MorphGrower: A Synchronized Layer-by-layer Growing Approach for Plausible Neuronal Morphology Generation

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On Machine Learning

Background

Neuroscience

Neuroscience provides insights into cognitive processes and neural mechanisms, inspiring AI algorithms.

A Virtuous Cycle

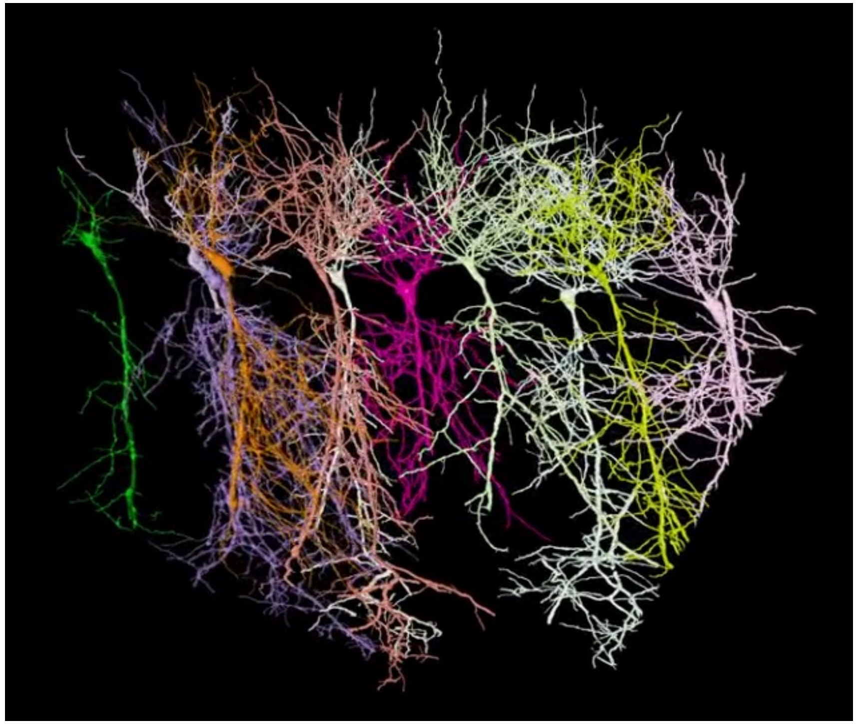
AI aids in analyzing complex neural data and simulating brain functions, enhancing neuroscience research.

AI

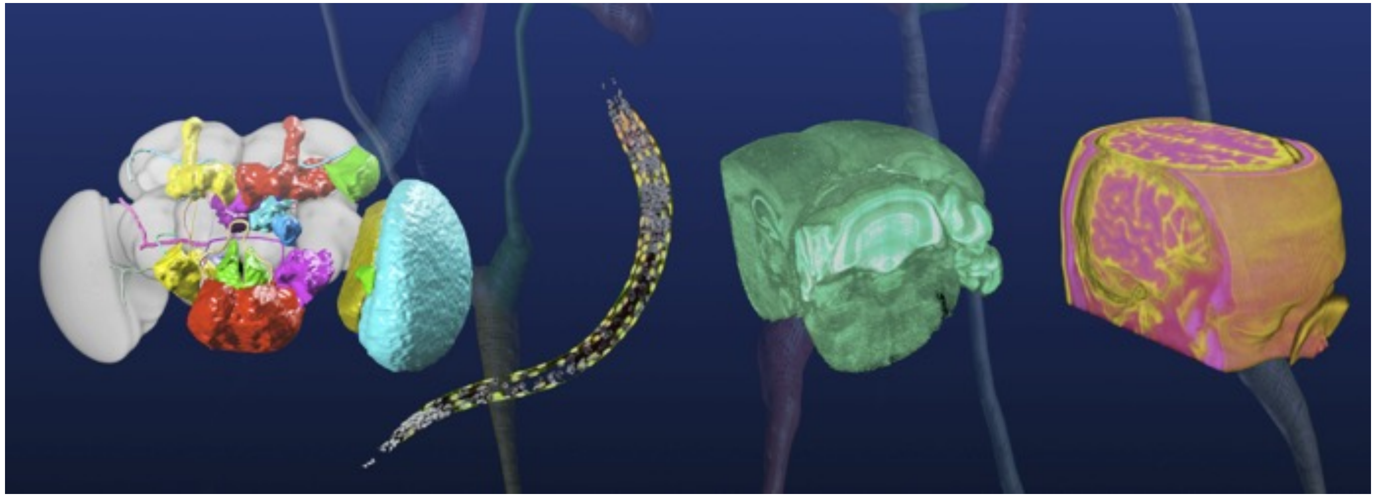
Background

Why morphology data are important?

- The morphology determines which spatial domain can be reached for a certain neuron, governing the connectivity of the neuronal circuits [1]
- Neuronal morphology also defines how a neuron integrates the signal inputs received from other neurons to produce outputs [2]
- Studying neuronal morphologies also facilitates the discovery of therapies for brain disorders and some degenerative diseases, e.g. mental retardation [3], autism[4] and Alzheimer [5]



Background



- A worm's brain: 302 neurons
- A fly's brain: 100,000 neurons
- A mouse's brain: 10^7~10^8 neurons
- A human being's brain: 10^{11} neurons

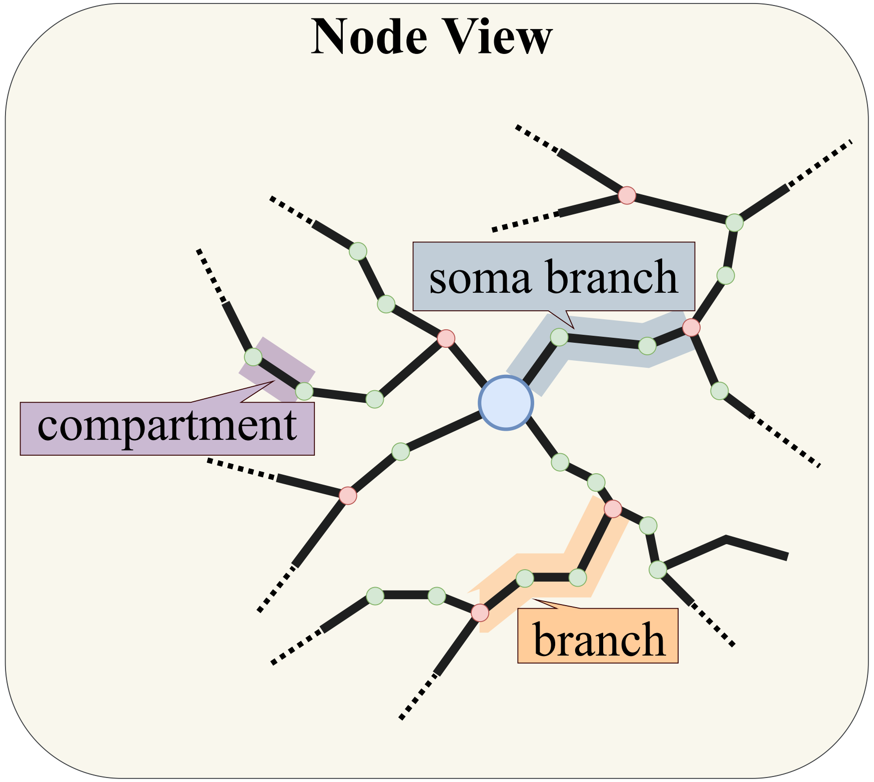
The traditional way to collect quality neuronal morphologies involves three key steps: *i)* histological preparation, *ii)* microscopic visualization and *iii)* accurate tracing.

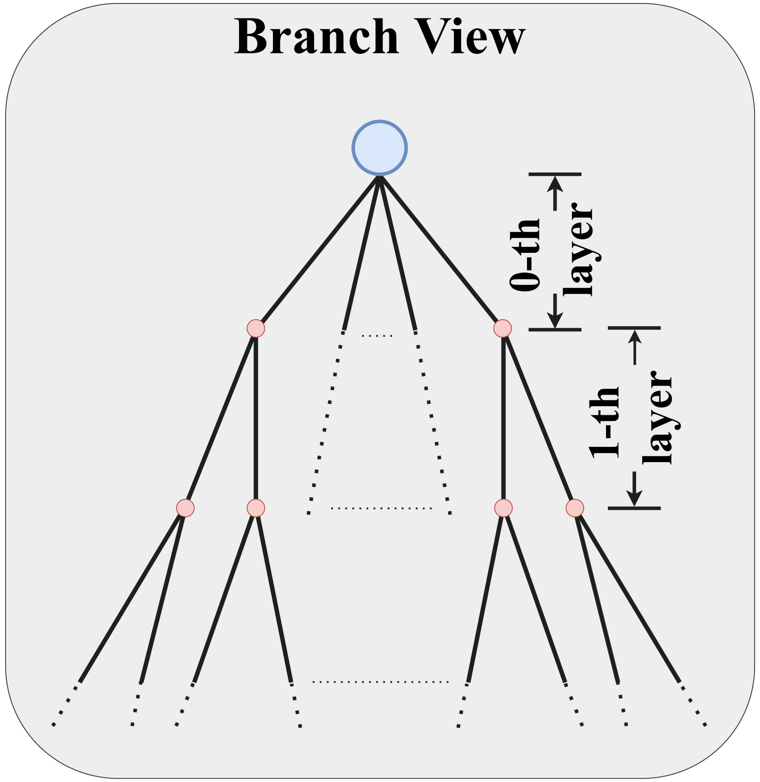
labor-intensive | time-consuming | potentially subject to human bias and error

We can opt to generate plausible morphology samples by computational approaches.

Baseline: MorphVAE [6]
the only existing learning-based method

Preliminaries





A neuronal morphology is described as a set of nodes in three-dimensional space, with each node associated with a coordinate in this space.

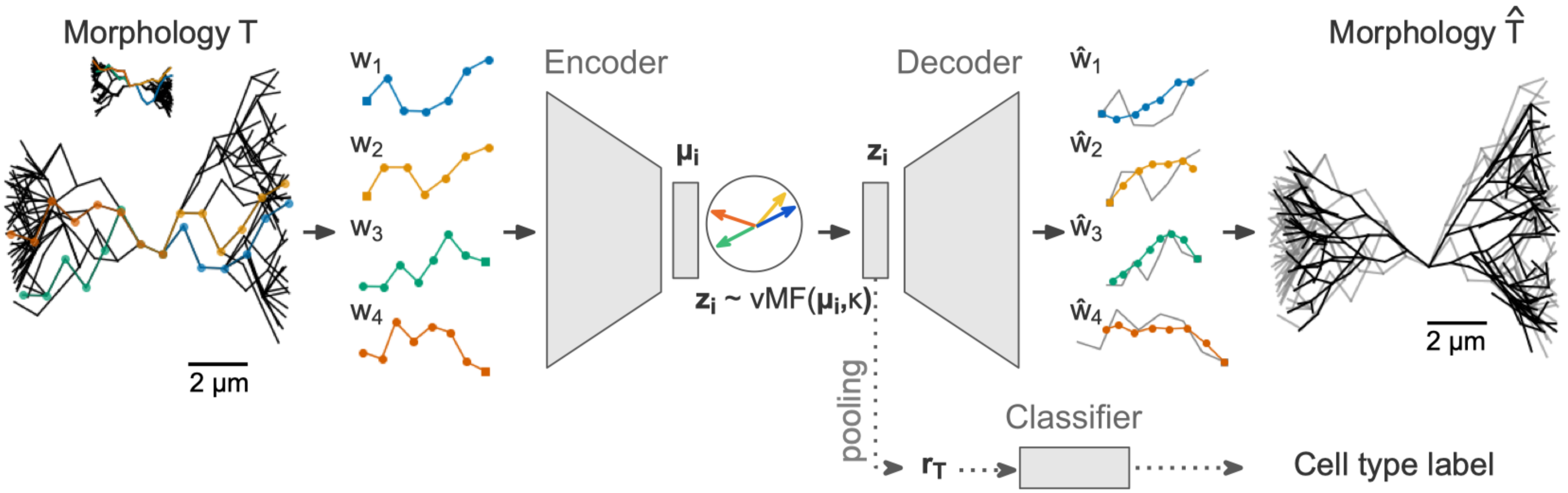
Neuronal morphology is a tree-like structure.

Key Concepts:

- **Soma:**
  the root node (unique)
  can have ≥ 2 outgoing edges 🌟
- **Tips:**
  the leaf nodes
- **Bifurcations:**
  can only have 2 outgoing edge 🌟
- **Branches:**
  the paths starting from a multifurcation (soma or bifurcation) and ending at a bifurcation or a tip

Brief Introduction to MorphVAE

The basic building block of MorphVAE: 3D-walk → **the path from the soma to a tip**



Two step:

- **generate all 3D-walks in one shot**
- **adopt a post-hoc clustering method on the generated 3D walks to aggregate some nodes of different 3D-walks**

→ **there may exist other nodes that have > 2 outgoing edges in the final generated morphology besides the soma**

This contradicts a commonly accepted notion that only the soma node can have more than two child branches!

Methodology

Layer-by-layer Generation Strategy

In practice, dendrites or axons grow from soma progressively and may diverge several times in the growing process.

Our strategy mimics the natural growth pattern of neurons to some extent.

MorphVAE violates this!

Following such a layer-by-layer strategy, a new morphology can be obtained by generating new layers and merging them to intermediate generated morphology regressively.

Methodology

Generating Branches in Pairs

As pointed out in previous works [7, 8, 9],

there exists a complex dependency between sibling branches.

If we separate sibling branches from each other and generate each of them individually, this dependency will be hard to model.

→ **MorphVAE fails in this regard**

A natural idea comes to our mind!

We can regard sibling branches as a whole and generate sibling branches in pairs each time, to implicitly model their internal dependency

Methodology

Conditional Generation

A Key Observation: **grown branches could influence their subsequent branches**

Condition

We propose to encode the intermediate morphology which has been generated into an embedding and restrict the generation of branch pairs in the following layer to be conditioned on this embedding we obtain.

We further split the condition into **local condition** and **global condition**.

Assuming that we are generating one certain pair of branches, we define:

the path from soma to the bifurcation from which the pair to be generated starts → **local condition**

its previous layers structure → **global condition**

Methodology

Conditional Generation (Cont.)

Justifications for the Conditions from a Neuroscience Perspective:

Local: Previous studies [10, 11] show that the dendrites or axons usually extend away from the soma without making any sharp change of direction, thus reflecting that the orientation of a pair of sibling branches is mainly determined by the overall orientation of the path from the soma to the start point of the siblings.

Global: Dendrites/axons establish territory coverage by following the organizing principle of self-avoidance [12, 13, 14]. Self-avoidance refers to dendrites/axons that should avoid crossing, thus spreading evenly over a territory [15]. Since the global condition can be regarded as a set of the local conditions and each local condition can roughly decide the orientation of a corresponding pair of branches, the global condition helps us better organize the branches in the same layer and achieve an even spread.

Methodology

The Distinction of the Soma Branch Layer

There is no proper definition of conditions for the soma branch layer.

The soma branch layer cannot be unified to the conditional generation formulation.

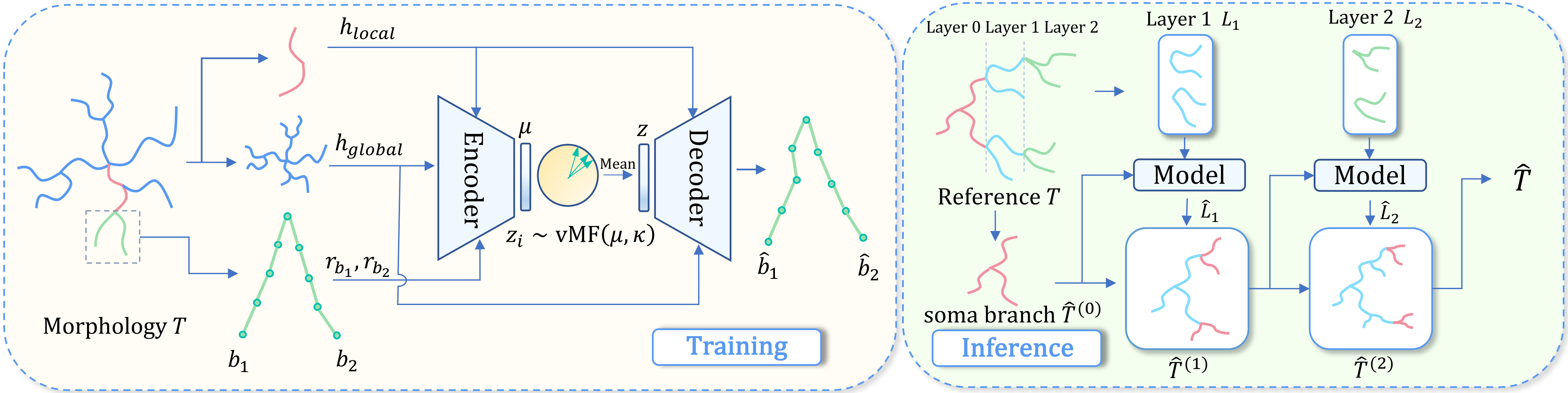
Two approaches

A straightforward solution is to directly present the soma branches as conditional input to the model, which are fairly small in number compared to all the branches → **MorphGrower**

Another slightly more complex approach is to generate the soma branch layer using another VAE without conditions → **MorphGrower†**

Methodology

Overview of MorphGrower



For details on the methods and model instantiation, feel free to scan the two QR codes on the right!

👉

Paper

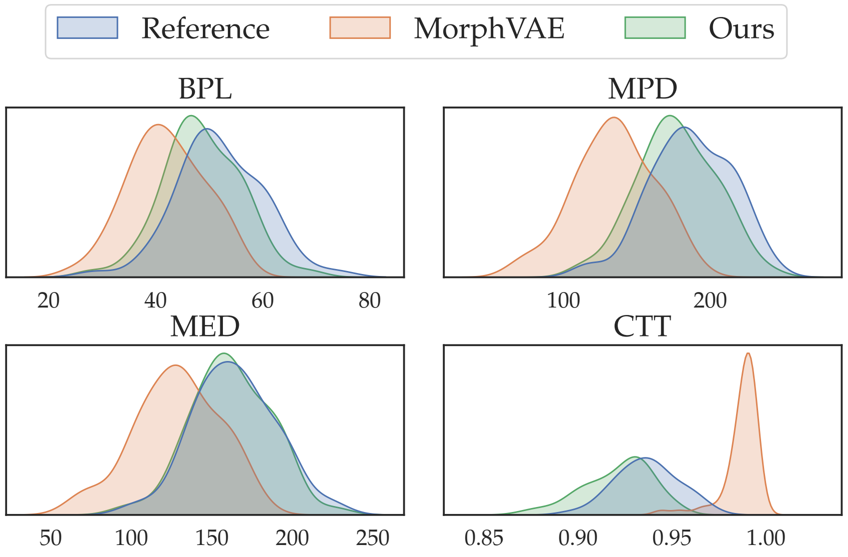
Code

Experiments

Quantitative Results on Morphological Statistics

Table 1: Performance on the four datasets by the six quantitative metrics. We leave MorphVAE's numbers on MBPL and MAPS blank because it may generate nodes with more than two subsequent branches that conflict with the definition of MBPL and MAPS for bifurcations. **MorphGrower** denotes the version where soma branches are directly provided. Meanwhile, **MorphGrower**† generates soma branches using another unconditional VAE. *Reference* corresponds to the statistical indicators derived from the realistic samples. A closer alignment with *Reference* indicates better performance. The best and the runner-up results are highlighted in **bold** and <u>underline</u> respectively.

Dataset	Method	MBPL / μm	MMED / μm	MMPD / μm	MCTT / %	MASB / °	MAPS / °
VPM	*Reference*	51.33 ± 0.59	162.99 ± 2.25	189.46 ± 3.81	0.936 ± 0.001	65.35 ± 0.55	36.04 ± 0.38
	MorphVAE	41.87 ± 0.66	126.73 ± 2.54	132.50 ± 2.61	0.987 ± 0.001	———	———
	MorphGrower	$\mathbf{48.29 \pm 0.34}$	$\mathbf{161.65 \pm 1.68}$	$\mathbf{180.53 \pm 2.70}$	$\underline{0.920 \pm 0.004}$	$\underline{72.71 \pm 1.50}$	$\mathbf{43.80 \pm 0.98}$
	MorphGrower†	$\underline{46.86 \pm 0.57}$	$\underline{159.62 \pm 3.19}$	$\underline{179.44 \pm 5.23}$	$\mathbf{0.929 \pm 0.006}$	$\mathbf{59.15 \pm 3.25}$	$\underline{46.59 \pm 3.24}$
RGC	*Reference*	26.52 ± 0.75	308.85 ± 8.12	404.73 ± 12.05	0.937 ± 0.003	84.08 ± 0.28	50.60 ± 0.13
	MorphVAE	43.23 ± 1.06	248.62 ± 9.05	269.92 ± 10.25	0.984 ± 0.004	———	———
	MorphGrower	$\mathbf{25.15 \pm 0.71}$	$\mathbf{306.83 \pm 7.76}$	$\mathbf{384.34 \pm 11.85}$	$\mathbf{0.945 \pm 0.003}$	$\mathbf{82.68 \pm 0.53}$	$\mathbf{51.33 \pm 0.31}$
	MorphGrower†	$\underline{23.32 \pm 0.52}$	$\underline{287.09 \pm 5.88}$	$\underline{358.31 \pm 8.54}$	$\underline{0.926 \pm 0.004}$	$\underline{76.27 \pm 0.86}$	$\underline{49.67 \pm 0.41}$
M1-EXC	*Reference*	62.74 ± 1.73	414.39 ± 6.16	497.43 ± 12.42	0.891 ± 0.004	76.34 ± 0.63	46.74 ± 0.85
	MorphVAE	52.13 ± 1.30	195.49 ± 9.91	220.72 ± 12.96	0.955 ± 0.005	———	———
	MorphGrower	$\mathbf{58.16 \pm 1.26}$	$\mathbf{413.78 \pm 14.73}$	$\mathbf{473.25 \pm 19.37}$	$\underline{0.922 \pm 0.002}$	$\mathbf{73.12 \pm 2.17}$	$\mathbf{48.16 \pm 1.00}$
	MorphGrower†	$\underline{54.63 \pm 1.07}$	$\underline{398.85 \pm 18.84}$	$\underline{463.24 \pm 22.61}$	$\mathbf{0.908 \pm 0.003}$	$\underline{63.54 \pm 2.02}$	$\underline{48.77 \pm 0.87}$
M1-INH	*Reference*	45.03 ± 1.04	396.73 ± 15.89	705.28 ± 34.02	0.877 ± 0.002	84.40 ± 0.68	55.23 ± 0.78
	MorphVAE	$\underline{50.79 \pm 1.77}$	244.49 ± 15.62	306.99 ± 23.19	0.965 ± 0.002	———	———
	MorphGrower	$\mathbf{41.50 \pm 1.02}$	$\mathbf{389.06 \pm 13.54}$	$\mathbf{659.38 \pm 30.05}$	$\underline{0.898 \pm 0.002}$	$\mathbf{82.43 \pm 1.41}$	$\underline{61.44 \pm 4.23}$
	MorphGrower†	37.72 ± 0.96	$\underline{349.66 \pm 11.40}$	$\underline{617.89 \pm 27.87}$	$\mathbf{0.876 \pm 0.002}$	$\underline{78.66 \pm 1.12}$	$\mathbf{57.87 \pm 0.96}$



MorphGrower significantly outperforms MorphVAE!

Experiments

Generation Plausibility with Real/Fake Classifier

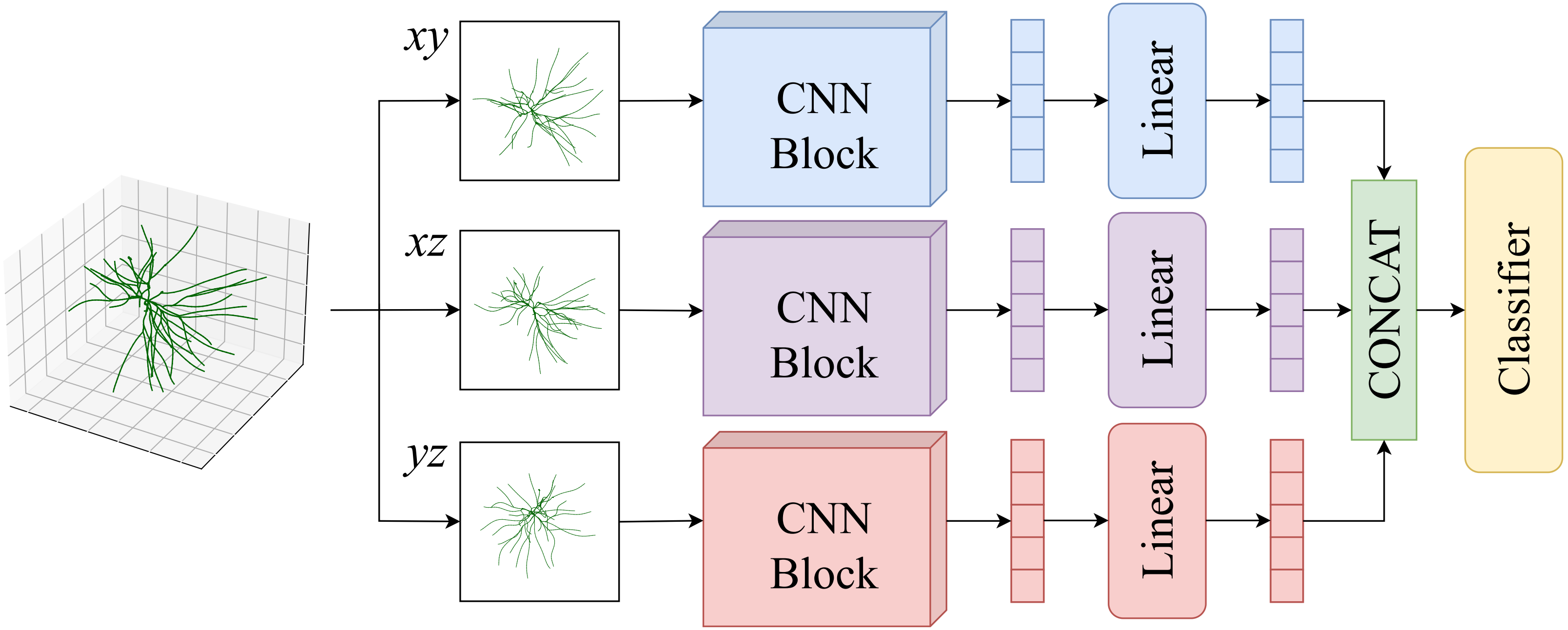


Table 2: Classification accuracy (%). Accuracy approaching 50% indicates higher plausibility.

Method \ Dataset	VPM	RGC	M1-EXC	M1-INH
MorphVAE	86.75 ± 06.87	94.60 ± 01.02	80.72 ± 10.58	91.76 ± 12.14
MorphGrower	54.73 ± 03.36	62.70 ± 05.24	55.00 ± 02.54	54.74 ± 01.63

👍 **we have presented our generated samples to neuroscience domain experts and receive positive feedback for their realistic looking**

harder to be distinguished from real samples

Experiments

The Electrophysiological Response Simulation Results

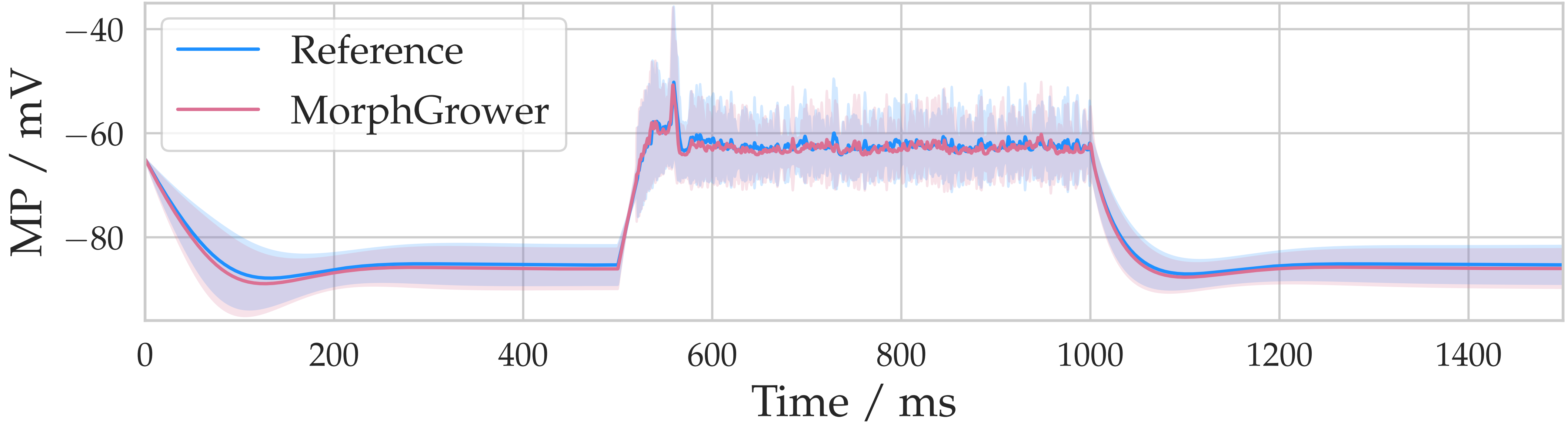


Table 3: Simulated recording statistical characteristics.

Metric	MMF / Hz	MMAPH / mV	MMAHPD / mV	MMAPA / mV
Reference	9.328	43.021	25.666	-77.231
MorphGrower	9.384	44.382	26.606	-77.837
Relative Error	0.60%	3.17%	3.66%	0.78%

The electrophysiological responses of real and our generated samples exhibit a high degree of similarity.

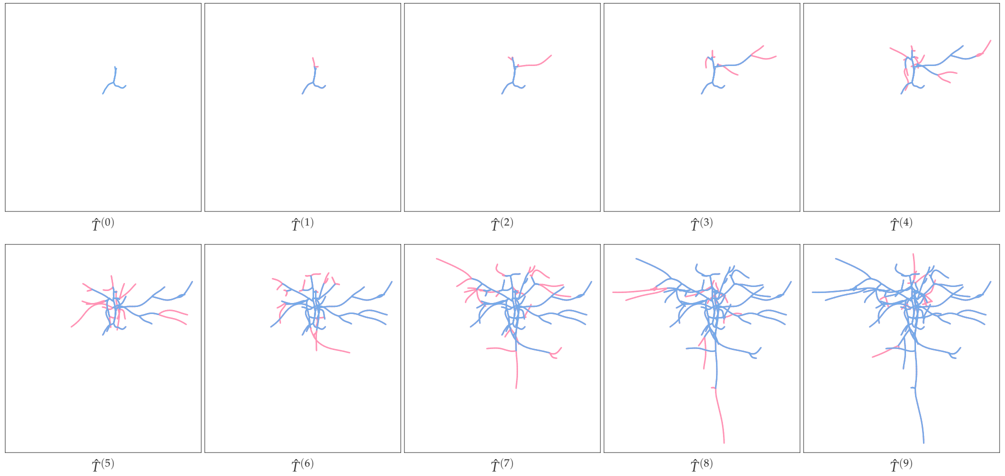
Experiments

Ablation study

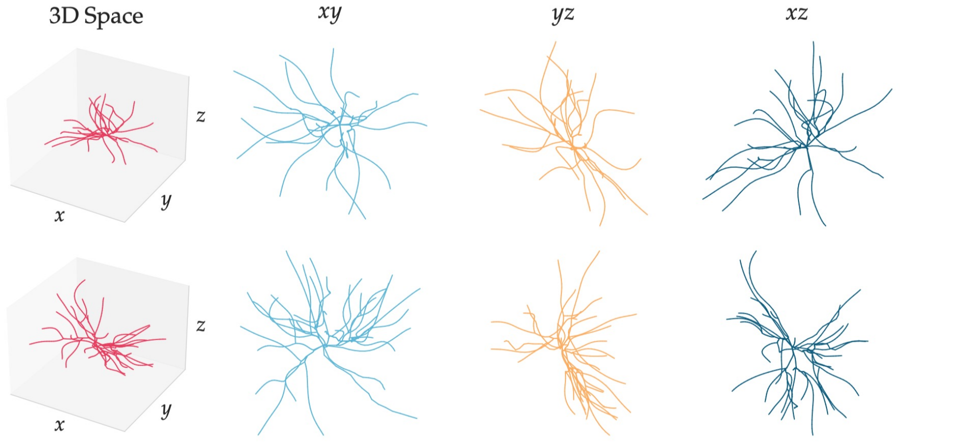
Table 10: The result of ablation study on the four datasets by six quantitative metrics. The best and the runner-up in each columns are highlighted in **bold** and underline respectively. We leave MorphVAE's numbers on MBPL and MAPS blank because it may generate nodes with more than two subsequent branches that conflict with the definition of MBPL and MAPS for bifurcations. A closer alignment with *Reference* indicates better performance.

Dataset	Method	MBPL / µm	MMED / µm	MMPD / µm	MCTT / %	MASB / °	MAPS / °
VPM	*Reference*	51.33 ± 0.59	162.99 ± 2.25	189.46 ± 3.81	0.936 ± 0.001	65.35 ± 0.55	36.04 ± 0.38
	MorphVAE	41.87 ± 0.66	126.73 ± 2.54	132.50 ± 2.61	0.987 ± 0.001	———	———
	MorphGrower	**48.29 ± 0.34**	161.65 ± 1.68	180.53 ± 2.70	0.920 ± 0.004	72.71 ± 1.50	**43.80 ± 0.98**
	LSTM → Transformers	47.40 ± 0.88	**162.46 ± 3.82**	**180.87 ± 3.09**	0.943 ± 0.010	**70.94 ± 2.77**	53.86 ± 0.99
	- Local Condition	40.90 ± 0.79	137.47 ± 2.63	162.53 ± 3.24	0.911 ± 0.006	74.55 ± 0.88	58.22 ± 0.32
	- Global Condition	44.51 ± 0.78	153.84 ± 3.56	173.58 ± 5.41	0.938 ± 0.003	71.29 ± 3.56	47.06 ± 0.59
	- EMA	45.24 ± 0.22	155.11 ± 1.98	173.68 ± 2.86	**0.936 ± 0.005**	67.79 ± 1.45	46.28 ± 0.08
RGC	*Reference*	26.52 ± 0.75	308.85 ± 8.12	404.73 ± 12.05	0.937 ± 0.003	84.08 ± 0.28	50.60 ± 0.13
	MorphVAE	43.23 ± 1.06	248.62 ± 9.05	269.92 ± 10.25	0.984 ± 0.004	———	———
	MorphGrower	**25.15 ± 0.71**	306.83 ± 7.76	384.34 ± 11.85	**0.945 ± 0.003**	82.68 ± 0.53	51.33 ± 0.31
	LSTM → Transformers	25.10 ± 0.65	**308.35 ± 7.34**	**387.67 ± 10.55**	0.948 ± 0.003	**84.04 ± 0.33**	52.35 ± 0.14
	- Local Condition	23.56 ± 0.74	294.01 ± 8.21	363.86 ± 11.36	0.954 ± 0.003	79.67 ± 1.17	54.44 ± 0.36
	- Global Condition	22.99 ± 0.83	293.87 ± 9.01	354.95 ± 11.85	0.954 ± 0.006	78.19 ± 4.10	**50.96 ± 0.63**
	- EMA	23.38 ± 0.66	295.09 ± 8.76	359.76 ± 8.76	0.951 ± 0.005	78.47 ± 1.84	52.25 ± 0.44
M1-EXC	*Reference*	62.74 ± 1.73	414.39 ± 6.16	497.43 ± 12.42	0.891 ± 0.004	76.34 ± 0.63	46.74 ± 0.85
	MorphVAE	52.13 ± 1.30	195.49 ± 9.91	220.72 ± 12.96	0.955 ± 0.005	———	———
	MorphGrower	**58.16 ± 1.26**	**413.78 ± 14.73**	**473.25 ± 19.37**	**0.922 ± 0.002**	73.12 ± 2.17	**48.16 ± 1.00**
	LSTM → Transformers	56.75 ± 1.49	415.90 ± 4.39	472.30 ± 7.99	0.942 ± 0.005	72.97 ± 1.75	51.06 ± 0.98
	- Local Condition	55.85 ± 1.24	409.66 ± 7.36	464.18 ± 9.07	0.940 ± 0.004	**73.81 ± 1.24**	51.54 ± 0.84
	- Global Condition	55.01 ± 0.65	404.42 ± 8.67	453.58 ± 11.90	0.955 ± 0.007	71.72 ± 1.23	48.48 ± 1.04
	- EMA	55.71 ± 1.24	407.29 ± 16.28	458.49 ± 12.29	0.951 ± 0.008	72.61 ± 4.35	50.20 ± 0.83
M1-INH	*Reference*	45.03 ± 1.04	396.73 ± 15.89	705.28 ± 34.02	0.877 ± 0.002	84.40 ± 0.68	55.23 ± 0.78
	MorphVAE	50.79 ± 1.77	244.49 ± 15.62	306.99 ± 23.19	0.965 ± 0.002	———	———
	MorphGrower	**41.50 ± 1.02**	**389.06 ± 13.54**	**659.38 ± 30.05**	**0.898 ± 0.002**	82.43 ± 1.41	61.44 ± 4.23
	LSTM → Transformers	40.55 ± 0.82	378.98 ± 12.21	645.68 ± 28.83	0.903 ± 0.003	**84.32 ± 0.85**	59.89 ± 0.91
	- Local Condition	39.33 ± 1.02	383.21 ± 10.06	641.00 ± 23.99	0.918 ± 0.003	77.30 ± 10.86	60.53 ± 0.75
	- Global Condition	38.12 ± 0.26	372.66 ± 10.30	613.76 ± 33.09	0.929 ± 0.003	78.29 ± 3.19	**57.21 ± 0.48**
	- EMA	38.97 ± 0.82	383.77 ± 14.04	636.61 ± 40.45	0.921 ± 0.004	80.09 ± 3.24	58.77 ± 0.91

Snapshots of the Generation



Visualization of Generated Samples



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Thanks

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