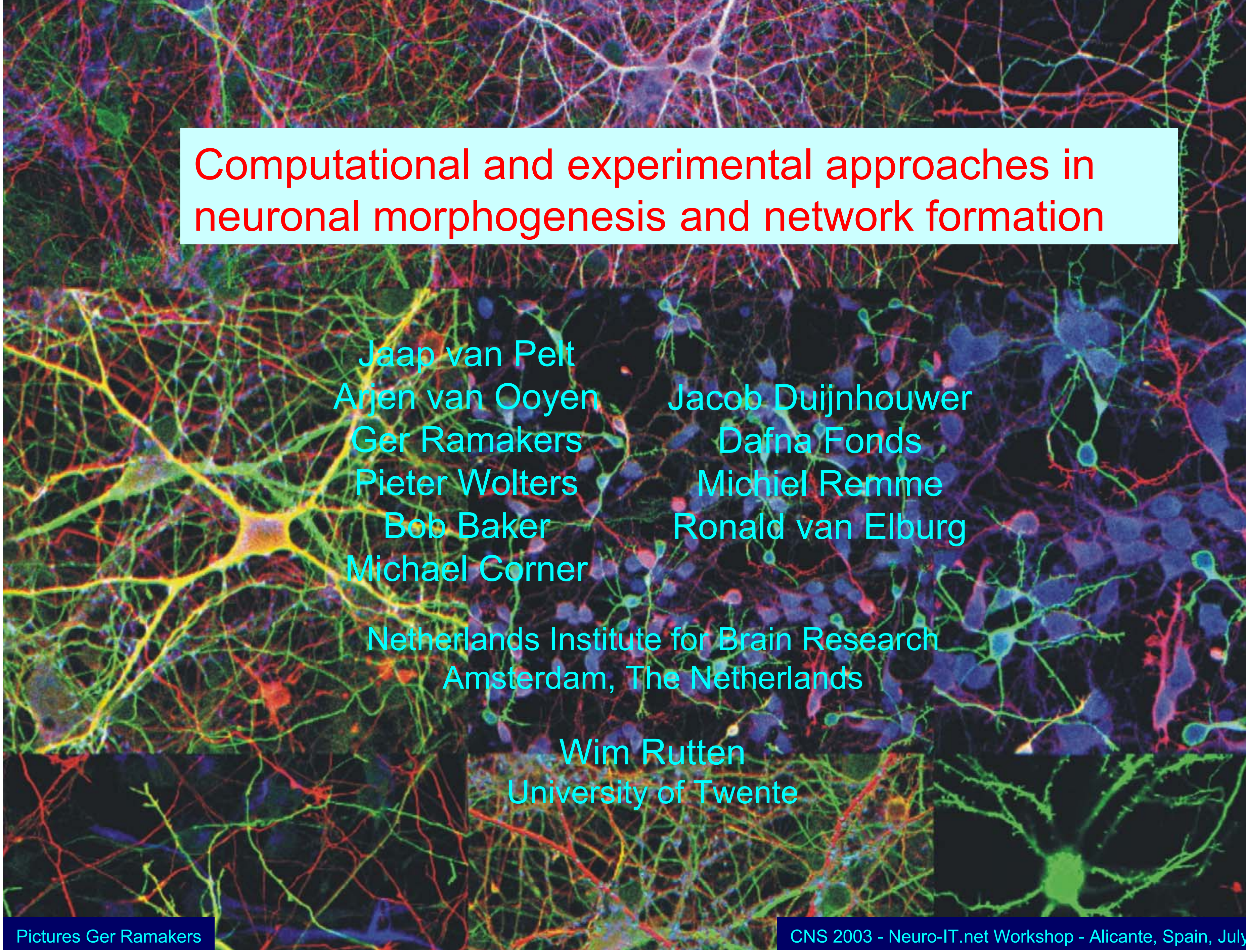

Computational and experimental approaches in neuronal morphogenesis and network formation

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Pictures Ger Ramakers

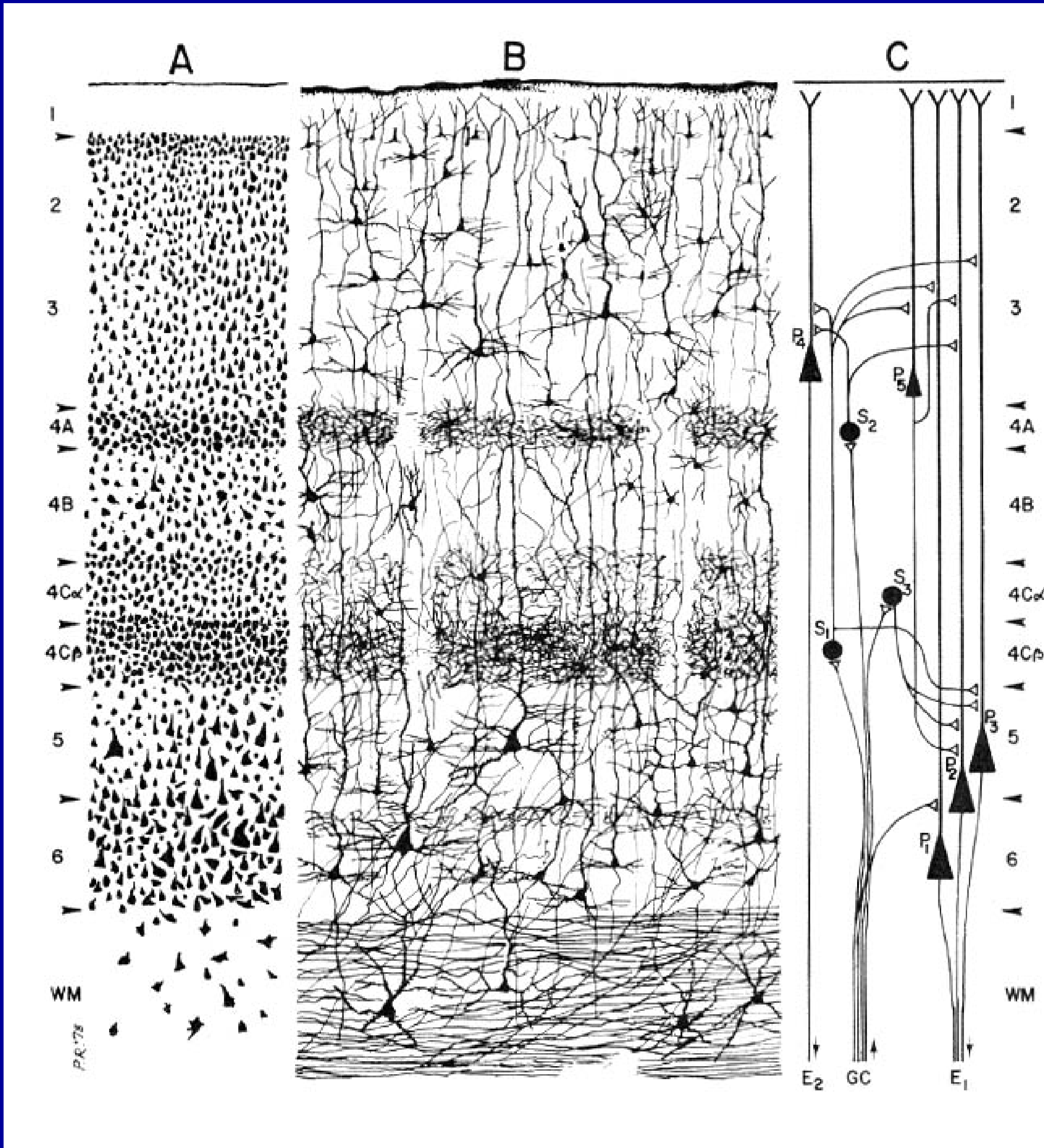
- Introduction
- Modeling dendritic morphological complexity
- Development of synaptic connectivity
- Spontaneous bioelectric activity in developing neuronal networks in vitro
- Balance of excitation and inhibition

Nervous system

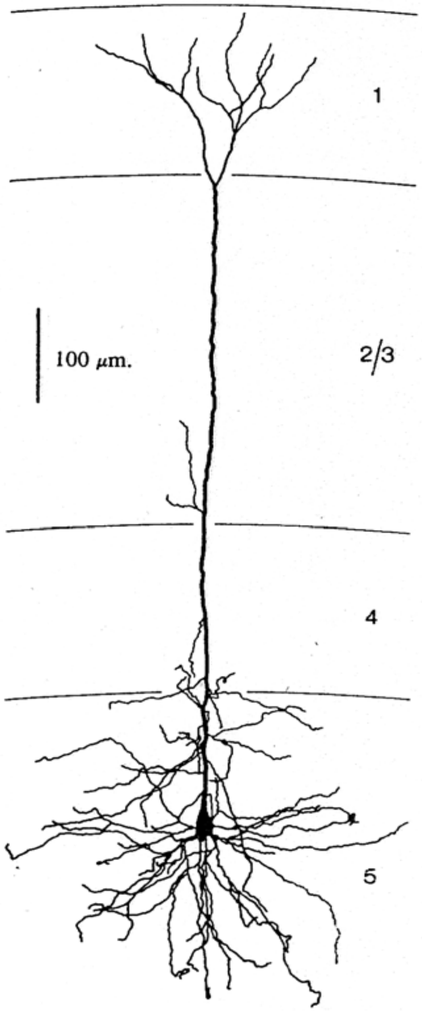
- neurons
- synaptic connections
- neuronal networks

Cortical organization

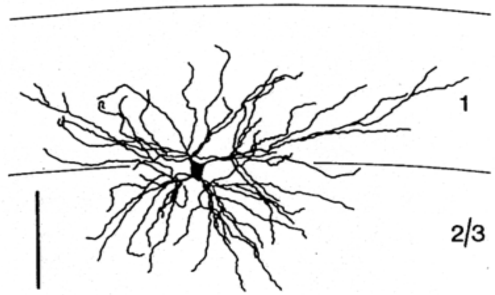
- Cell bodies
- Dendrites and axons
- Synaptic connections
- Layers
- Excitation - Inhibition



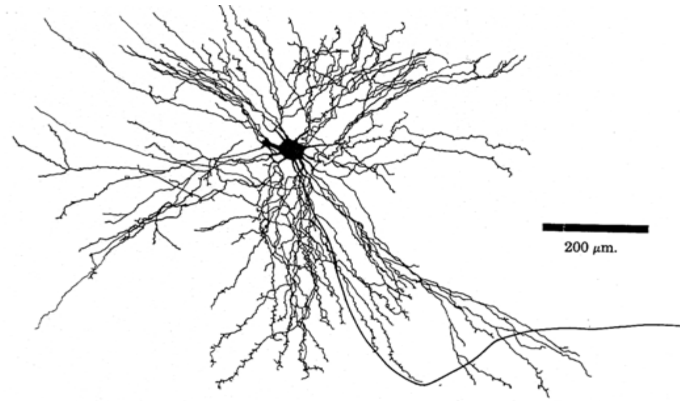
Neuronal morphological diversity



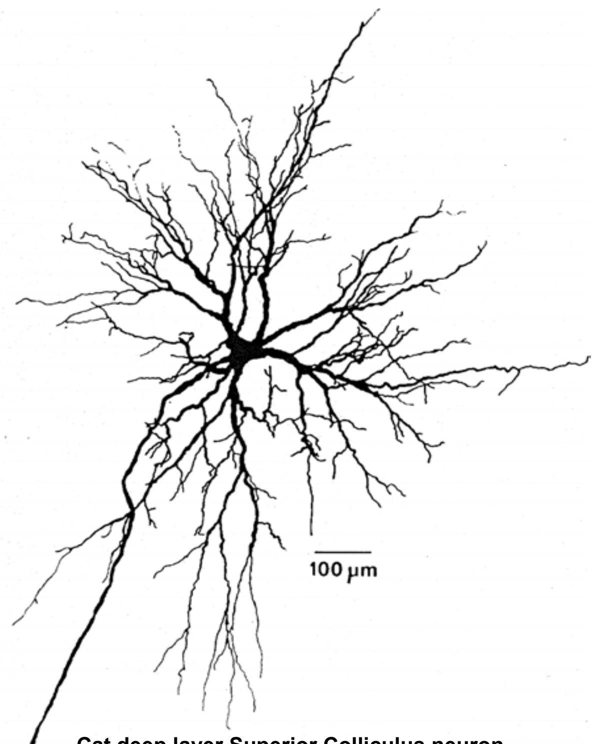
Rat visual cortex layer 5 pyramidal neuron
Larkman and Mason, J. Neurosc. 10 (1990) 1407



Rat visual cortex layer 2/3 pyramidal neuron
Larkman and Mason. J. Neurosc. 10 (1990) 1407



Cat hindlimb Moto neuron - Uhlfhake and Cullheim
J. Comp. Neurol. 278 (1988) 88

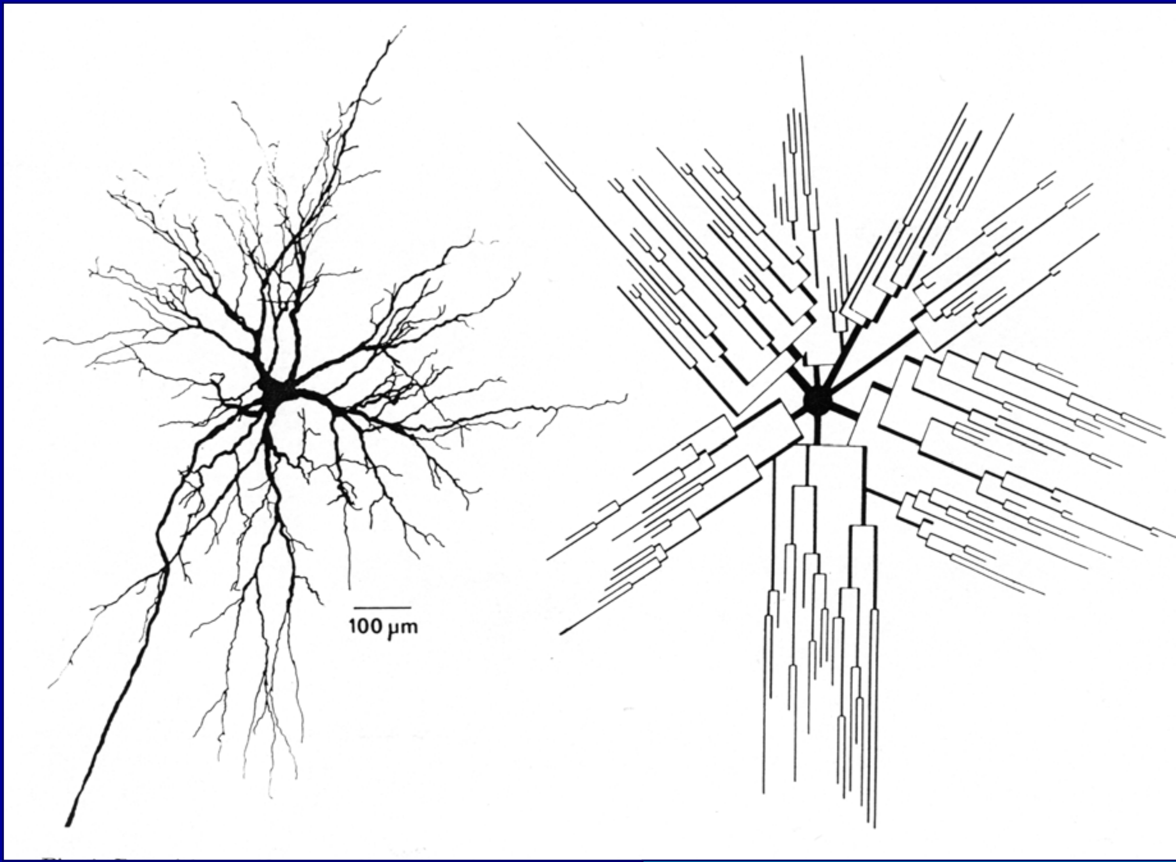


Cat deep layer Superior Colliculus neuron
Schierwagen, J. Hirnforsch. 27 (1985) 670

Rat cerebellar Purkinje cell - Berry and Bradley
Brain Res. 112 (1976) 1-35.

Shape parameters of dendritic branching patterns

- ➢ Number of segments
- ➢ Length of segments
- • Diameter of segments
- ➢ Topological structure
- • Curvature of segments
- • 3D embedding



Cat deep layer superior colliculus neuron
A. Schierwagen J. Hirnf. 27 (1986) 679

Modeling dendritic morphological complexity using principles of neuronal development

Quantification of dendritic morphological variability

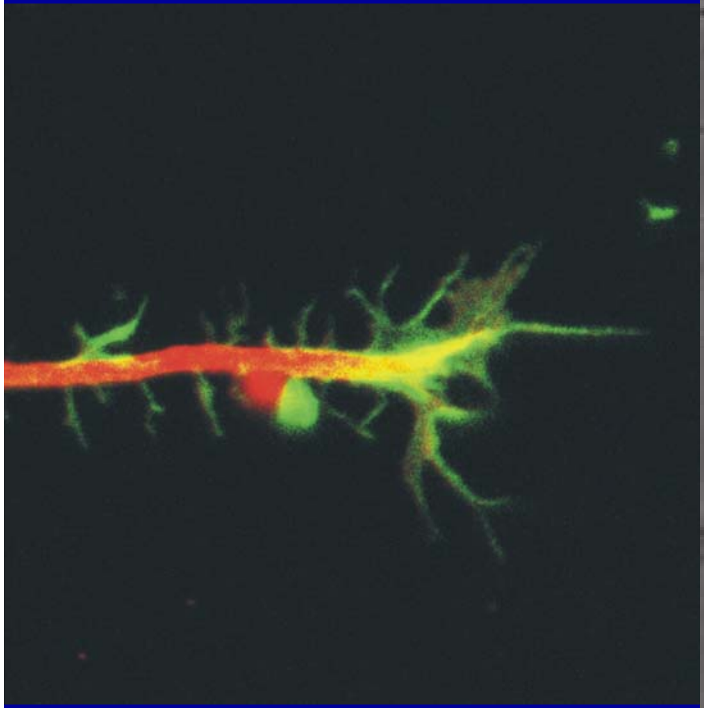
Source of morphological variability

Morphological differences between cell types

‘Design rules’ of dendritic morphology

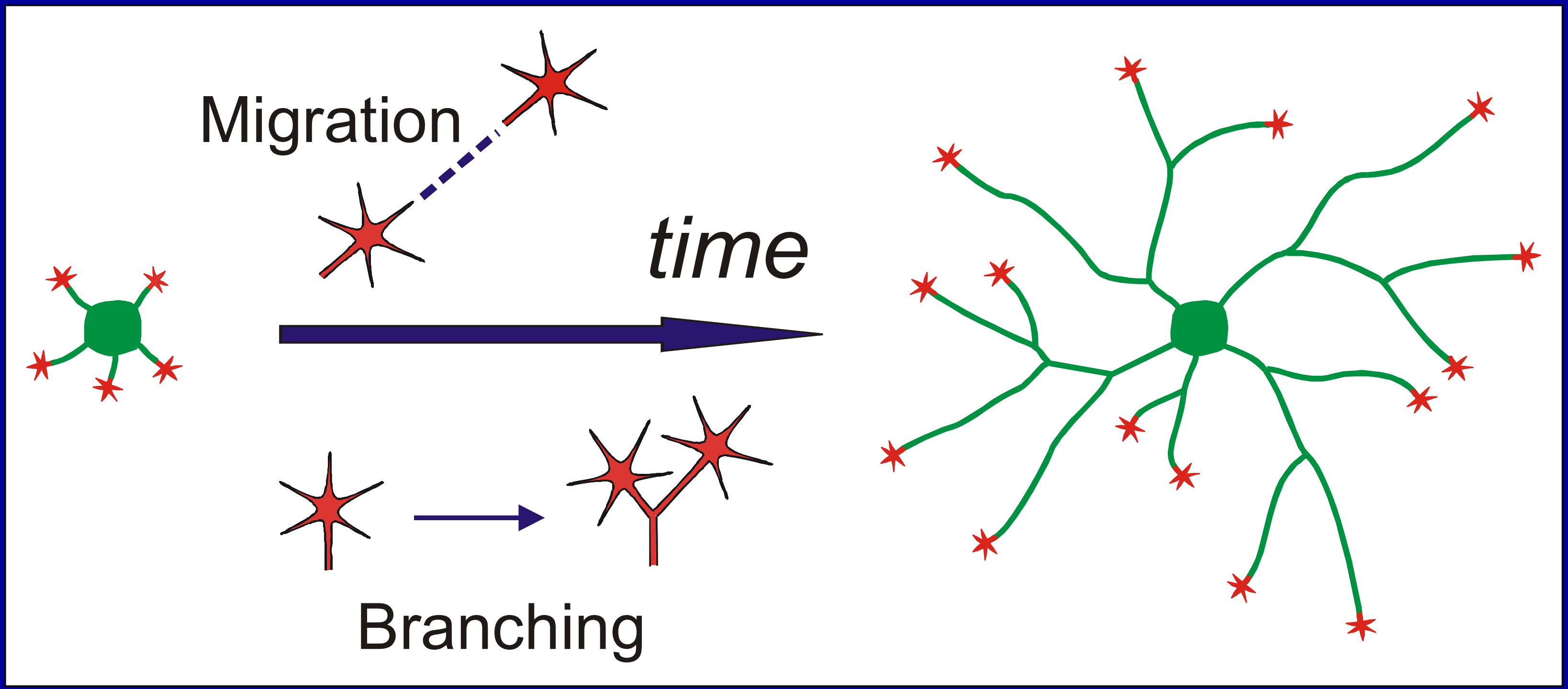
Functional implications of dendritic shape characteristics

Axonal and dendritic outgrowth through growth cone elongation, branching, and retraction

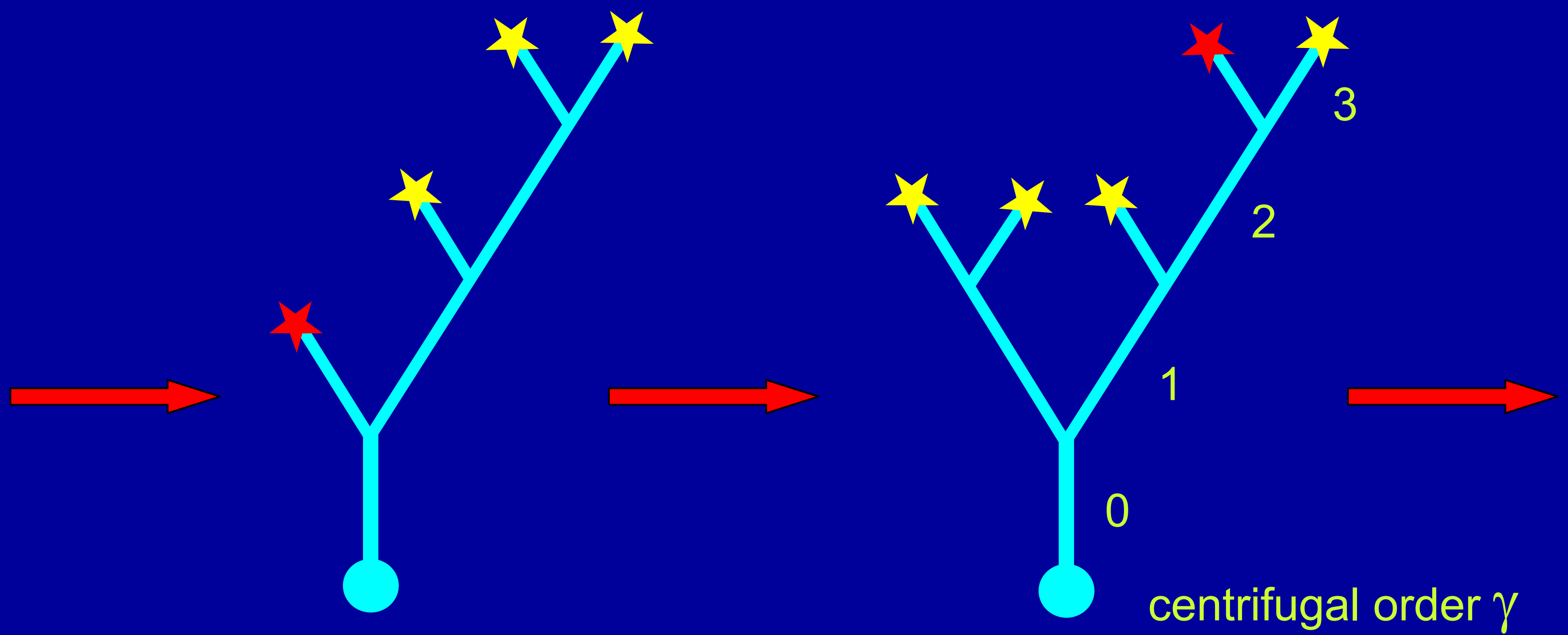


Modeling dendritic morphological complexity

find minimal phenomenological rules for reproducing dendritic morphological complexity



Random selection of segment for branching

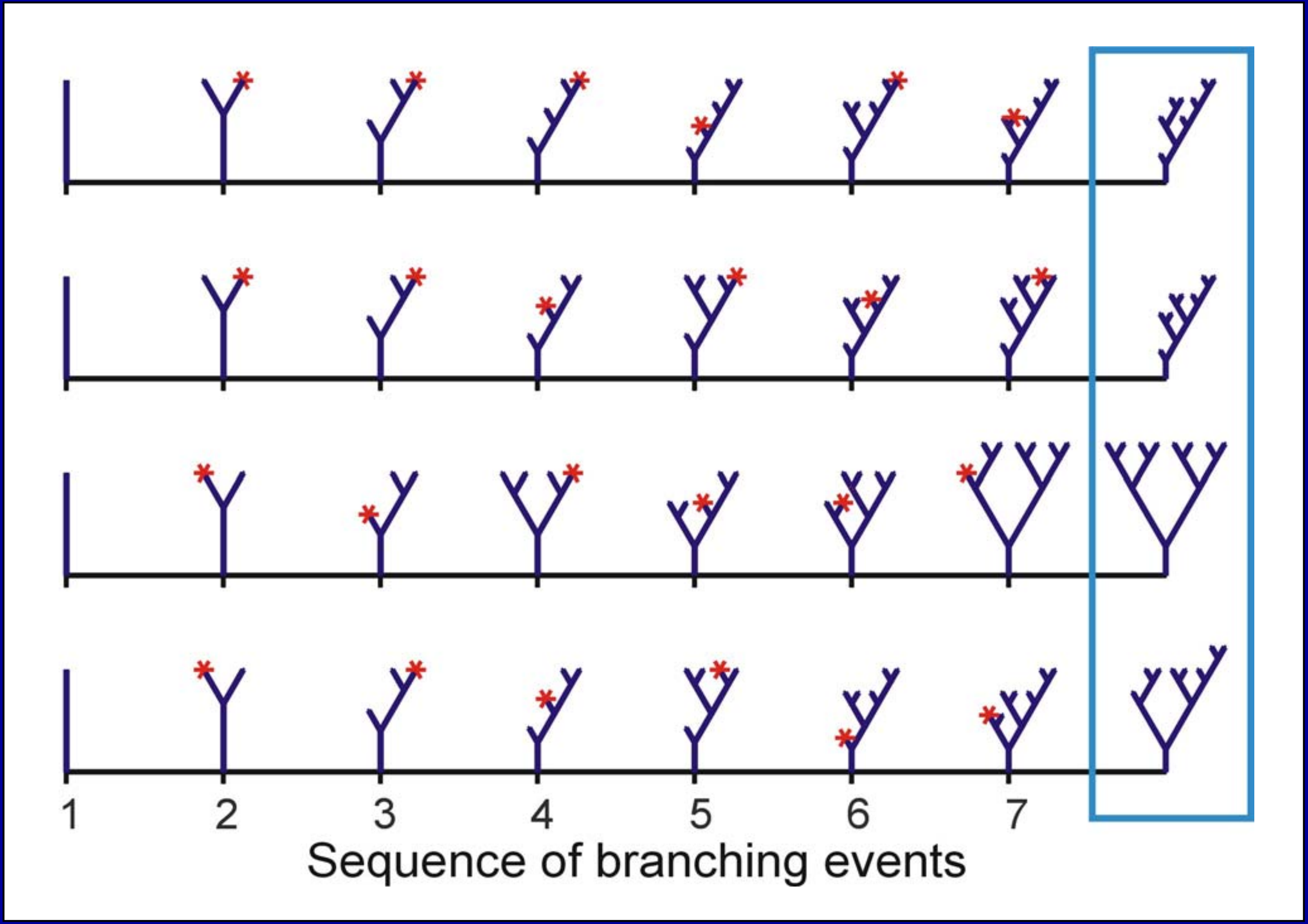


$$p_i \approx 2^{-S\gamma_i} / C$$

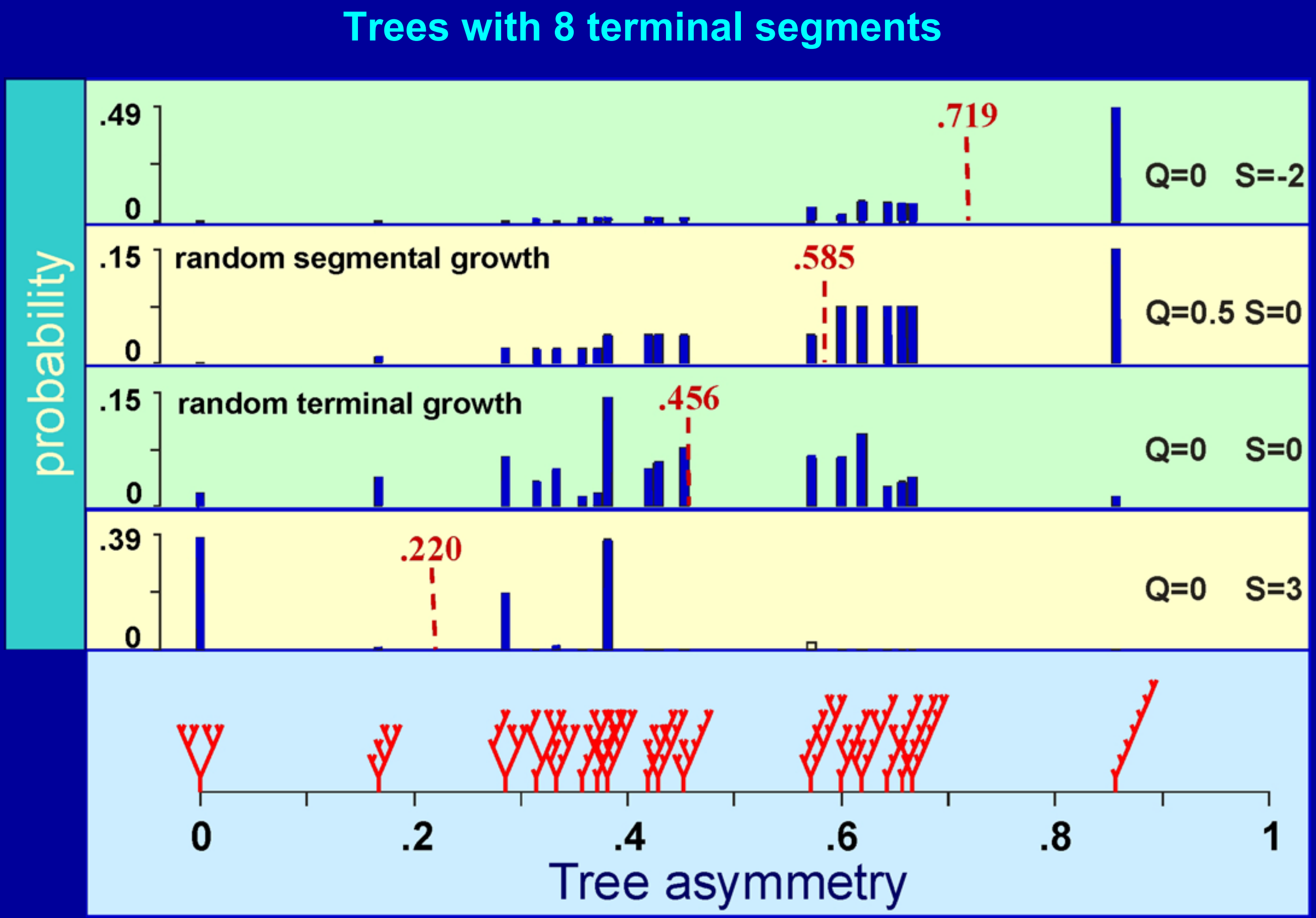
Selection probability of a terminal segment for branching depends on its centrifugal order

Topological variation due to random branching

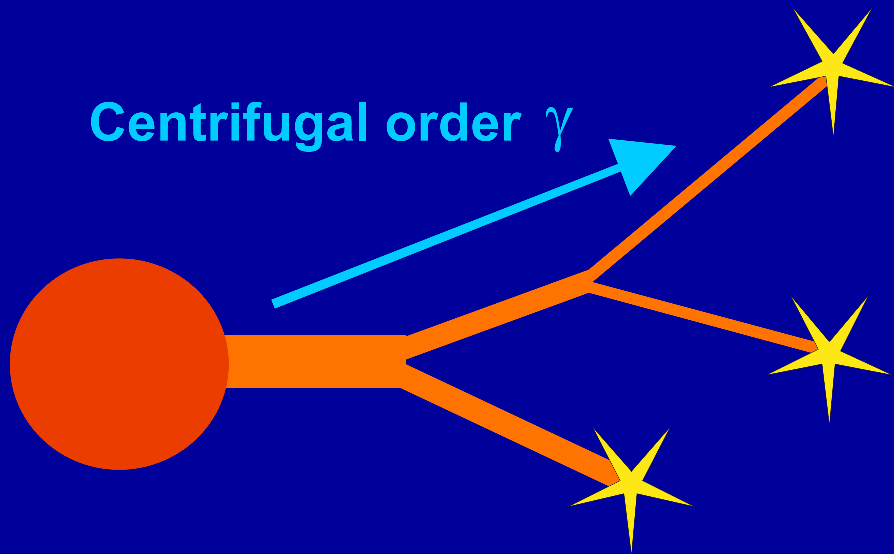
S=0 p_i =1/n equal selection probabilities



Tree-type probabilities depend on mode of branching



Branching in continuous time



n(t): number of tips at time t

Branching probability per unit of time of a tip:

$$p_b(t) = D(t) \cdot n(t)^{-E} \cdot \left\{ 2^{-S\gamma} / C \right\}$$

D(t): baseline branching rate

$$B(t) = \int_0^t D(s)\,ds$$

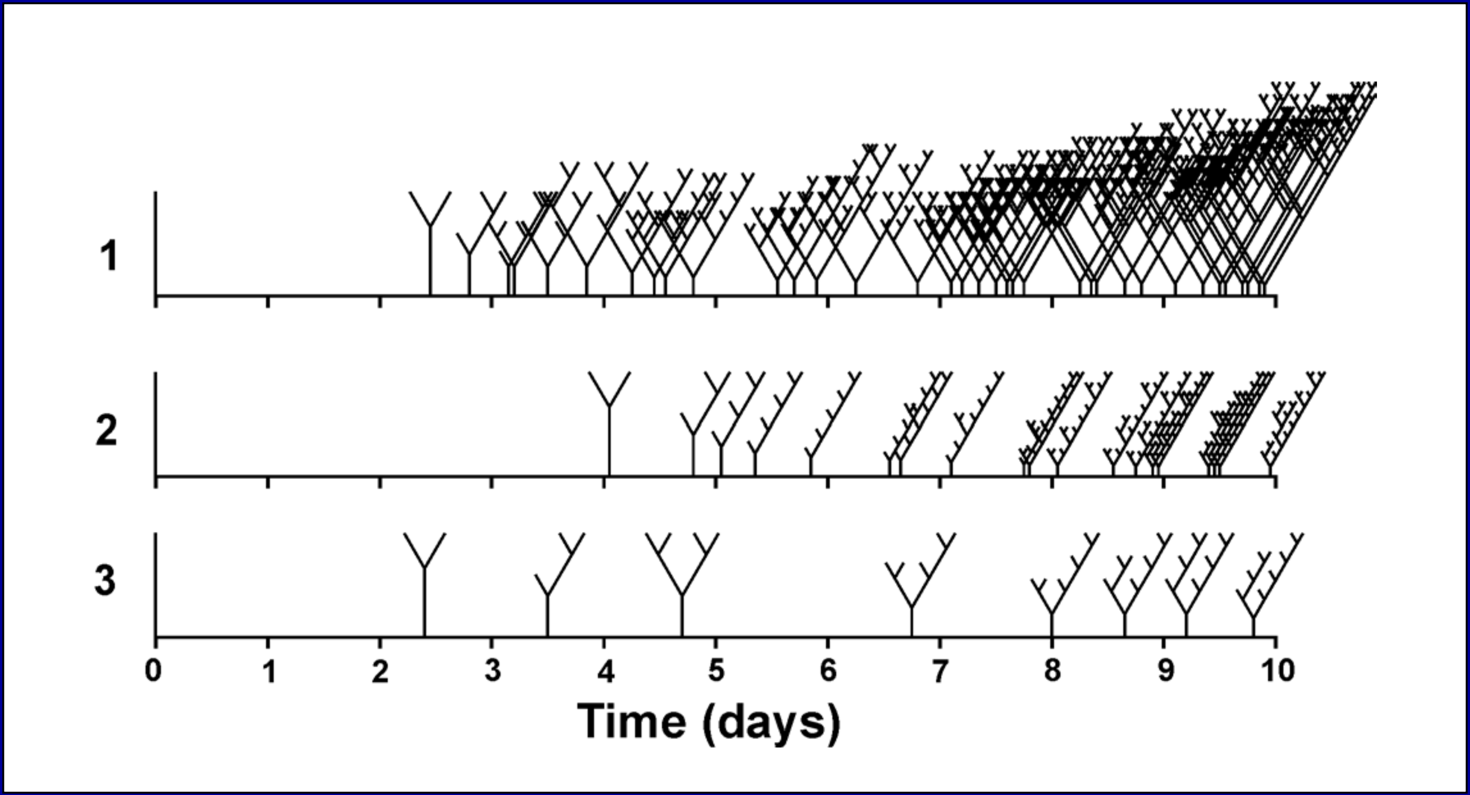
E: “competition parameter”

S: modulation of order dependency

C: normalization factor

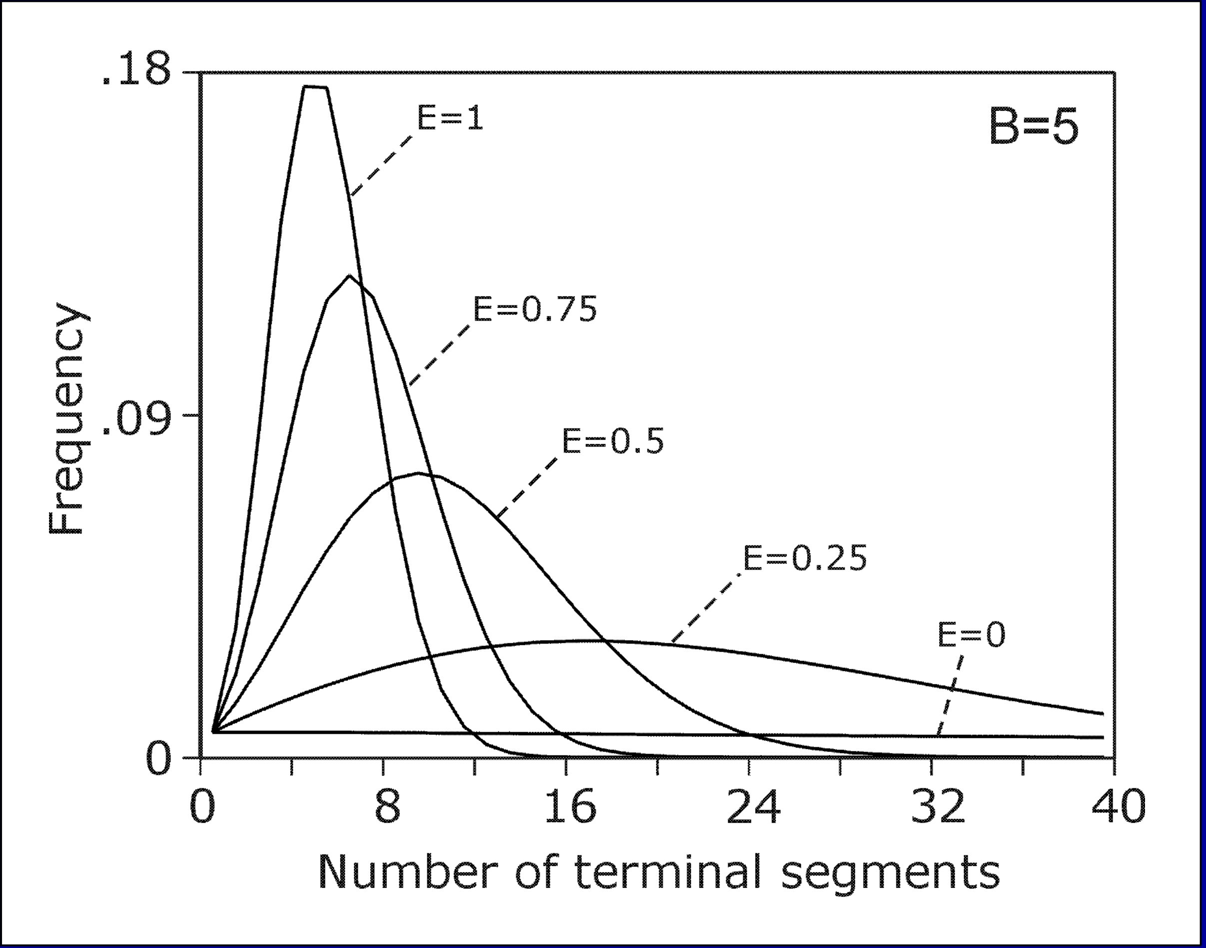
Random branching sequences

E = 0 (no competition) ❖
B = 3 D = B / 10 = 0.3 / day (constant)



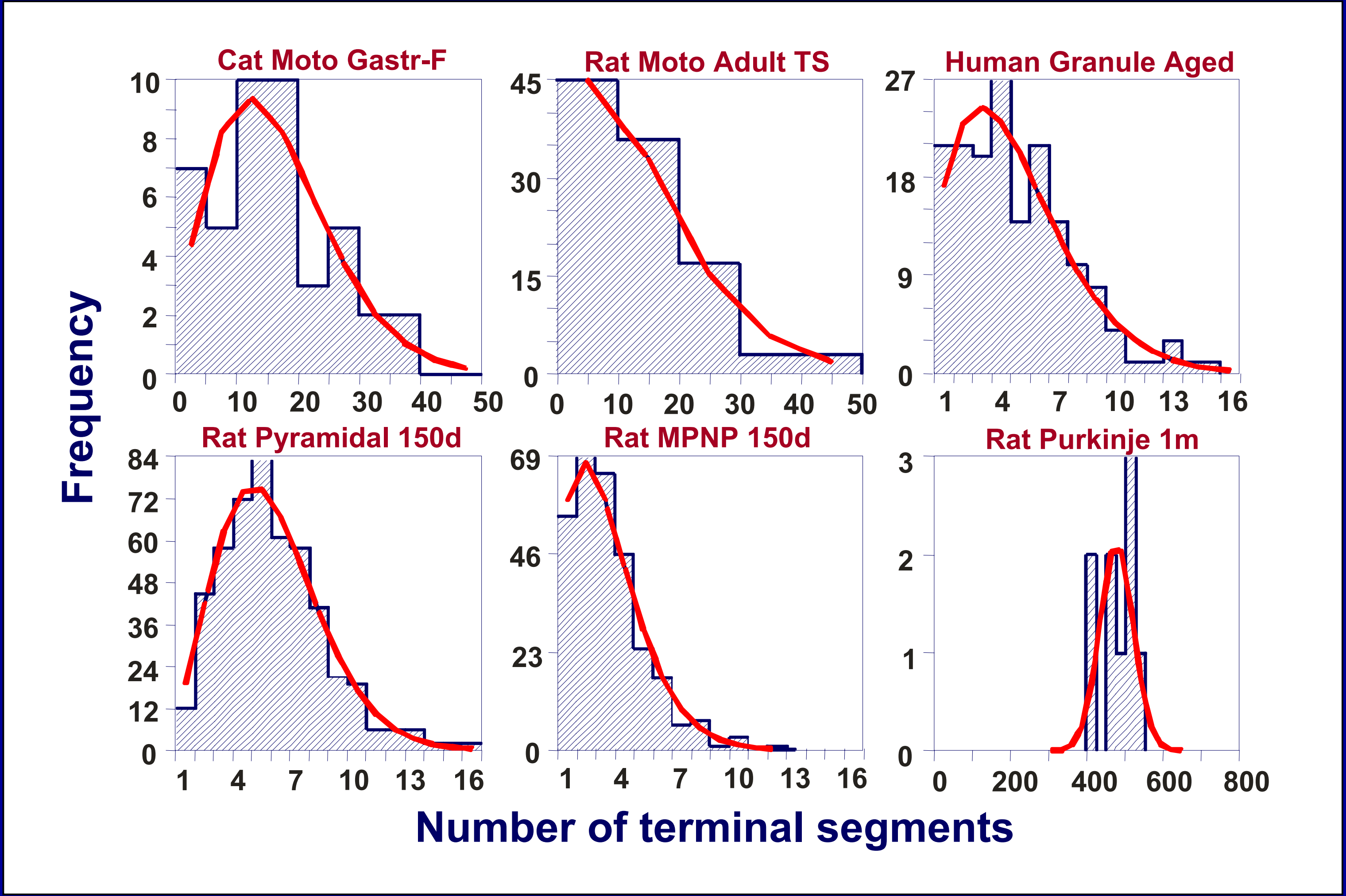
❖ *Unrestricted proliferation of the number of terminal segments*

Competition parameter E determines shape of terminal segment number distribution

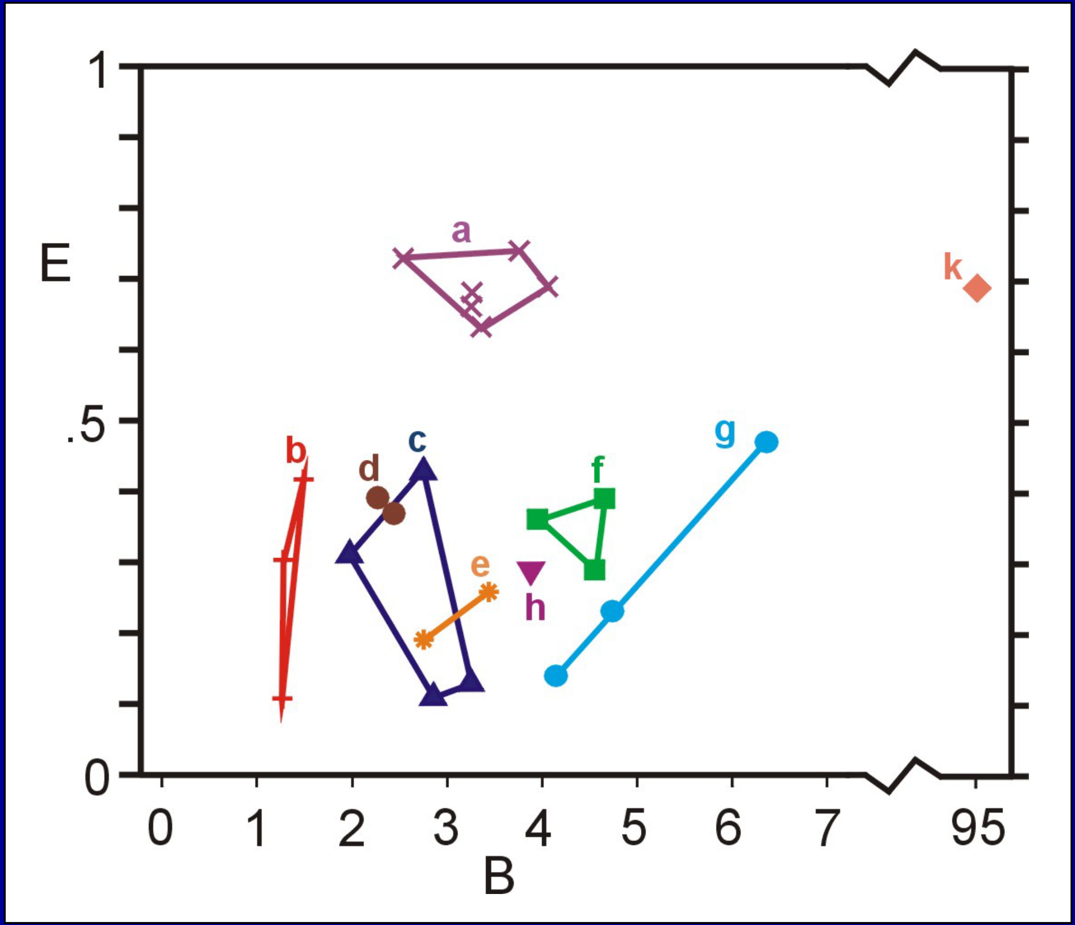


Variation in terminal segment number

Matching between distributions of observed and model trees



Optimized branching parameters B and E



a - rat cortical pyramidal neurons

b - rat cortical multipolar nonpyramidal

c - rat motoneurons

d - human dentate granule

e - cultured cholinergic interneurons

f - cat motoneurons

g - frog motoneurons

h - cat deep layer superior colliculus

k – guinea pig cerebellar Purkinje cells

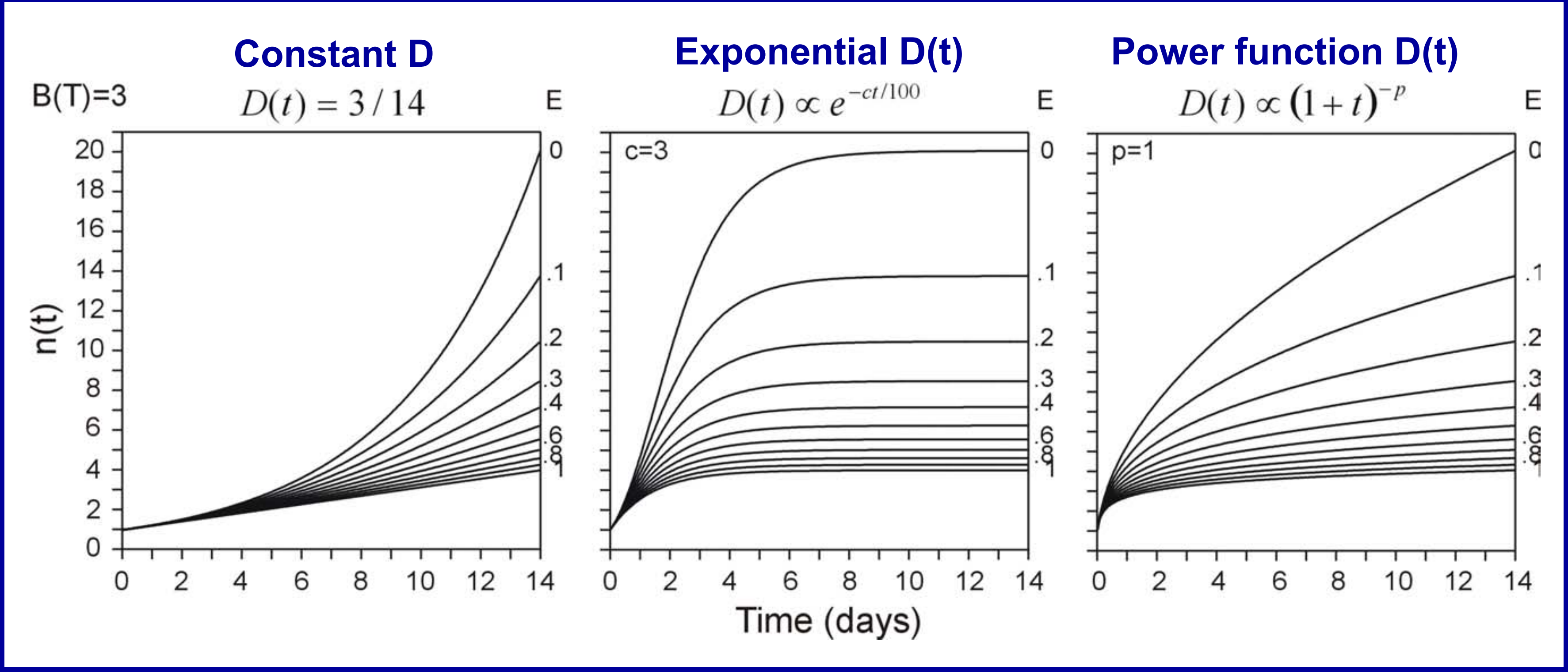
Growth function n(t) - influence of baseline branching rate function D(t)

$$\frac{dn(t)}{dt} = D(t)n(t)^{1-E}$$

$$n(t) = [1 + EB(t)]^{1/E}$$

$$n(t \mid E = 0) = e^{B(t)}$$

$$B(t) = \int_0^t D(s)ds$$



Growth curve for the number of tips n(t)

Rat multipolar nonpyramidal dendritic trees
(Parnavelas, Uylings)

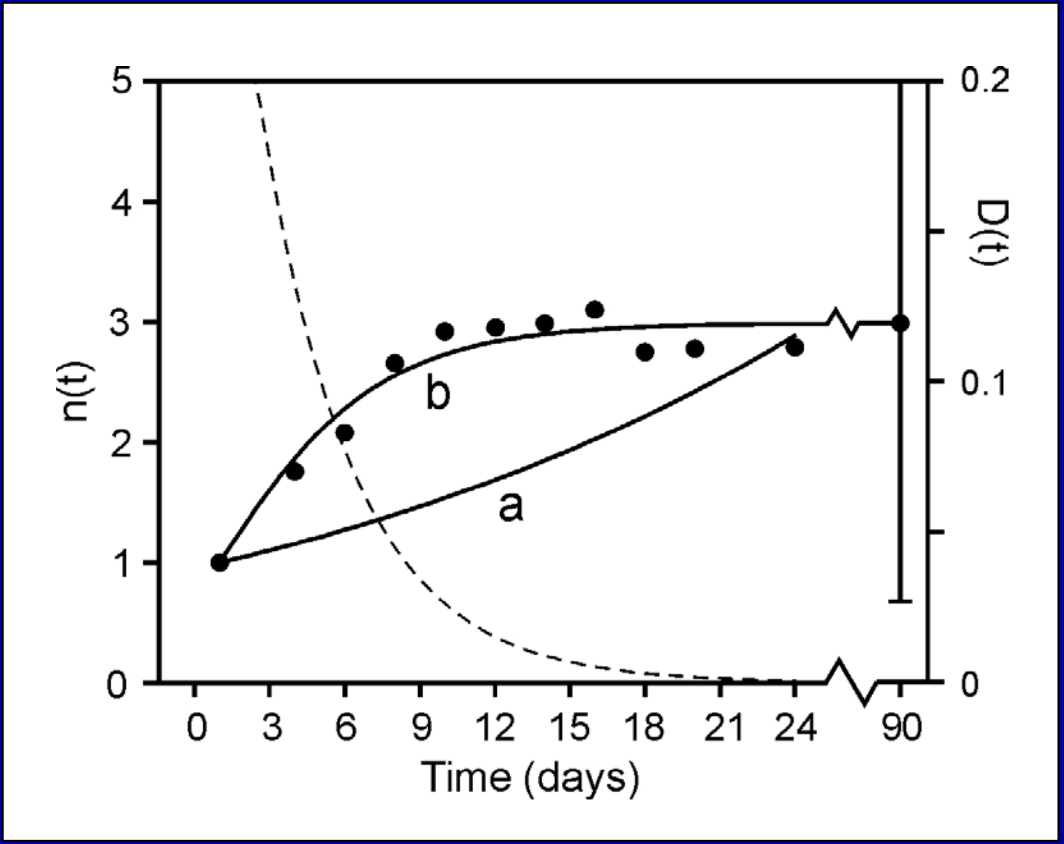
Growth function n(t) for

(a) constant basal branching rate

$$D = 0.049$$

(b) exponential basal branching rate

$$D(t) = 0.3e^{-(t-1)/3.7}$$



Segment length distributions

"Segment lengths determined by both neurite branching and elongation"

Model approach:
step 1: optimize branching process
step 2: include elongation into mode

Model optimized on S1-rat layer 2/3 pyramidal basal dendrites

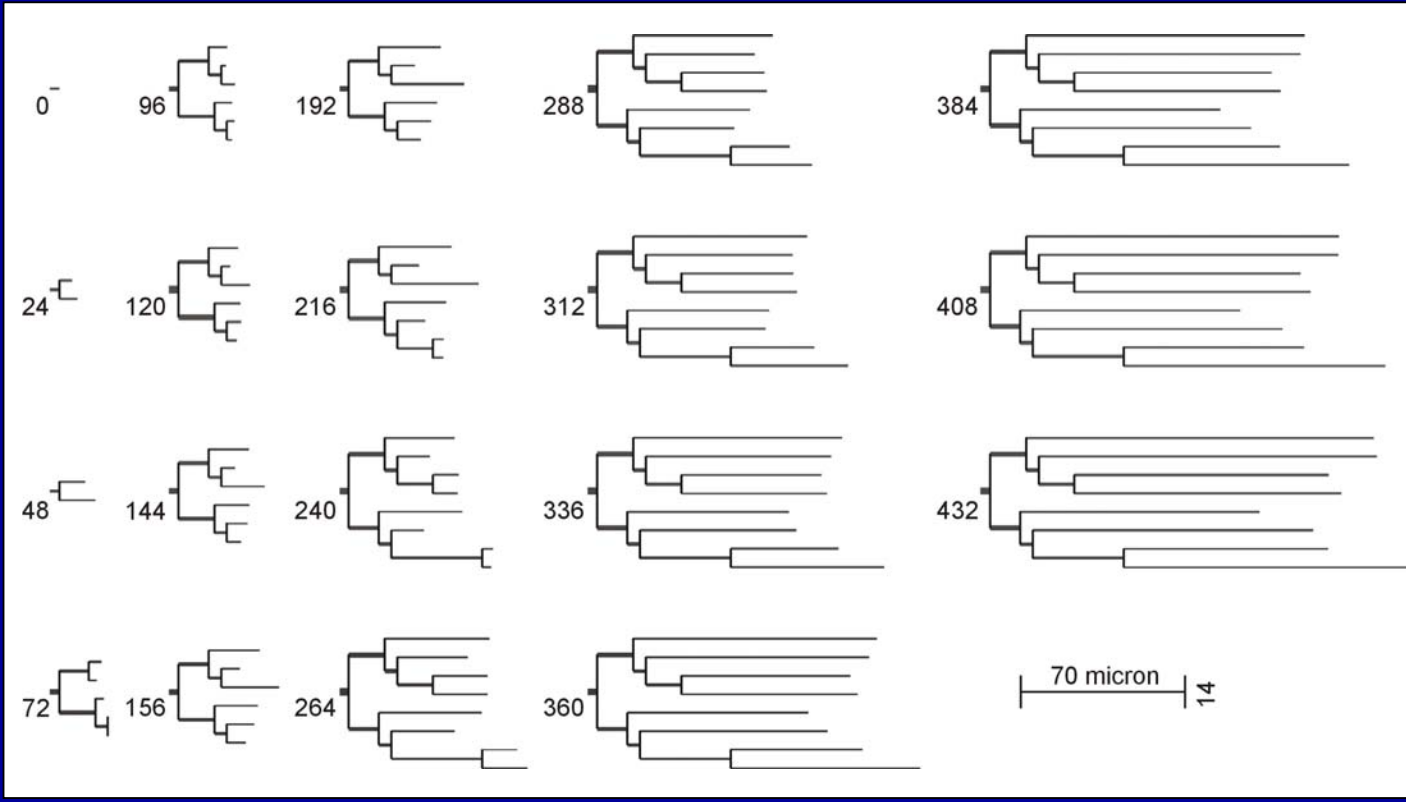
Branching:
B = 3.85
E = 0.74
S = 0.87

Elongation:
V_{be}= 0.22 μm/h
V_e = 0.51 μm/h
CV = 0.28

Empirical:
T_0 = -24 h
T_{be}= 240 h
T_e = 432 h

This example for constant D

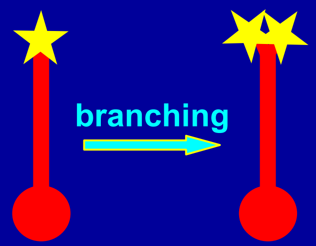
Growth of a model tree

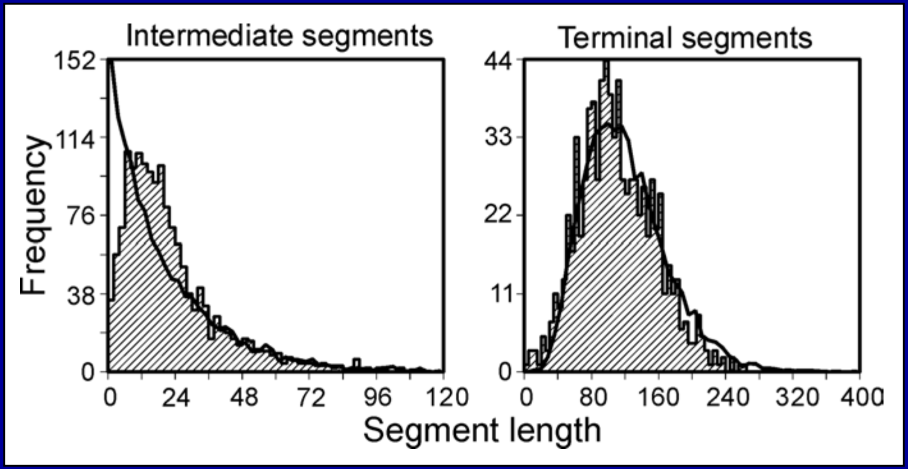


Initial length after branching event

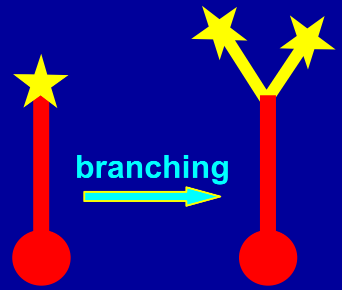
After branching event:

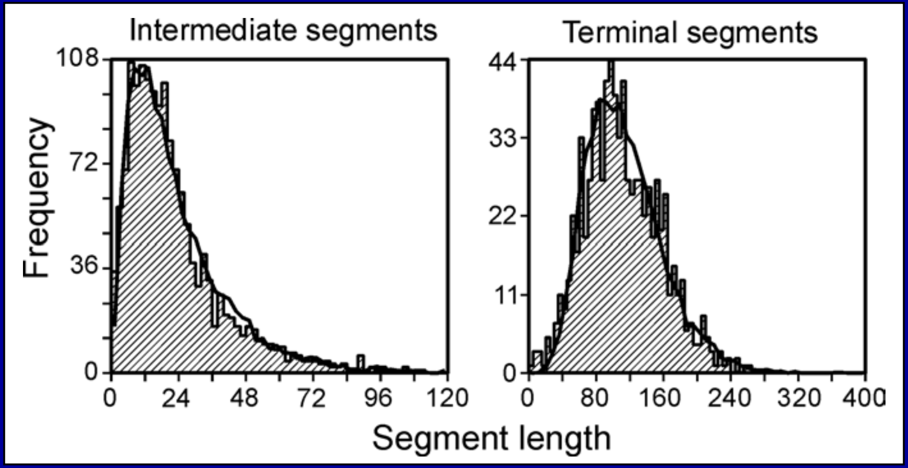
S1-rat layer 2/3 Pyramidal basal dendrites





Daughter segments
start with *zero* length





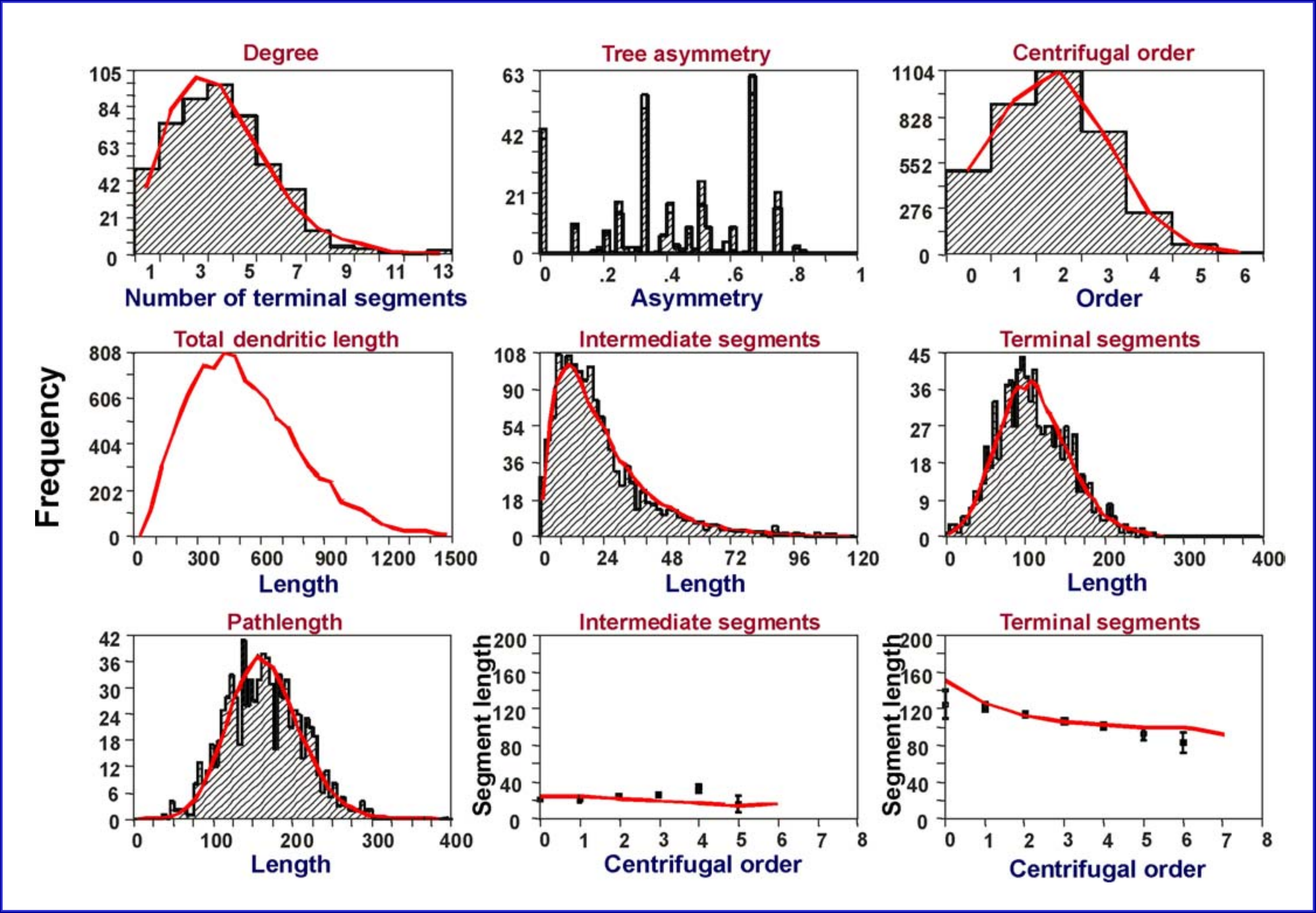
Daughter segments
start with *initial* length

S1-rat layer 2/3 Pyramidal basal dendrites

Branching:
B = 2.52
E = 0.73
S = 0.5

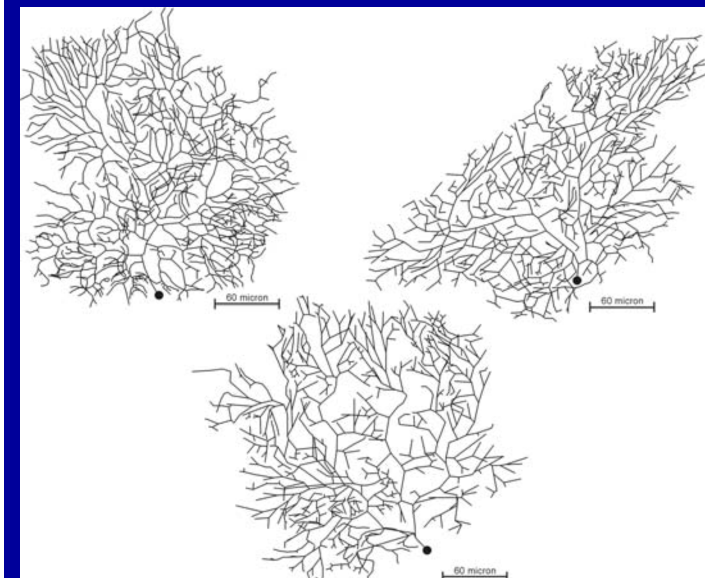
Elongation:
l_{in} = 6 μm
$\sigma(l_{in})$ = 5
v_{be} = 0.22 μm/h
v_e = 0.51 μm/h
cv = 0.28

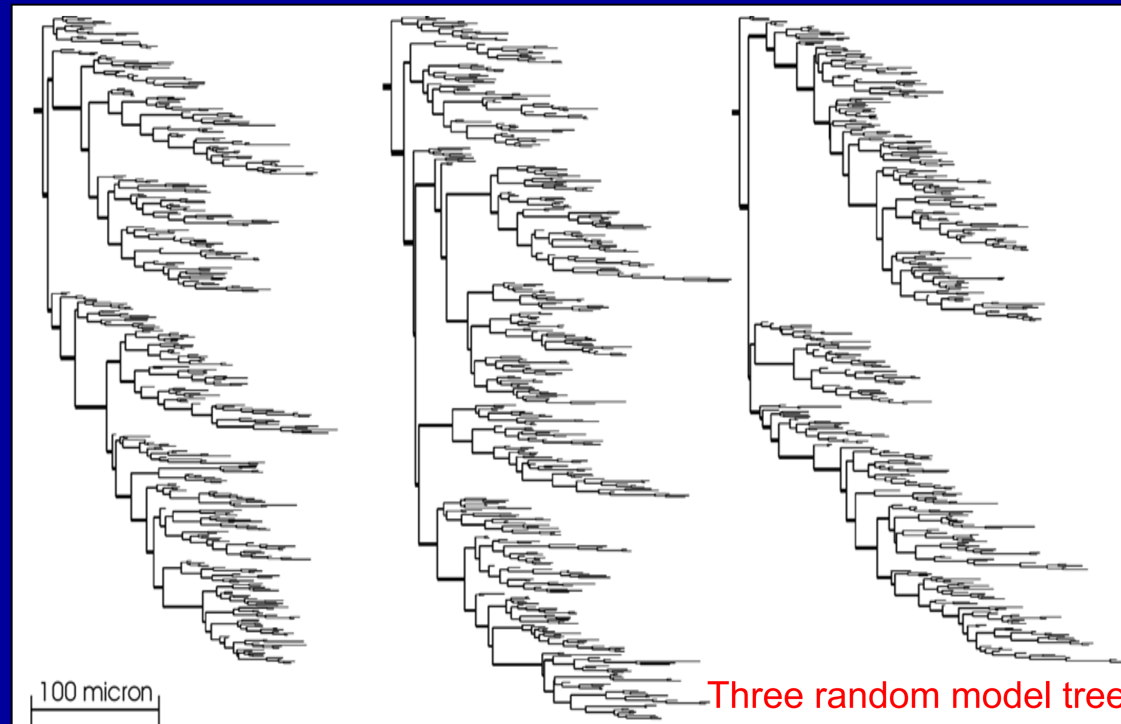
Empirical:
T_0 = 24 h
T_{be} = 240 h
T_e = 432 h



Modeling guinea pig cerebellar Purkinje cell dendritic trees

Reconstructions:
M. Rapp et al., J. Physiol. 474 (1994) 101-118

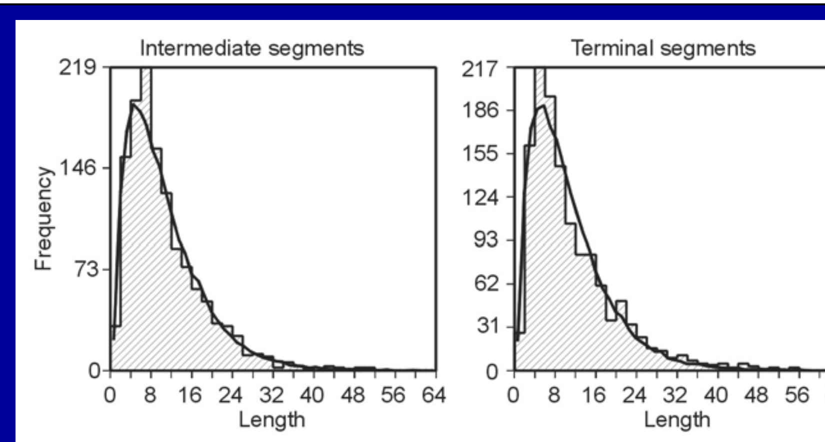




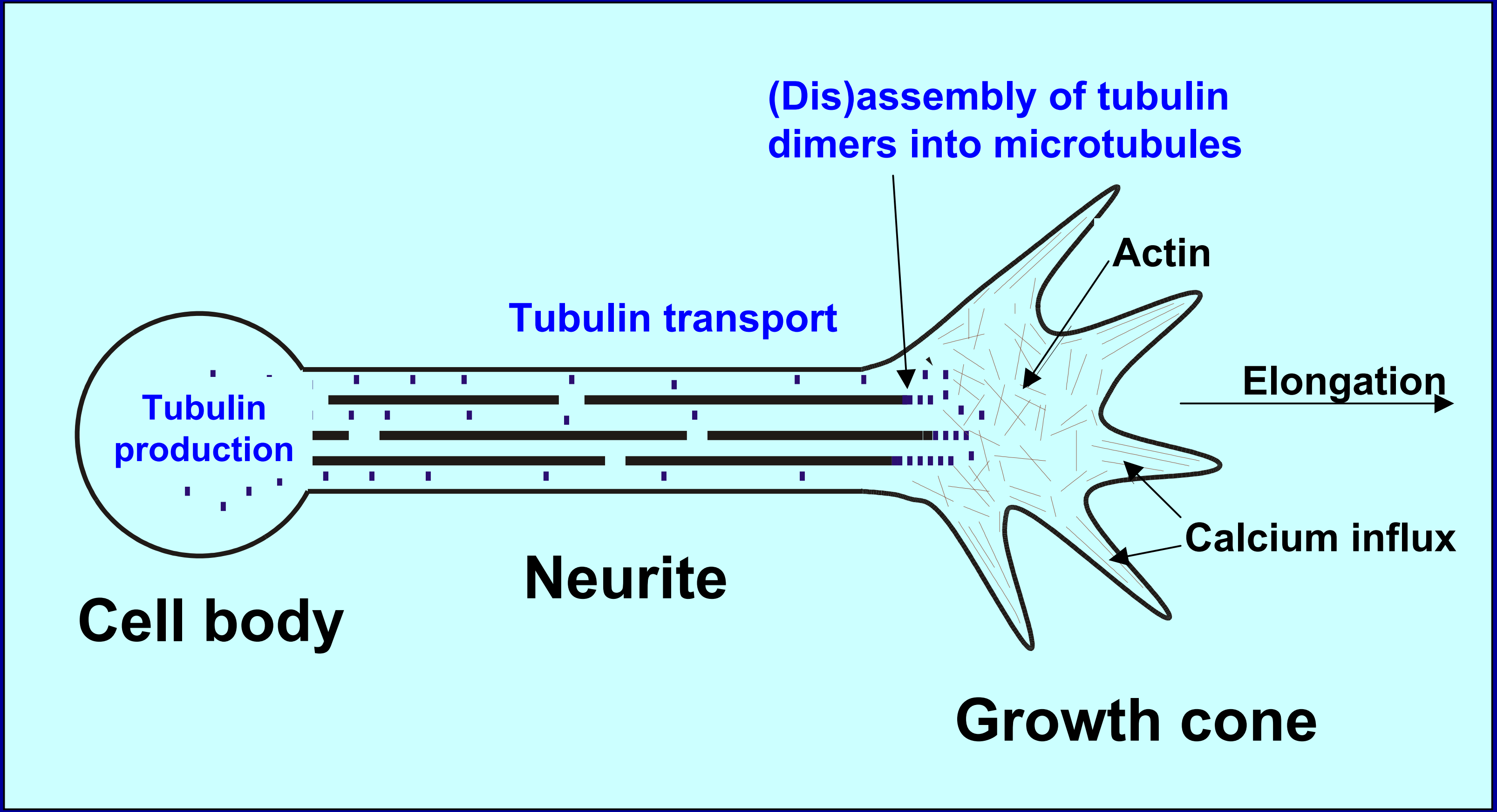
Branching:
B = 95
E = 0.69
S = -0.14

Elongation:
$\alpha(l_{in})$ = 0.7 μm
l_{in} = 10.63 μm
$\sigma(l_{in})$ = 7.53

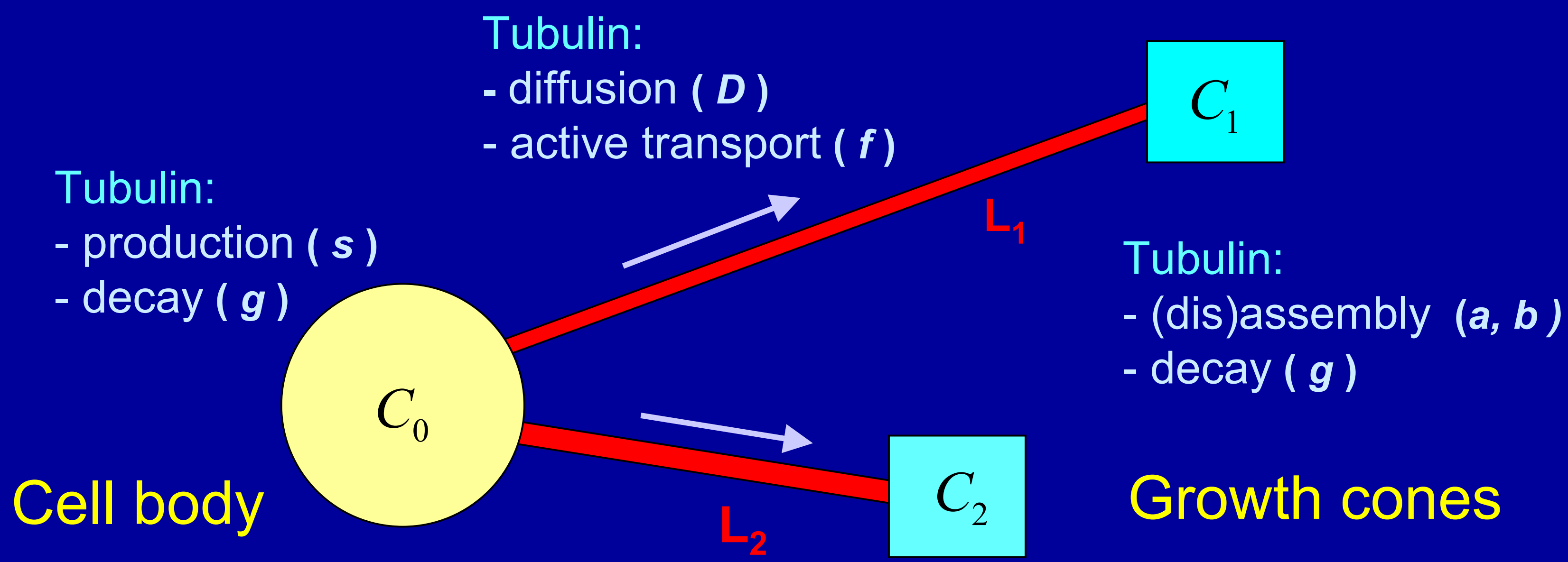
	Observed trees		Model trees	
Shape parameter	*Mean*	*Sd*	*Mean*	*Sd*
Degree	436	31.8	436	32
Asymmetry index	0.5		0.49	
Centrifugal order	13.7	5.1	13.8	5.9
Total length	9577	1105	9265	683
Terminal length	11.3	8.8	10.6	7.5
Intermediate length	10.6	7.5	10.6	7.6
Path lenth	189.3	64.1	166	66



Elongation by polymerization of tubulin



Tubulin model

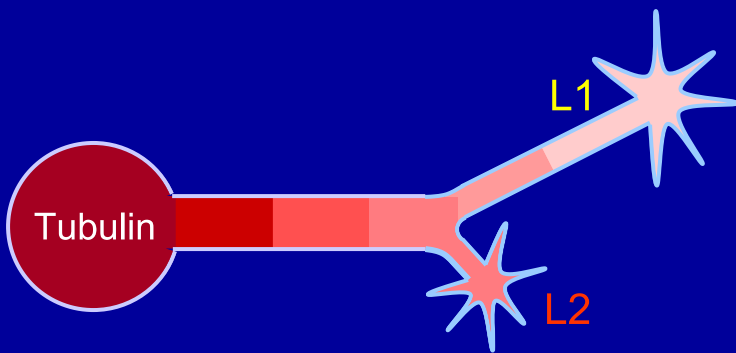


$$\frac{dL_i}{dt} = a_i C_i - b_i$$

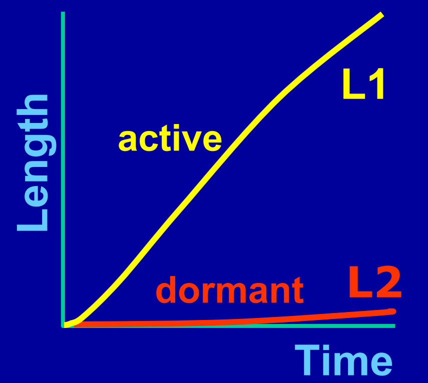
$$\frac{dC_i}{dt} = b_i - a_i C_i + \frac{D}{L_i + k}(C_0 - C_i) + fC_0 - gC_i$$

$$\frac{dC_0}{dt} = s - \sum_{i=1}^{n} \frac{D}{L_i + k}(C_0 - C_i) - \sum_{i=1}^{n} fC_0 - gC_0$$

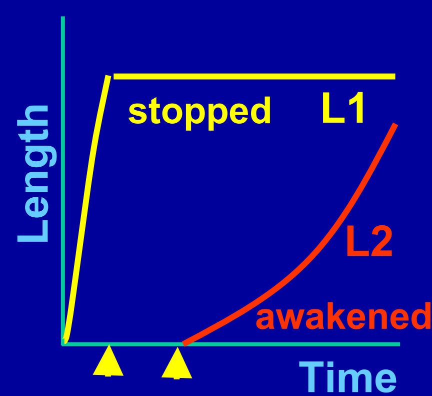
Competition for tubulin

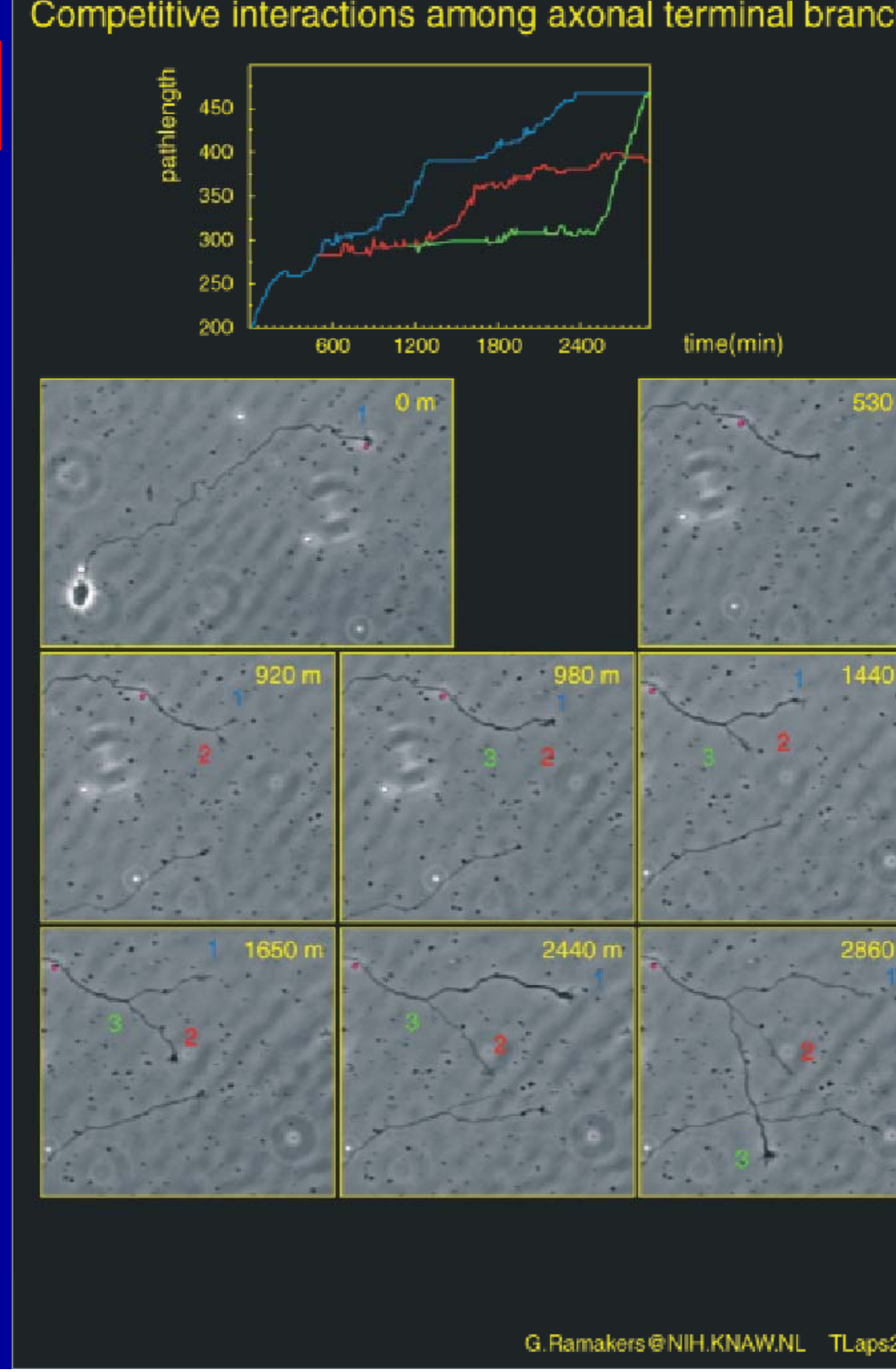


Difference in assembly / disassembly rates results in competition



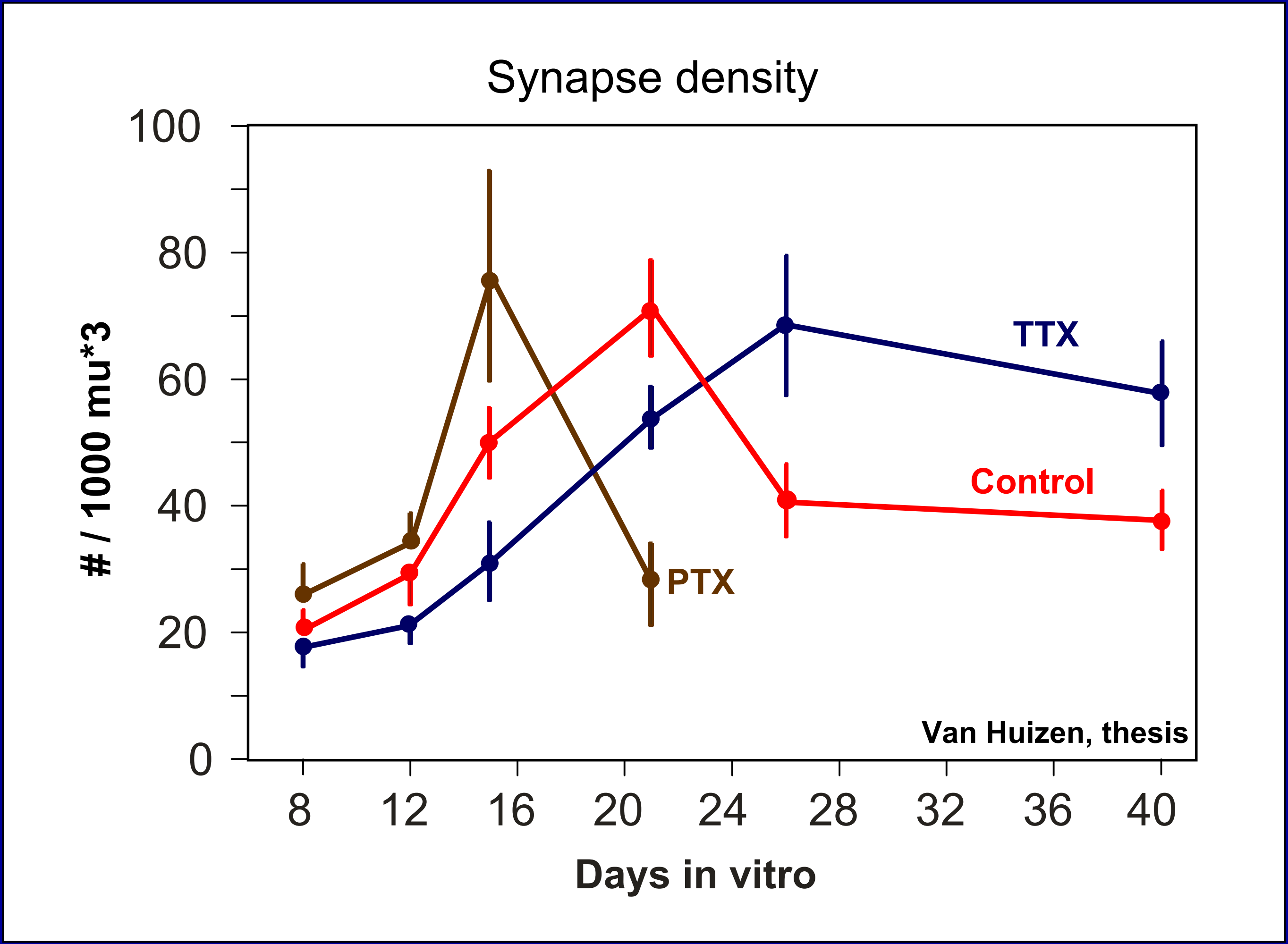
Stop of L1 outgrowth activates “dormant” growth cone after characteristic delay



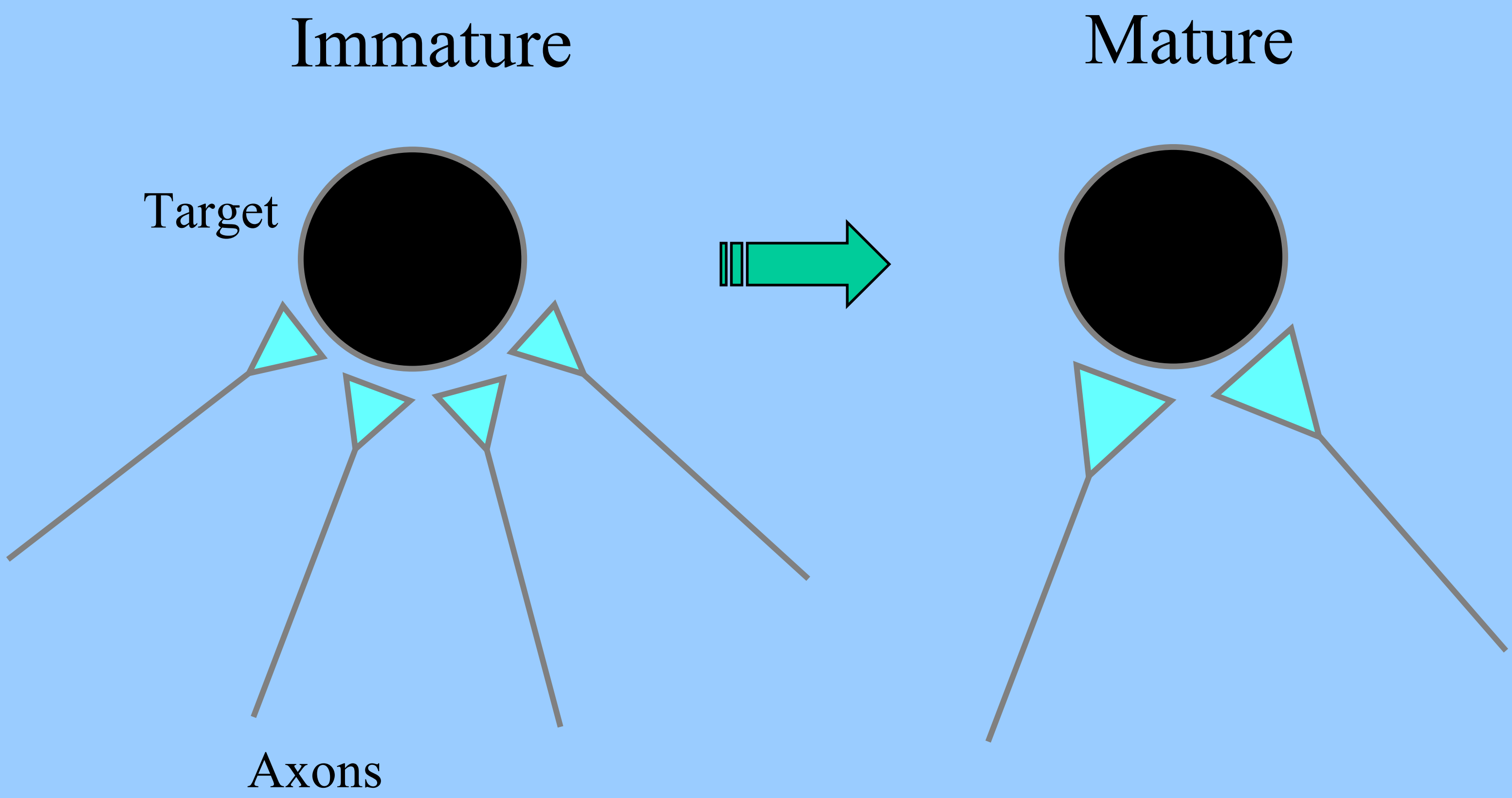


Development of synaptic connectivity

Developing neuronal networks show an overshoot in number of synaptic connections



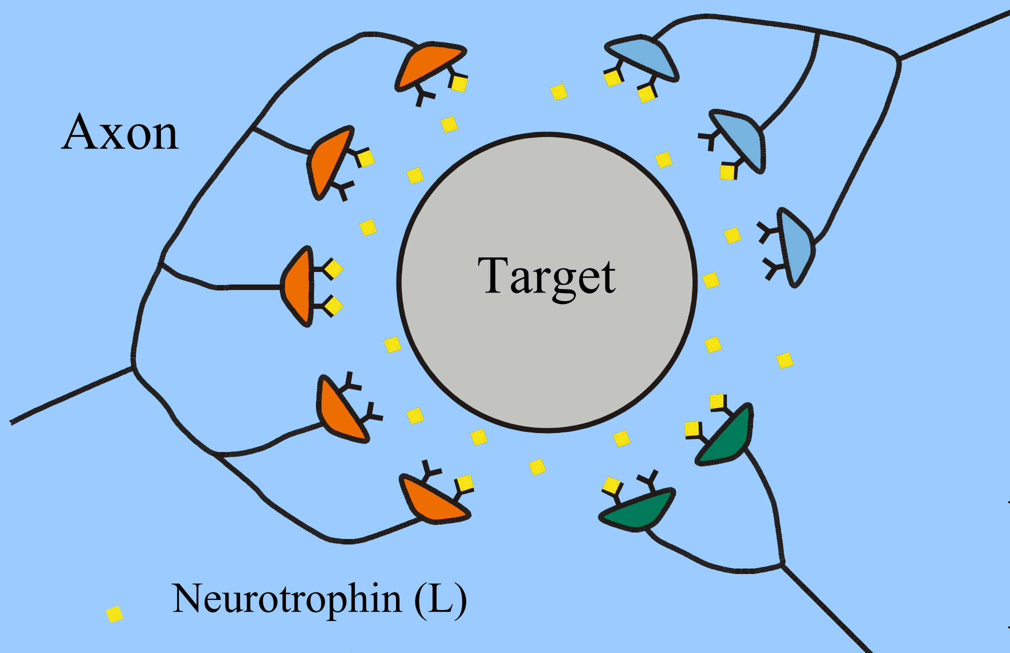
Elimination of connections



Arjen van Ooy

Van Ooyen & Willshaw's model

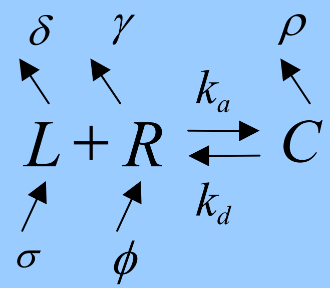
"competition for target-derived neurotrophins"



Neurotrophin (L)

Receptor (R)

Neurotrophin-receptor complex (C)



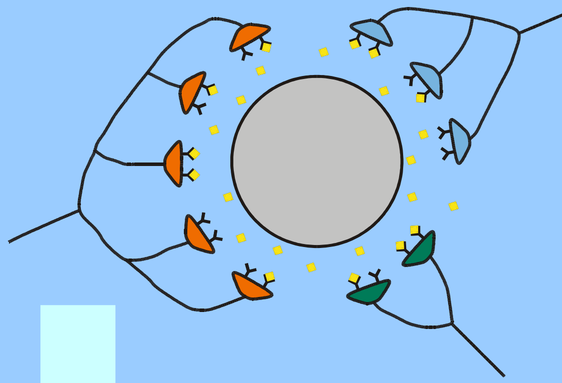
$$\frac{dC_i}{dt} = (k_{a,i} L R_i - k_{d,i} C_i) - \rho_i C_i$$

$$\frac{dR_i}{dt} = \varphi_i - \gamma_i R_i - (k_{a,i} L R_i - k_{d,i} C_i)$$

$$\frac{dL}{dt} = \sigma - \delta L - \sum_{i=1}^{n} (k_{a,i} L R_i - k_{d,i} C_i) / v$$

Effects of neurotrophins

Bound neurotrophins enhance axonal branching

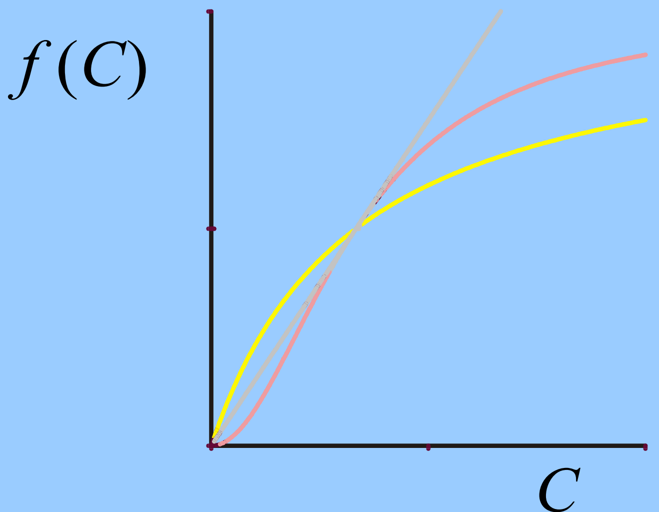


➡ more receptors

Thus, $\varphi_i = f_i(C_i)$

But lags behind:

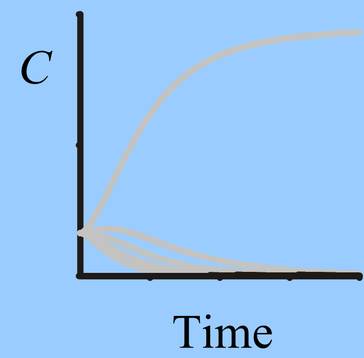
$$\tau \frac{d\varphi_i}{dt} = f_i(C_i) - \varphi_i$$

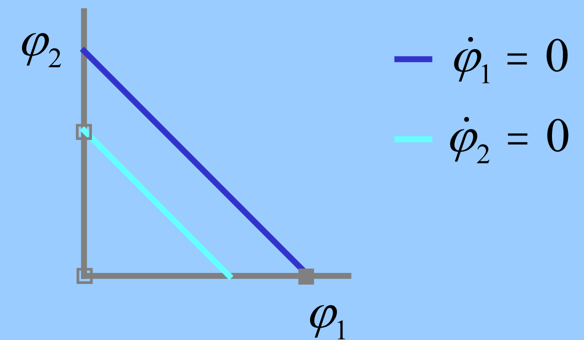


Arjen van Oo

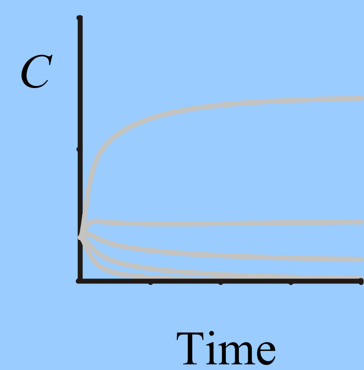
Innervation patterns

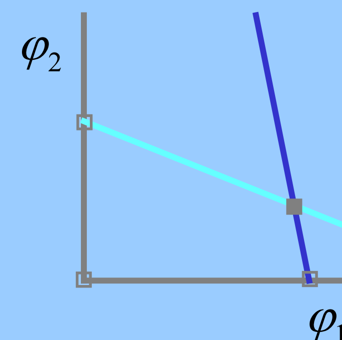
- **Class I:** Single



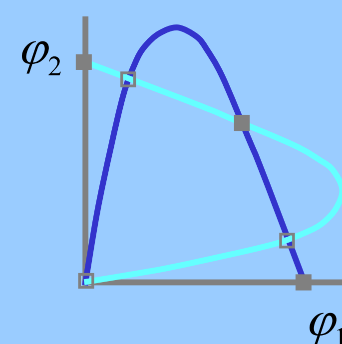


- **Class II:** Multiple, Single



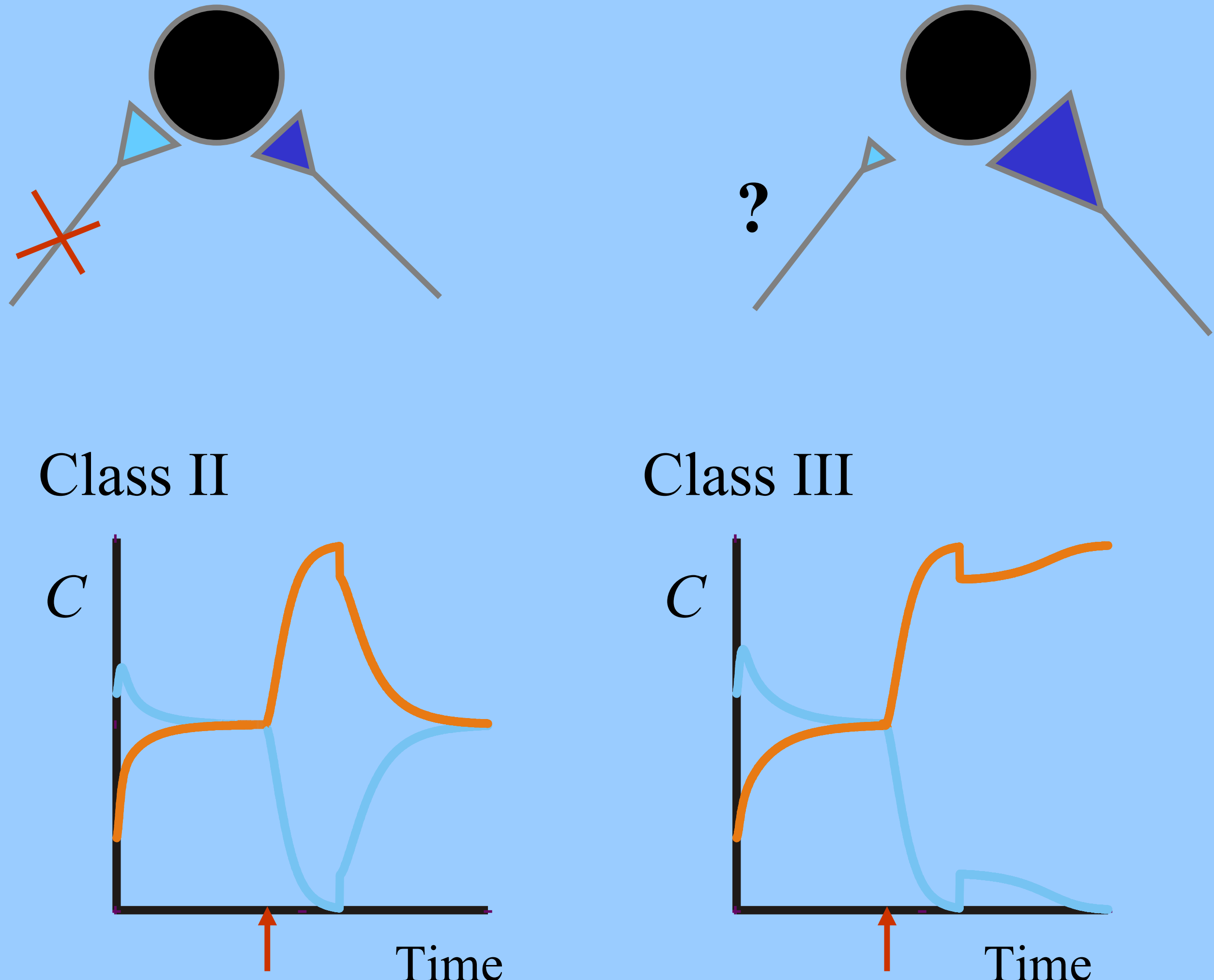


- **Class III:** Multiple and single, Single



Arjen van Oo

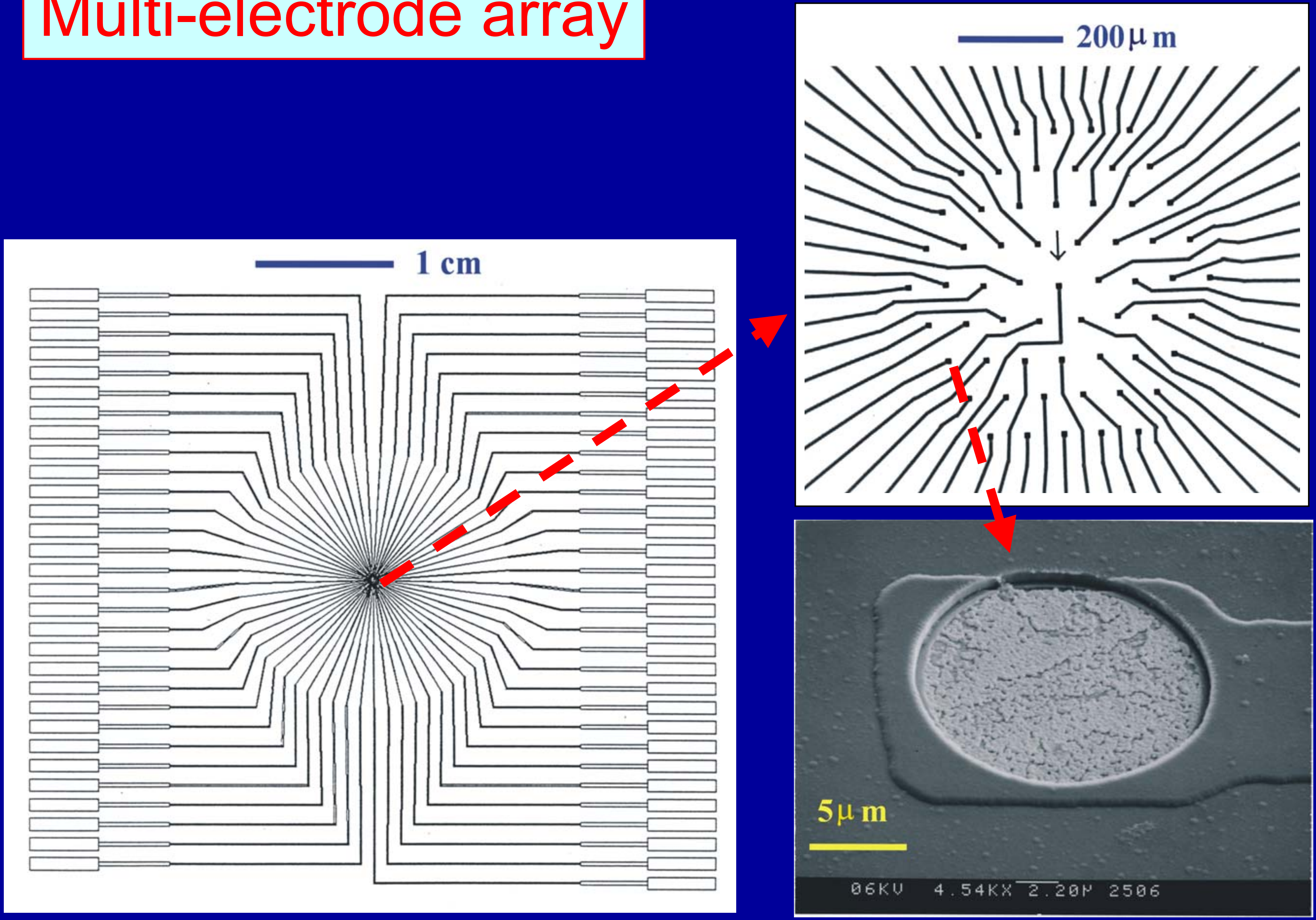
Regeneration



Arjen van Oo

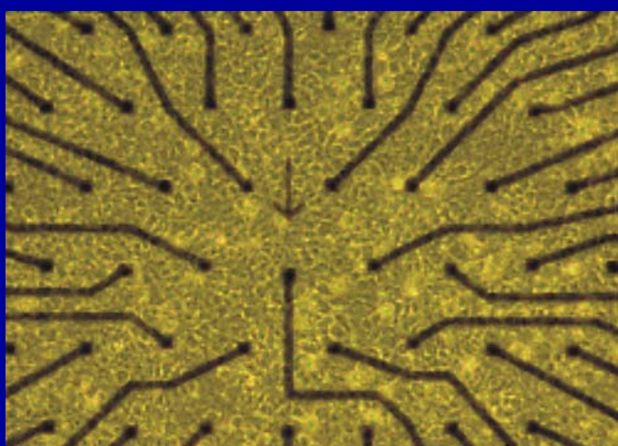
Spontaneous bioelectric activity in developing neuronal networks in vitro

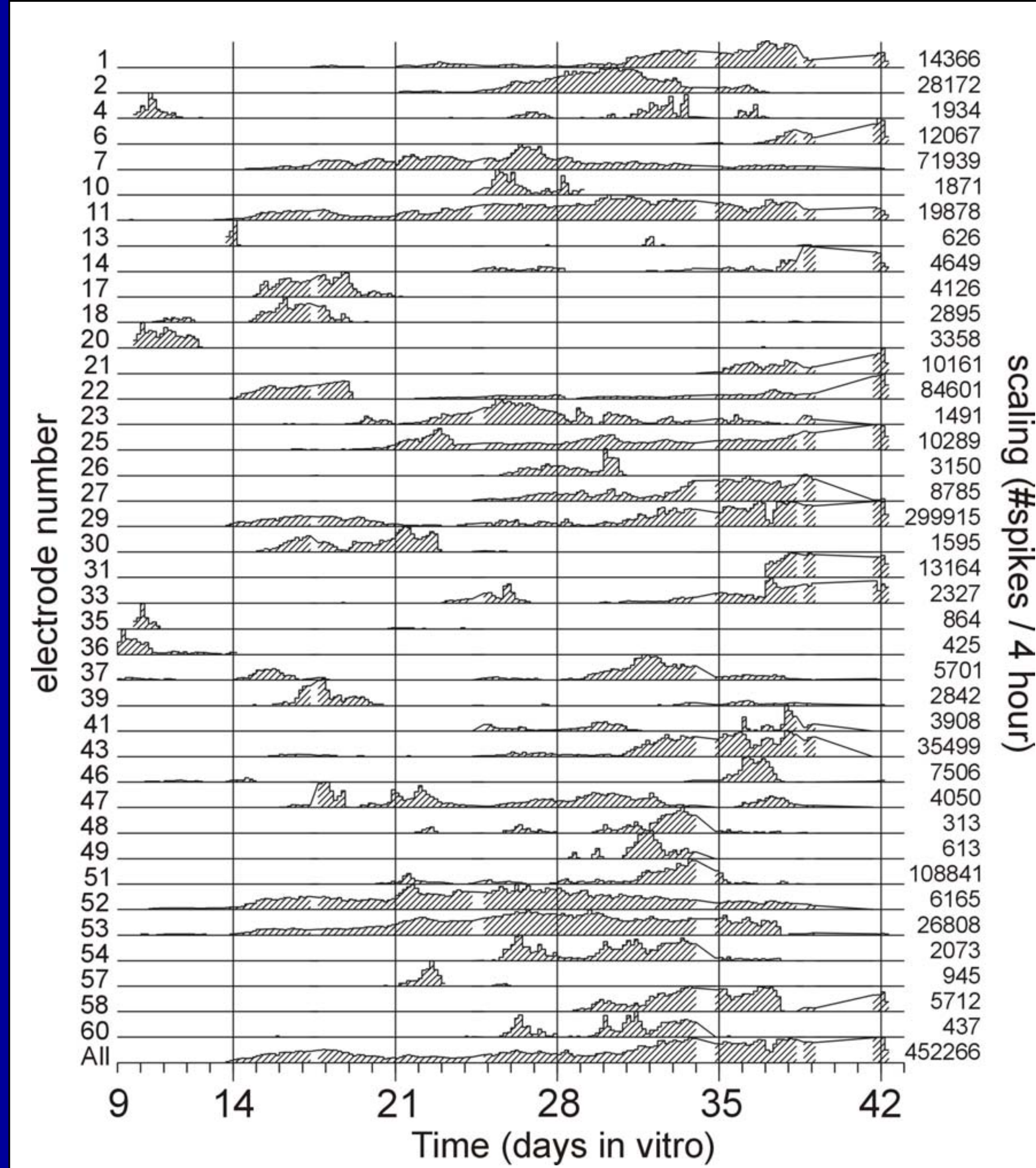
Multi-electrode array



Long-term longitudinal recording of firing activity

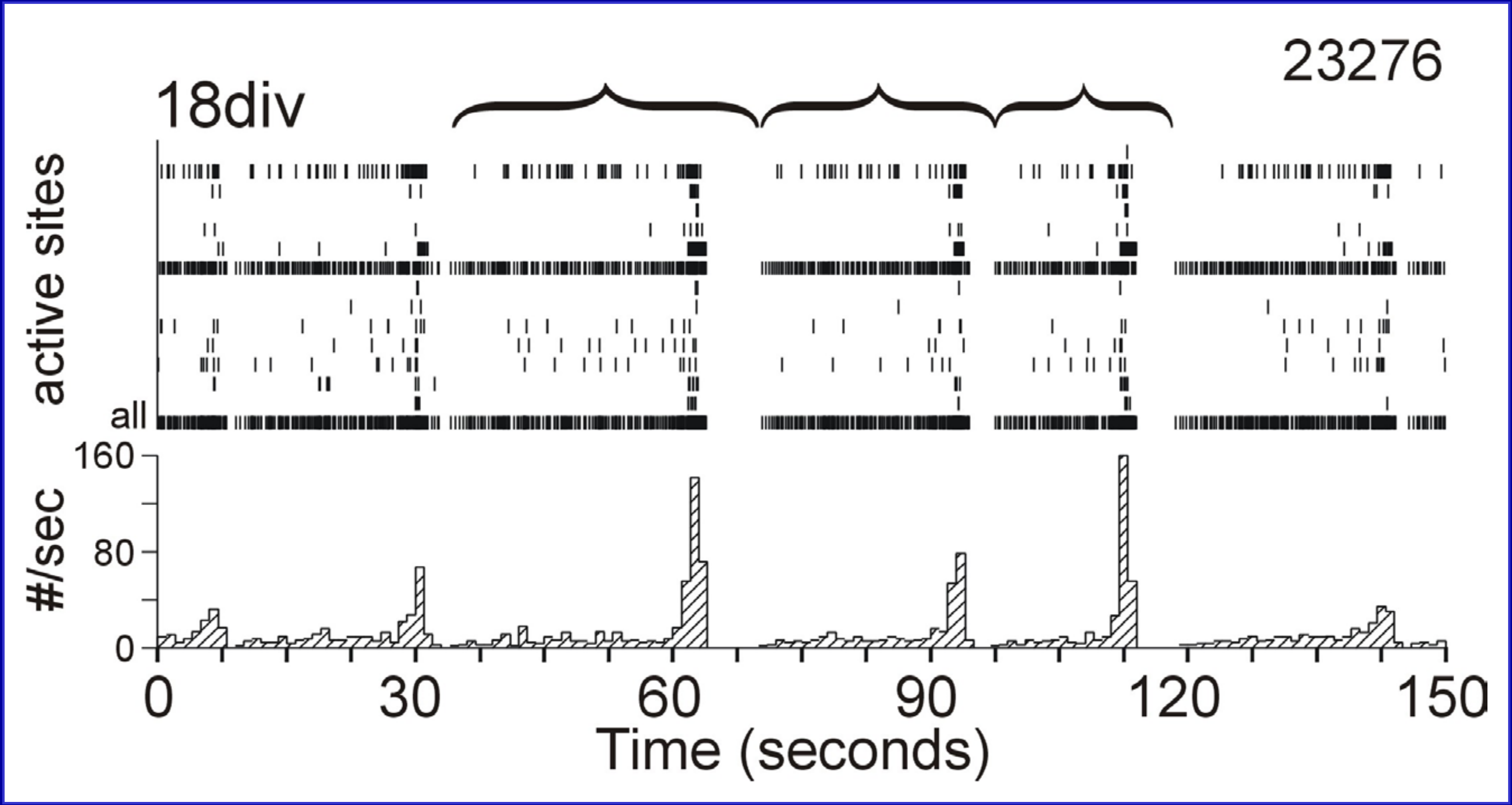
Dissociated rat cortical culture on a multi-electrode array



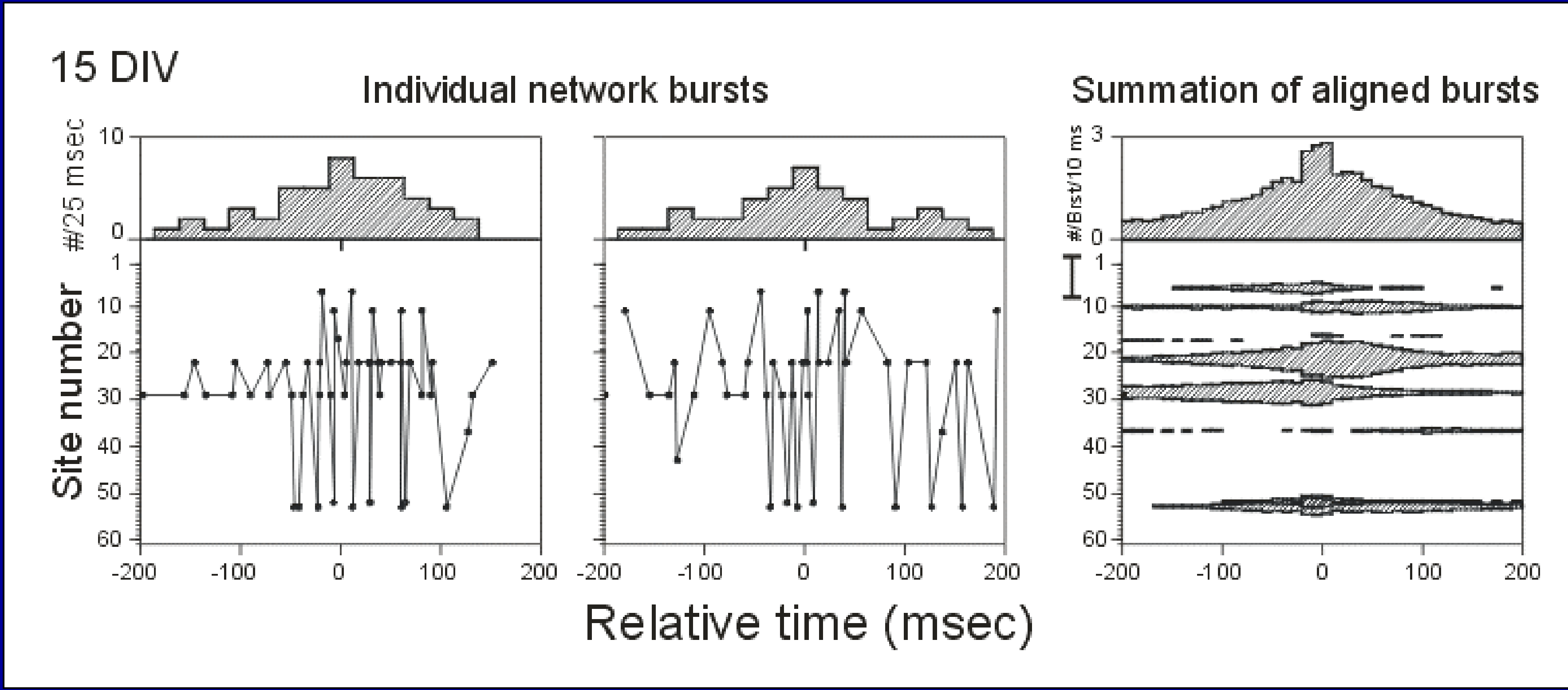


18 DIV

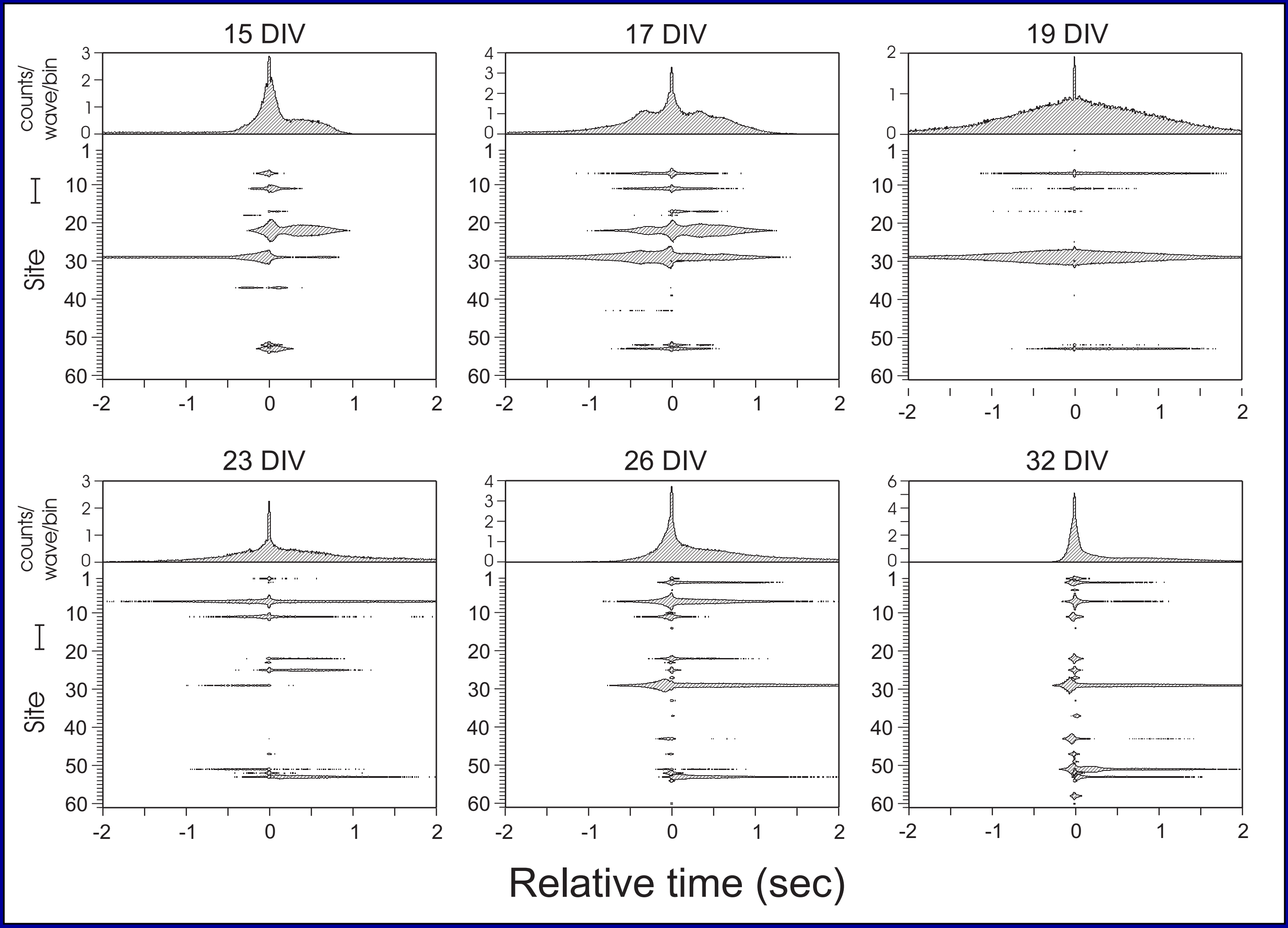
Active / quiescent phases and network bursts

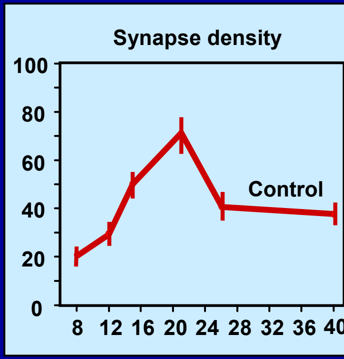


Probabilistic structure of network bursts



Developmental changes in network bursts





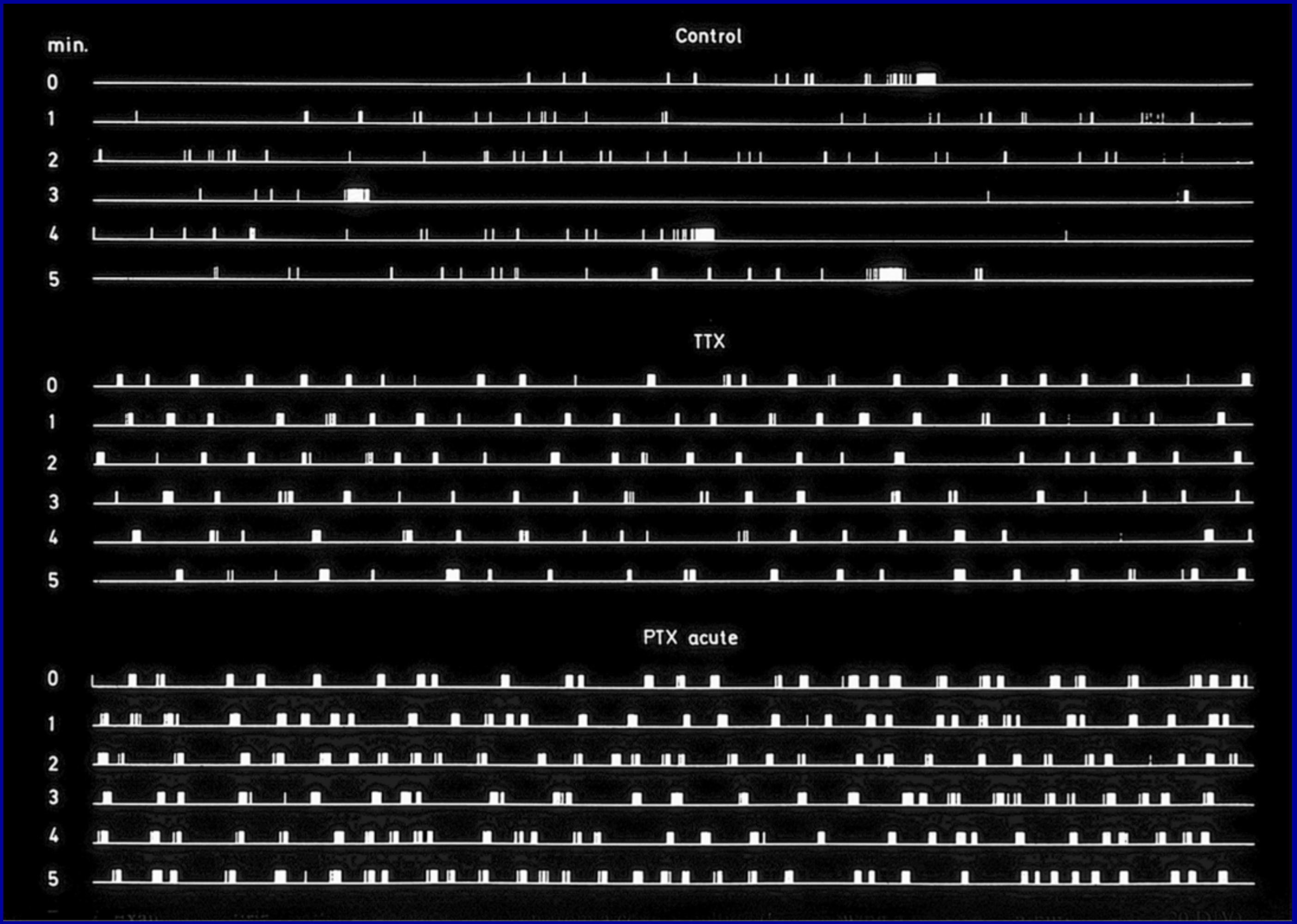
Balance of excitation and inhibition

Chronic silencing of spontaneous activity induces disinhibition

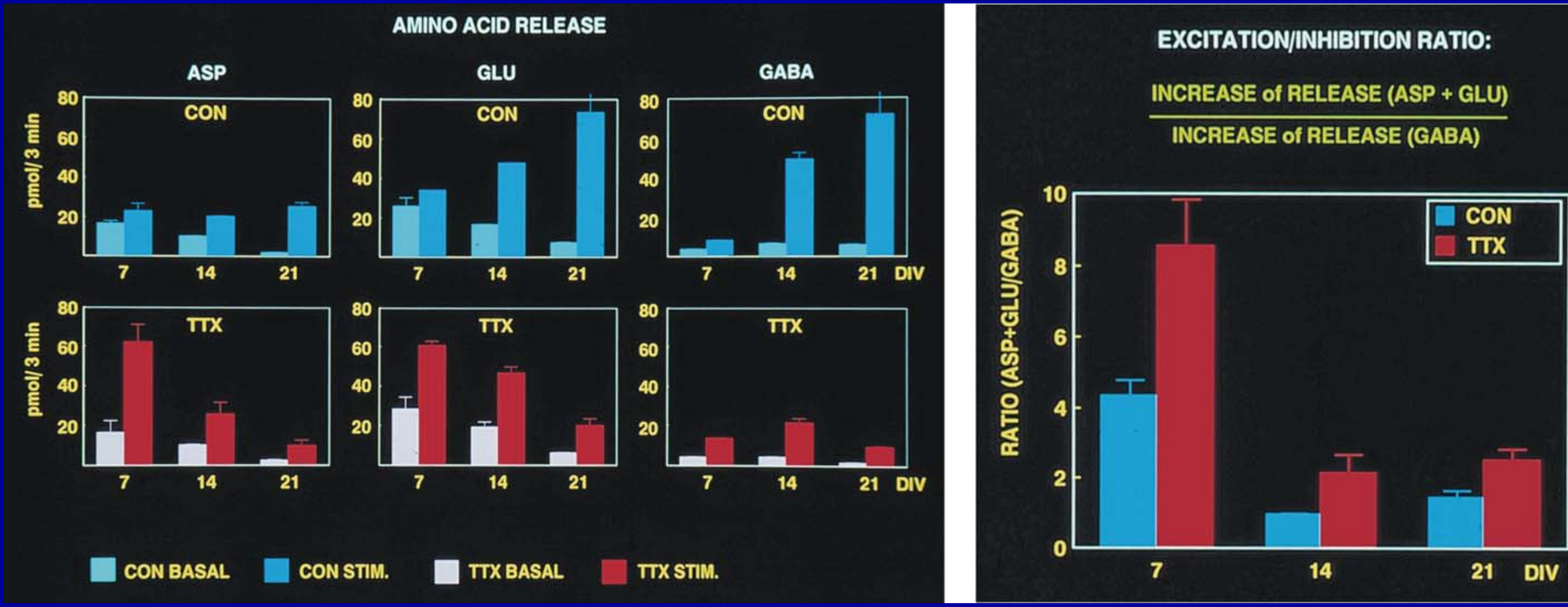
Control condition

After chronic TTX application

During acute PTX application



Chronic suppression of spontaneous activity increases the excitation / inhibition ratio



Working hypothesis:
activity-dependent regulation of excitatory and inhibitory network development