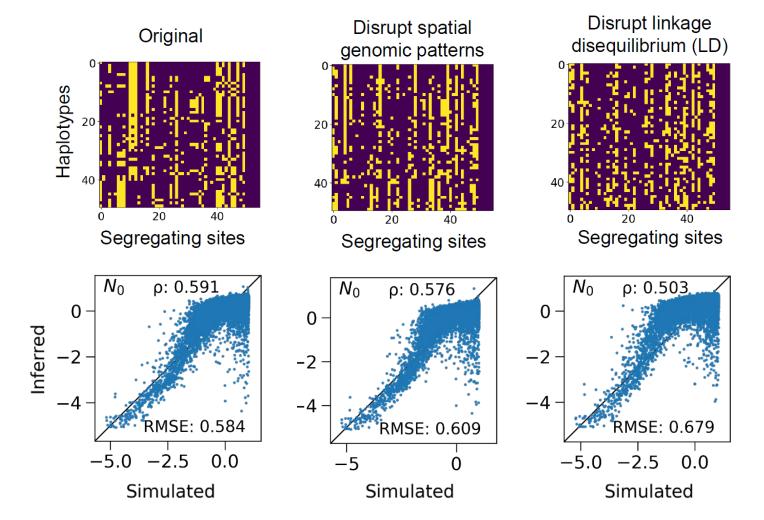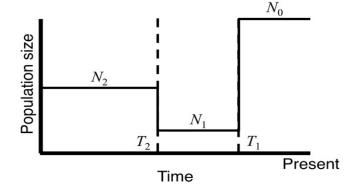# The Unreasonable Effectiveness of Convolutional Neural Networks in Population Genetic Inference 🔓

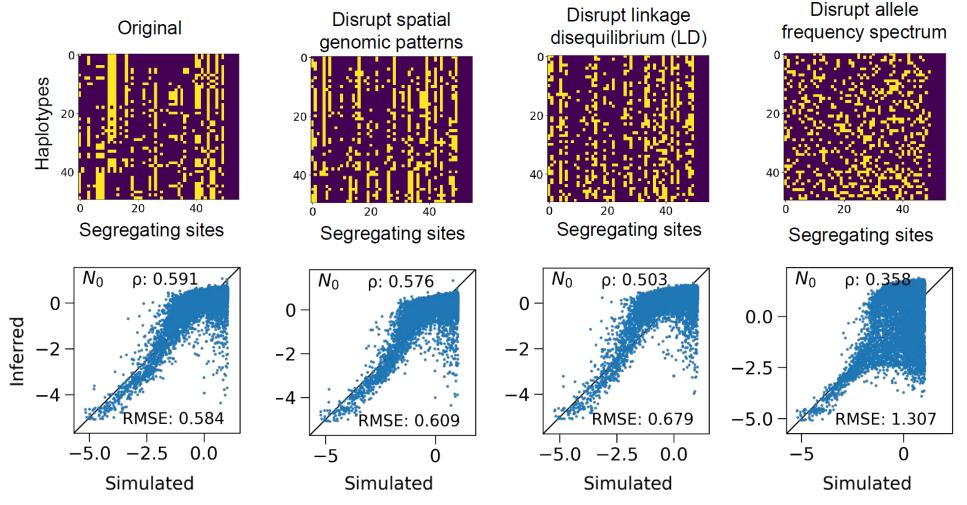Lex Flagel, Yaniv Brandvain, Daniel R Schrider ✉

Regression

Original

Disrupt spatial genomic patterns

Disrupt linkage disequilibrium (LD)

Disrupt allele frequency spectrum

Haplotypes

Segregating sites

N_0 ρ: 0.591 RMSE: 0.584

N_0 ρ: 0.576 RMSE: 0.609

N_0 ρ: 0.503 RMSE: 0.679

N_0 ρ: 0.358 RMSE: 1.307

Inferred

Simulated

The Unreasonable Effectiveness of Convolutional Neural Networks in Population Genetic Inference

Lex Flagel, Yaniv Brandvain, Daniel R Schrider ✉
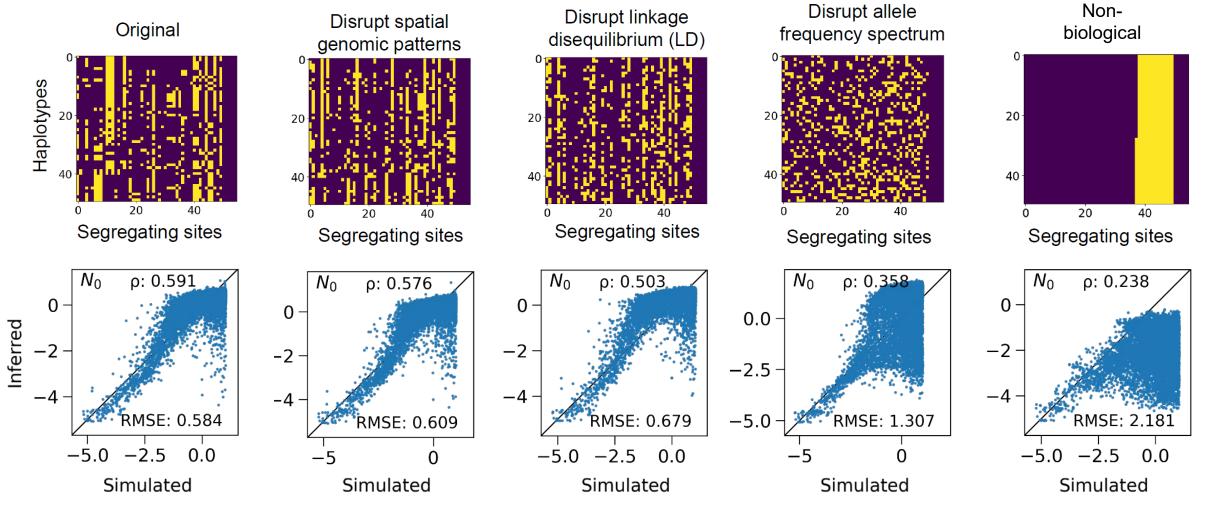
Regression

Summary

- ConfuseNN: interpreting CNN inferences by disrupting genomic data features based on population genetic summary statistics.

- For most CNNs, we found the known features that primarily drives inference.

- We can use domain knowledge to inform and evaluate the adoption of deep learning algorithms for domain-specific problems.

in linhnhtran

Intran26/ConfuseNN

Coming soon!