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Automatic tracing of ultra-volumes of neuronal images.

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To the Editor:

Despite substantial advancement in the automatic tracing of neuronal morphology in recent years[1,2,3], it is challenging to apply the existing algorithms to large image data sets containing billions or even trillions of voxels. Most neuron-tracing methods published to date were not designed to handle such data. We introduce UltraTracer (Fig. 1), a solution designed to extend any base neuron-tracing algorithm to allow the tracing of ever-growing data volumes. We applied this approach to neuron-tracing algorithms with different design principles and tested it on human and mouse neuron data sets that have hundreds of billions of voxels. Results indicate that UltraTracer is scalable, accurate, and more efficient than other state-of-the-art approaches.

The core algorithm of UltraTracer (Fig. 1) reconstructs a neuron structure from the available image data on the basis of a formulation of maximum-likelihood estimation. The underlying assumption is that the occurrence of a specific neuron structure could be modeled using the joint probability of all of its subparts given the image. Briefly, UltraTracer iteratively factorizes the joint probability based on progressive maximization of conditional probabilities of the occurrence of salient and continuous subparts of a neuron (Supplementary Note). Therefore, UltraTracer explores an image by following where the neurite signal goes, on the basis of either adaptive windows generated based on the already reconstructed neuron structure or certain domain knowledge (prior information or statistics) of neuron morphology, to help refine the choice of the next tracing subarea (Supplementary Note). This process repeats until the neuron structure grows as completely as possible. We

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Author contributions

H.P. conceived this project, designed and managed this study, proposed the theoretical framework of the method, and wrote the paper with assistance from Z.Z. and other coauthors. Z.Z. developed the tip-queue-based neuron growth algorithm, implemented the software, and generated results, with the help of coauthors.

Data availability. UltraTracer is open source and available in Vaa3D software (vaa3d.org) and as Supplementary Software. The sample data are publicly available and can be downloaded from GitHub (https://github.com/Vaa3D/Vaa3D_Data/releases/download/v0.9/ultratracer_testing_data.zip).

Ethics declarations

Competing interests

The authors declare no competing financial interests.

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designed the UltraTracer software to quickly extract an arbitrary subvolume of interest from large neuron image files (Supplementary Note), and thus smoothly traced an image archive without the need to load a large number of image voxels into computer memory.

As a crucial utility that was not previously available to reconstruct large-scale data sets, UltraTracer extends an arbitrary base tracer to make it possible to trace an ever-increasing image volume. We tested this by considering ten representative base tracing algorithms ported to BigNeuron[3] (https://github.com/BigNeuron/BigNeuron-Wiki/wiki/Neuron-Reconstruction-Algorithms) that have different design principles, performances, and output formats (Supplementary Figs. 1, 2, and 3; Supplementary Note). The performance gain of UltraTracer over the direct use of certain base tracers was within the range of 3–6 times (Supplementary Fig. 1b). UltraTracer results were accurate, as their average spatial distances to independent manual reconstructions were around 3 voxels, comparable to the spatial distance of the manual reconstructions themselves (3.56 voxels) (Supplementary Fig. 1b). In addition, for two base tracers, NeuTube[4] and MOST[5], UltraTracer had a gain of 10–30-fold in tracing accuracy (Supplementary Fig. 1b). Testing of six other base tracers (Supplementary Fig. 2) indicated similar improvement. When a computer with smaller memory was used or the image volume increased greatly, UltraTracer was consistently superior to the conventional approach (Supplementary Fig. 3).

The APP2 algorithm[6] was a good base tracer, in terms of speed–accuracy trade-off (Supplementary Fig. 1), for both laser-scanning and brightfield images (Supplementary Figs. 3,4,5,6,7). The APP2-based UltraTracer scaled robustly in tracing the sparse neuronal structures in images with 521 billion voxels, reducing the data volume in tracing between 3 and 40 times (Supplementary Fig. 3). Typically a bigger data-volume reduction rate was achieved for a larger image volume. Measured in terms of spatial distance, bifurcation points, and five other morphological and topological features, and compared against the statistics drawn from collections of reconstructions produced using control images (Supplementary Note), the accuracy of reconstructions produced by UltraTracer was consistent with that of reconstructions generated using the traditional approach when the image data set could be accommodated by the computer memory (Supplementary Fig. 3, bottom left).

We used UltraTracer to combine multiple different base tracers (Supplementary Note; Supplementary Figs. 8 and 9), for example using APP2 in the soma area while using NeuTube and MOST to trace curvilinear structures. In a more complicated case, for every adaptively searched image region, we profiled the reconstructions generated by several base tracers, and then chose either the best reconstruction or their consensus as the result from the current image region (Supplementary Fig. 9). In this way UltraTracer could provide more consistent reconstructions compared to manual work. We also used UltraTracer to reconstruct human neurons, including their axons and dendrites, from separate but serial slices of brain tissue (Supplementary Note; Supplementary Fig. 10). Additional information about the algorithm can be seen in Supplementary Figures 11,12,13.

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Supplementary Material

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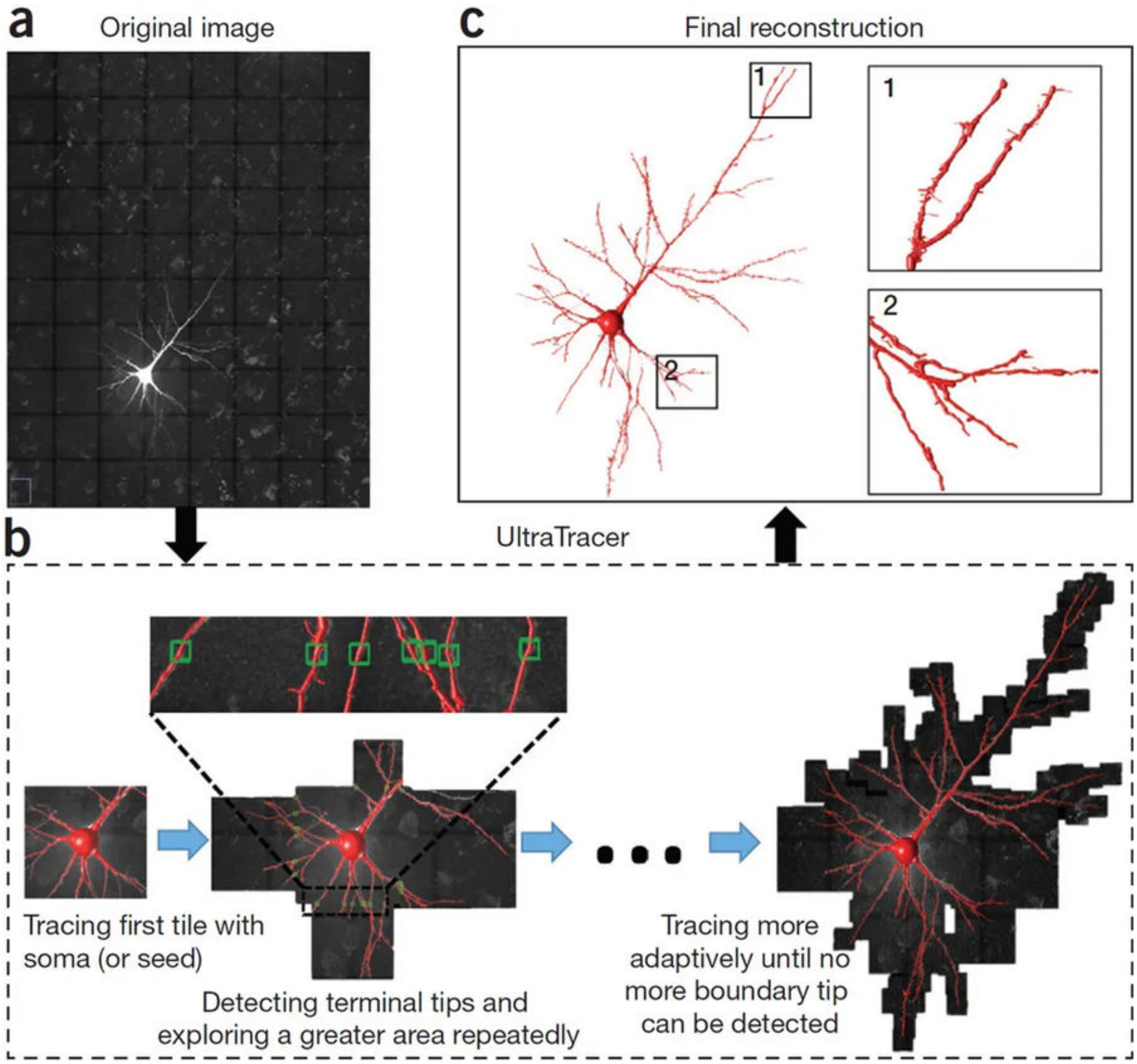

Figure 1: Workflow of UltraTracer for tracing a large 3D image volume.

(a) 3D confocal image stack of a Lucifer-Yellow-labeled human pyramidal neuron. The voxel size is 0.18 × 0.18 × 0.5 μm, and the overlaid grid (black lines) indicates how the image volume is subdivided into uniform tiles. (**b**) UltraTracer first traces the subarea containing the soma and then detects the neuron terminal tips in the reconstruction, and adaptively explores and traces neighboring subareas. Green boxes indicate terminal tips detected in tracing a subarea. (**c**) Final reconstruction produced by UltraTracer, with zooms of two parts for detailed visualization.