A three state model can explain the dynamics of class IV Drosophila dendritic tips

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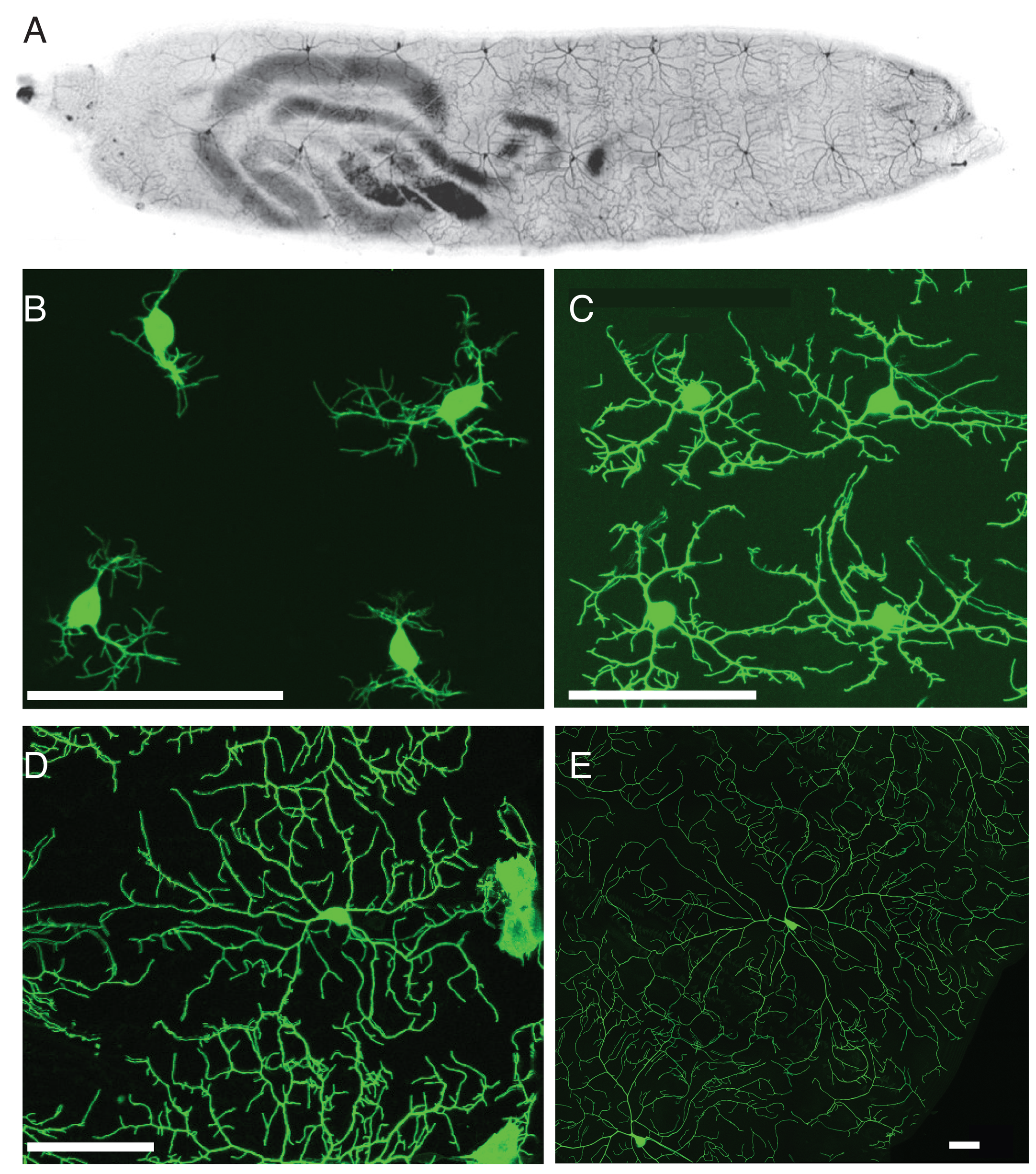
Abstract

Individual neurons form highly intricate dendritic structures that receive synaptic input from other neurons or sensory input from the outside world. The precise dendritic morphology is crucial for the proper connectivity and information processing of neural circuits. However, little is known how the dendrites form and grow.
We observed that the dendrites of our model system, Drosophila class IV neuron, are highly dynamic. Using an automated tip tracking 'Matlab' Software, we characterized the dynamics of the dendritic tips and observed that the tip traces can be segmented into regions of growth (G), shrinkage (S) and paused (P) states. We were able to identify these regions by fitting a piecewise linear function to the traces. There are fast algorithms by which we can fit piece-wise linear function to the individual traces to get the distributions of these three states (G, S and P). Finally, we were able to calculate the velocity distribution of all the traces and mean velocities of growth and shrinkage. The mean velocities turned out to be around 1.5 micron per minute. We also calculated the transition rates among the different states.

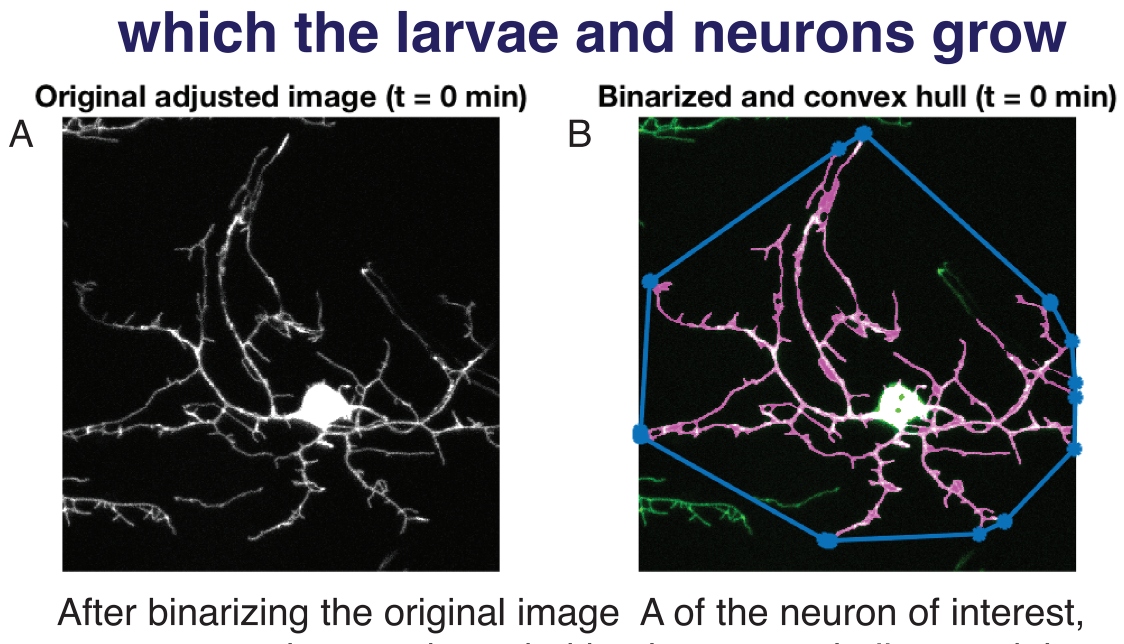
Using the above mentioned dynamic parameters (growth and shrink velocities and transition rates) we will be able to simulate an in silico model to quantitatively compare whether the morphologies predicted by the model capture the complexities of the morphologies observed during development.

Dendritic tips of Drosophila class IV sensory neurons are highly dynamic



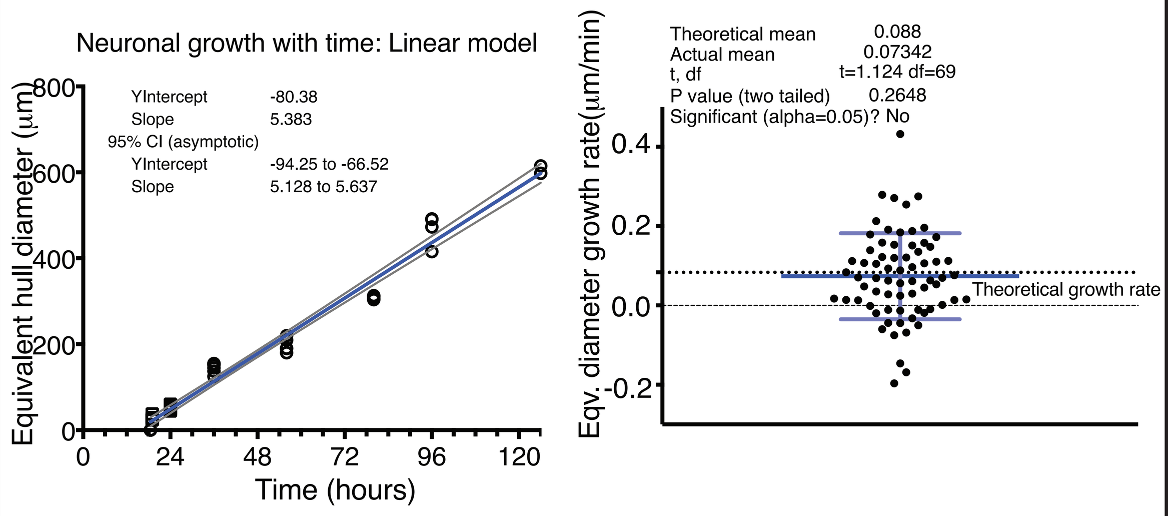
Model system and growth of neurons: We are in interested in the morphology of Drosophila class IV dendritic arbor. A) Our model system drosophila larva showing the tiled class IV neurons. B-D) Represents the size of individual neuron at different stages of the larva (18h, 24 h ,36 h and 96 h after egg laying respectively).

We discovered the imaging condition at which the larvae and neurons grow



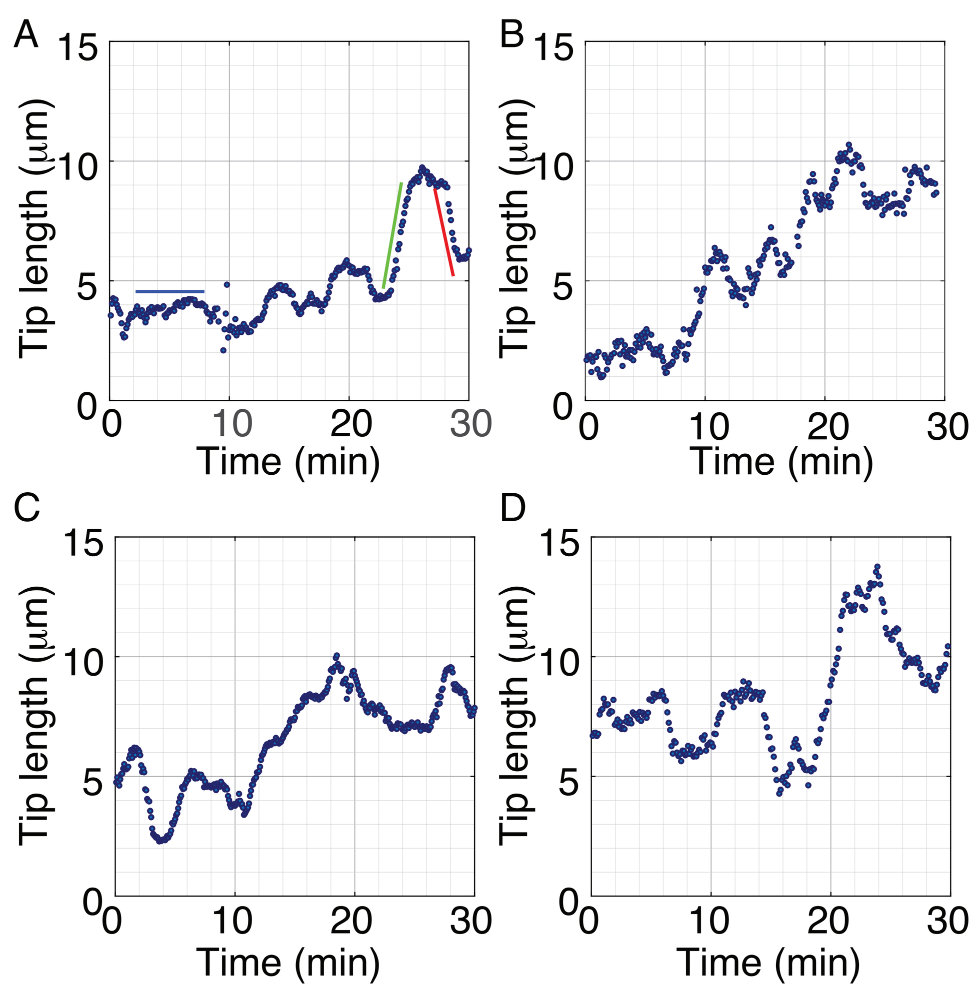
After binarizing the original image A of the neuron of interest, we measure the area bounded by the convex hull around the neuron as shown in B. Convex hull marks the boundary and produces a good measurement of the coverage area of the neuron.By calculating the equivalent diameter of the hull area and plotting as a funtion of time, we can measure the growth rate of the individual neurons.

Neurons grow at expected rate in our imaging condition



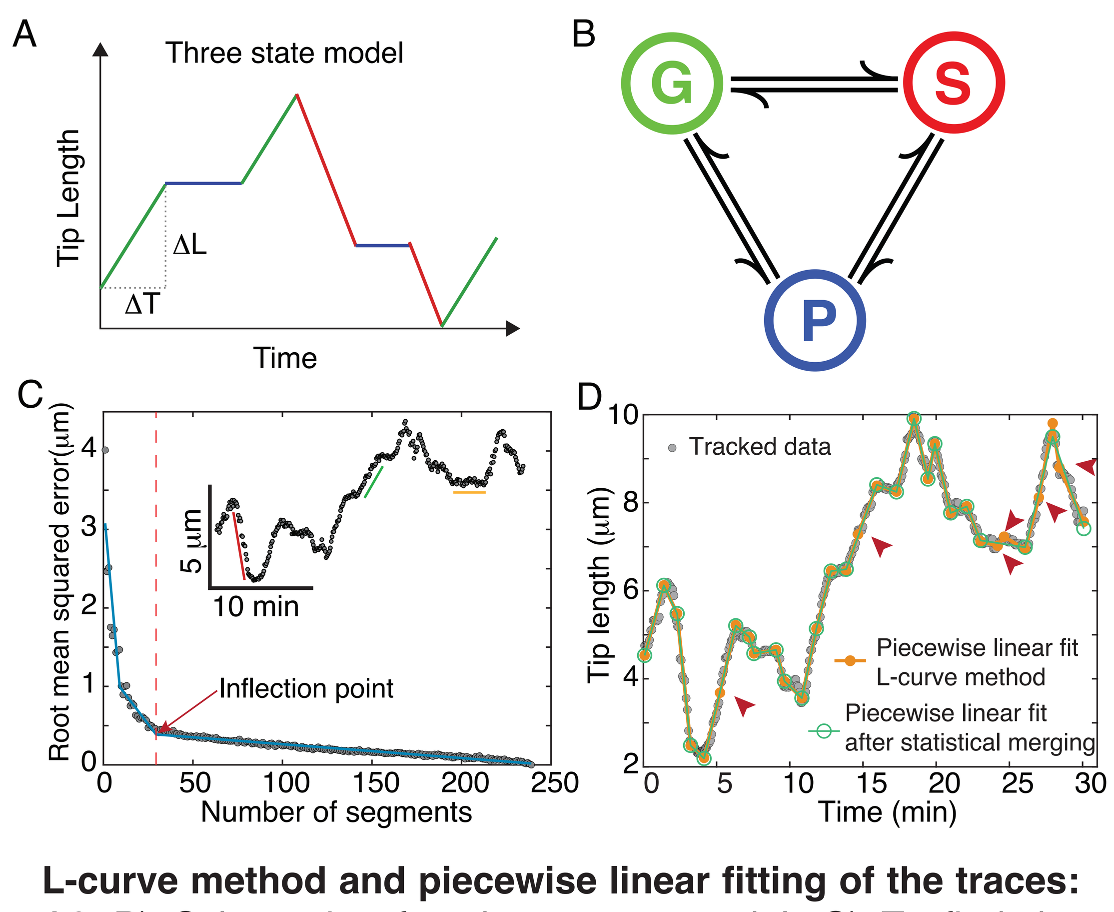
We measured the gowth rate of the neuron by imaging them at different stages of their lifecycle and measured theequivalent diameter. the slope turned out to be 5.38 μm/hour (0.088 μm/min). We measured 70 individual neuron diameters from 10 different embryos and compared with the expected growth rate. We found out that the there is no significant difference between the expected growth rate and measured growth rate.

Automatic filment tracking software can track the dynamics dendritic tips with reasonable accuracy



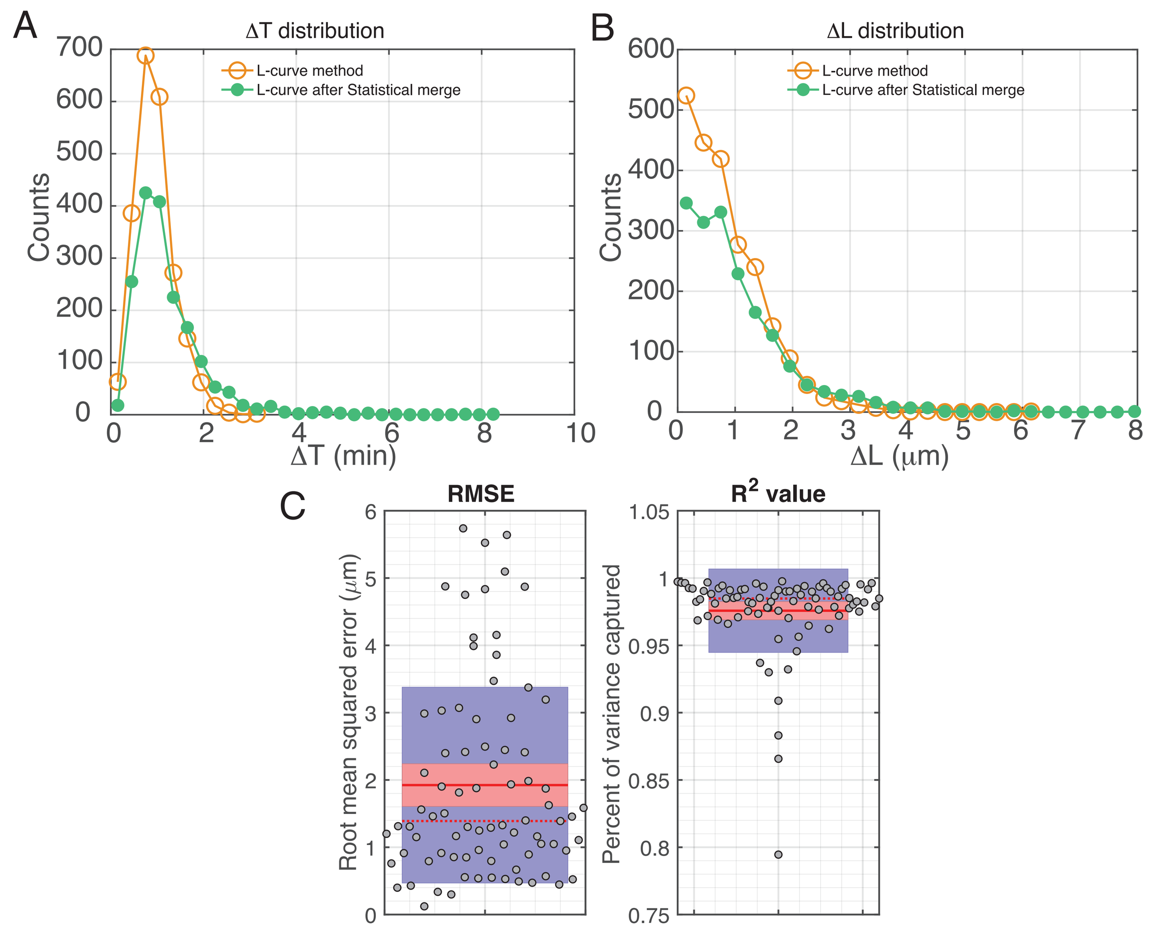
Exaple of traces: We developed a filament tracking Matlab software to track the tips of the dendrites. A-D represents some typical examples of the length vs time trajectories of dendritic tips. Interestingly, the traces show regions of growth (green line), shrinkage (red line) and paused (blue line) events.

Fitting a three state piecewise linear model to the traces: L-curve method



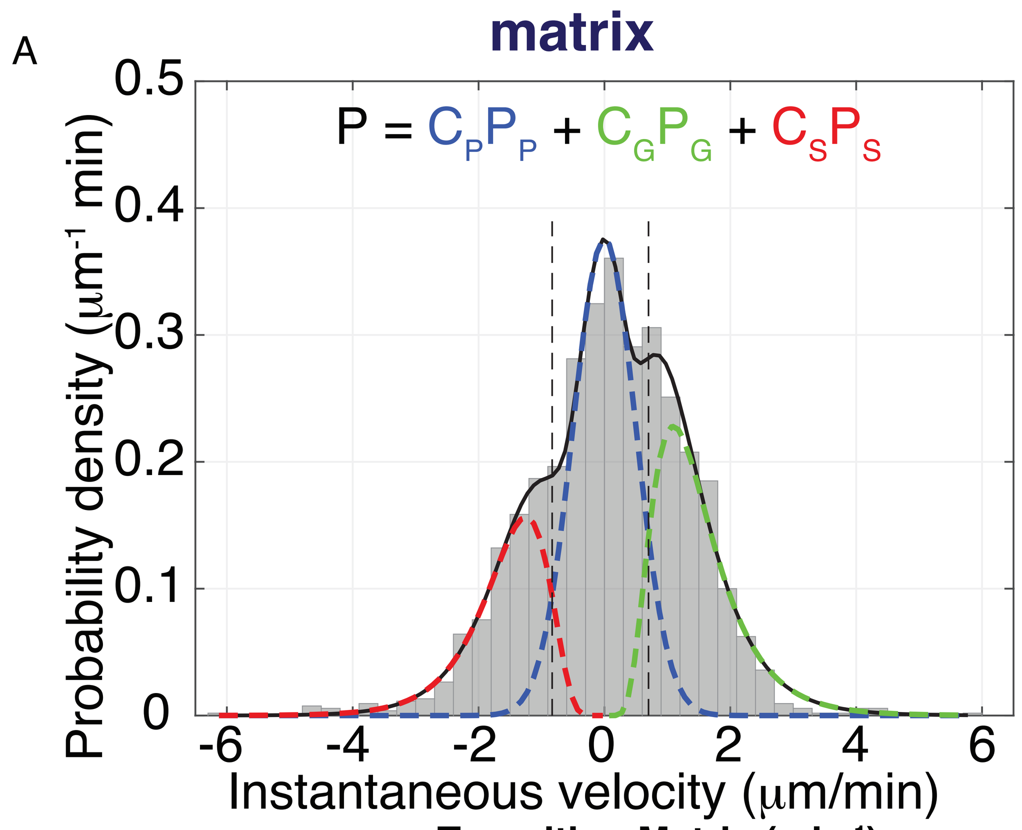
L-curve method and piecewise linear fitting of the traces: A& B) Schematic of a three state model. C) To find the 'optimal number of segments' to fit the individual tracks, we plot root mean squared error from piecewise linear fitting[1] as a function of segment number. We choose this turning/inflection point as the initial guess value of number of segments to fit the traces. A typical example of the piecewise linear fitting to a trace (trace C from Above figure). The orange dots connected by lines represents the initial segmentation of the data. However, L-curve method often puts unnecessary segments. To circumvent this issue, we merge consecutive segments if the slopes are not statistically different from each other. The merging events are shown in red arrowheads.

Statistically merged L-curve algorithm performs reasonably well and capture 98% variation of the data



Time & velocity distribution with fiting statistics :A & B)The time and velocity distribution respectively after L-curve method. These distributions clear capture long events as shown by the long tails of the green curve beacuse of the marging algorithm. C) The statistics of fitting shows that the mean RMSE is ~ 2 microns and R2 statistics shows that we capture almost 98% of the vriance of the data.

The velocity distribution shows three humps in accordance with the three state model and we can calcuate the transition matrix



B

Transition Matrix (min^{-1})

	Paused	Shrinking	Growing
Paused		0.08652	0.1459
Shrinking	0.09727		0.08184
Growing	0.1445	0.09119	

Velocity distribution and transition matrix : A) The gray histogram represents the instantaneous velocity of the all the traces (81). The distribution clearly depicts humps in positive and negative velocity regions. To calculate the mean growth and shrinkage velocity, we fit the distribution with a central Gaussian peak and two Lognormal distributions on both sides of zero. The text on top the figure represents the general form of the fitting function. C's are proportionality constants and sum of CP, CG and CS is constrained to be equal to 1. P's are the normalized probability distributions of the aforementioned forms.The two black dashed vertical lines characterize the intersections between the probability distributions. C) We threshold all the traces using the two intersection values for growth and shrinkage as mentioned before and counted the transition between different states to calculate the transition matrix. The transition rates are presented in the matrix.

Conclusions

The three state model successfully captures the mesoscopic process of the dendritic growth, shrinkage and paused states and the transition rates between the states. Using these measured parameters we can build an in silico model to predict the final morphology of the dendritic arbor. Finally, we can investigate how these individual parameters change under different mutations and how that lead to different morphologies[2].

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References:

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2.Emoto K, He Y, Ye B, Grueber WB, Adler PN, Jan LY, Jan YN., Cell. 2004 Oct 15;119(2):245-56

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