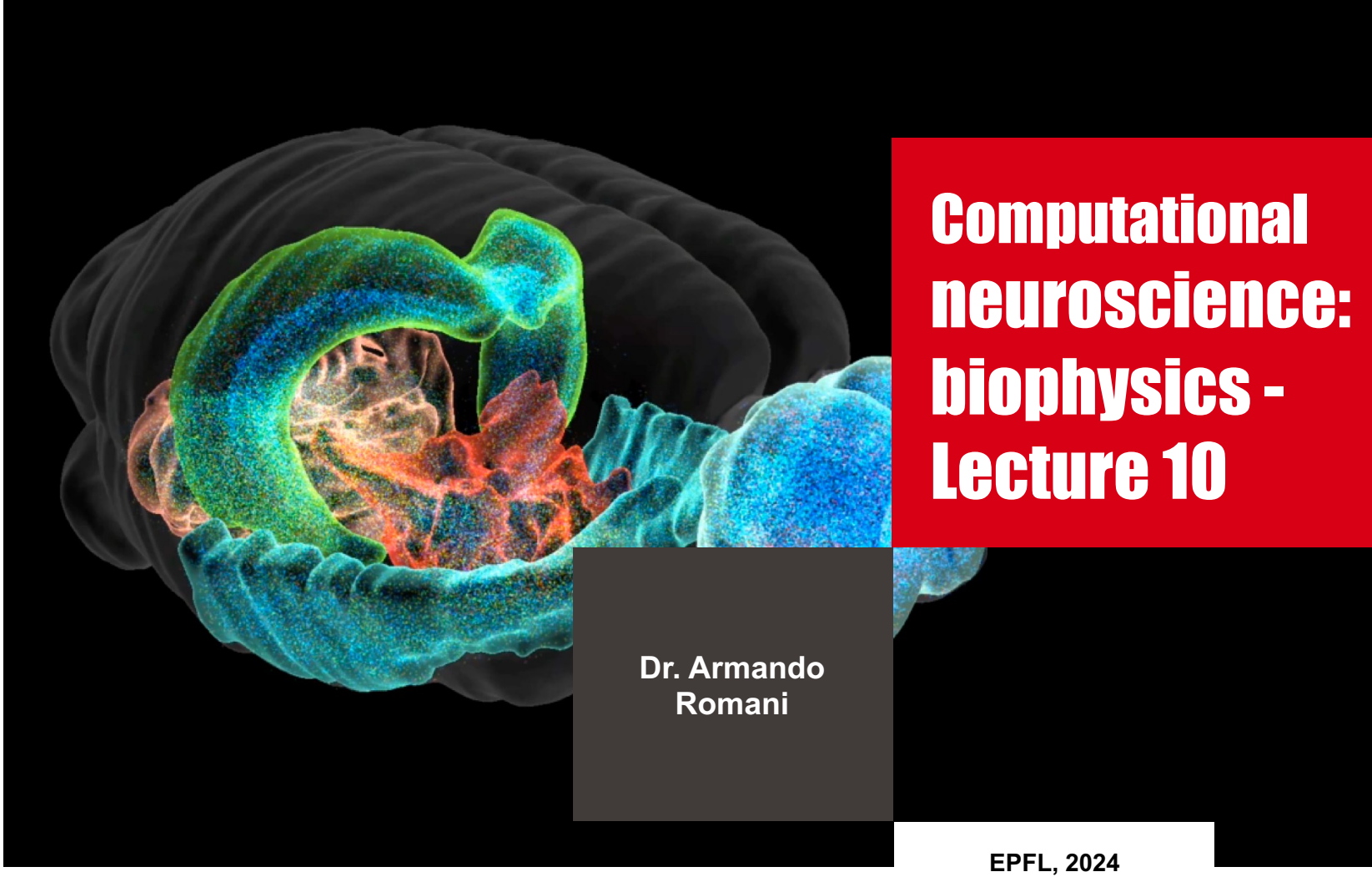

Computational neuroscience: biophysics - Lecture 10

Dr. Armando Romani

EPFL, 2024

Circuit 1
Part 1: assembling the pieces

Lecture Overview

- Scope
- Approaches
- Applications

Lecture Overview

- **Scope**
- Approaches
- Applications

Assembling the pieces

- We have all the building blocks (ion channels, morphologies, single cell models, connections, synapses)
- We have to assemble them to make a network
- What do we have to do?

➢ We need to define the space and populate it with our neurons

Lecture Overview

- Scope
- **Approaches**
- Applications

Define the space

- Arbitrary volumes
- Simplified volumes
- Atlases
- Intermediate approaches

Arbitrary volume

- Volume is not taken into account
- Cells and synapses have spatial coordinates
- Some simulators require the definition of a space
- Anyway, the volume is arbitrary

Simplified volume

- Regular geometry
- The volume can be more or less constrained experimentally
- Geometrical parameters vary greatly in experiments, so it is not straightforward to set the ‘correct’ parameters
- Positioning the cells is easier
- Performing analyses that require volume information is easier
- Poor reusability

Atlas-based volume

- The geometry is given, and we do not have to define it
- Atlases are generally noisy and should be curated
- Positioning the cells is more complicated
- Performing analyses that require volume information is more complicated
- High reusability
- Combine data and models that are registered in the same atlas space

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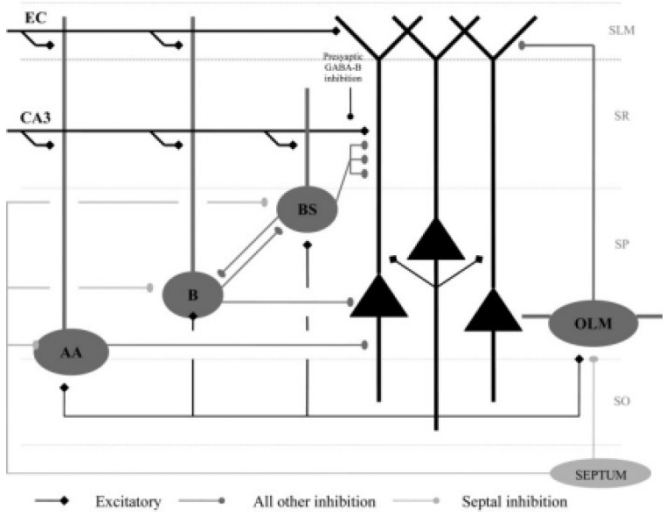
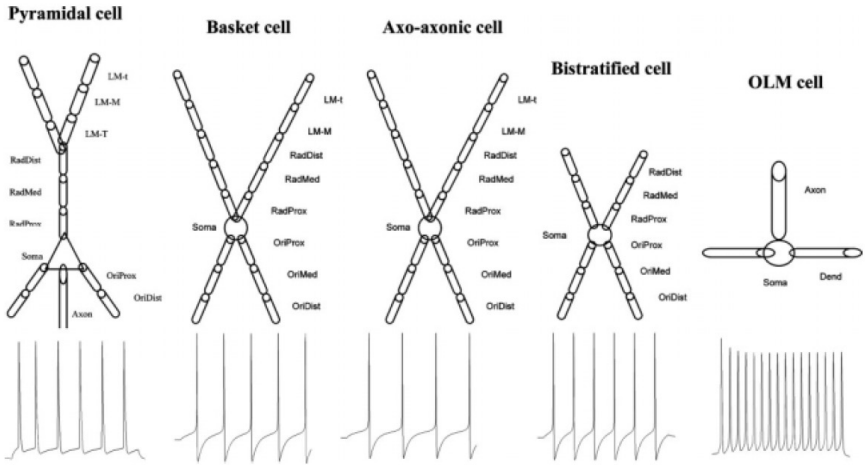
Lecture Overview

- Scope
- Approaches
- **Applications**

Arbitrary volumes

- (Rat) CA1 microcircuit
- The model consists of 100 pyramidal (P) cells, 2 basket (B) cells, 1 bistratified (BS) cell, 1 axo-axonic (AA) cell, and 1 oriens lacunosum moleculare (OLM) cell
- Simplified morphologies including the soma, apical and basal dendrites and a portion of axon, were used for each cell type.

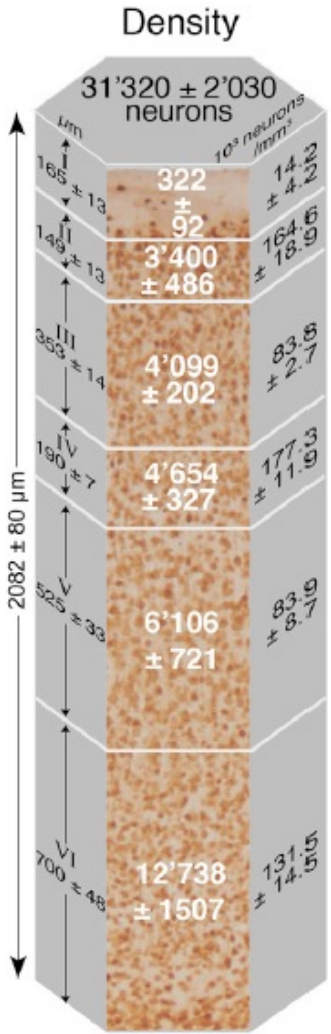


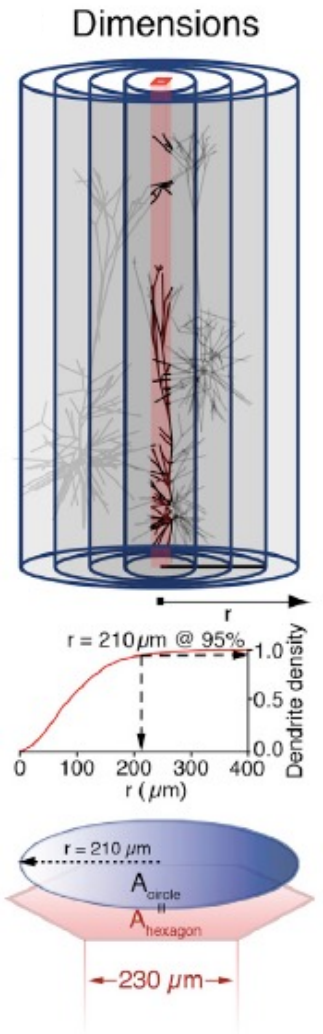


Cutsuridis et al., 2010

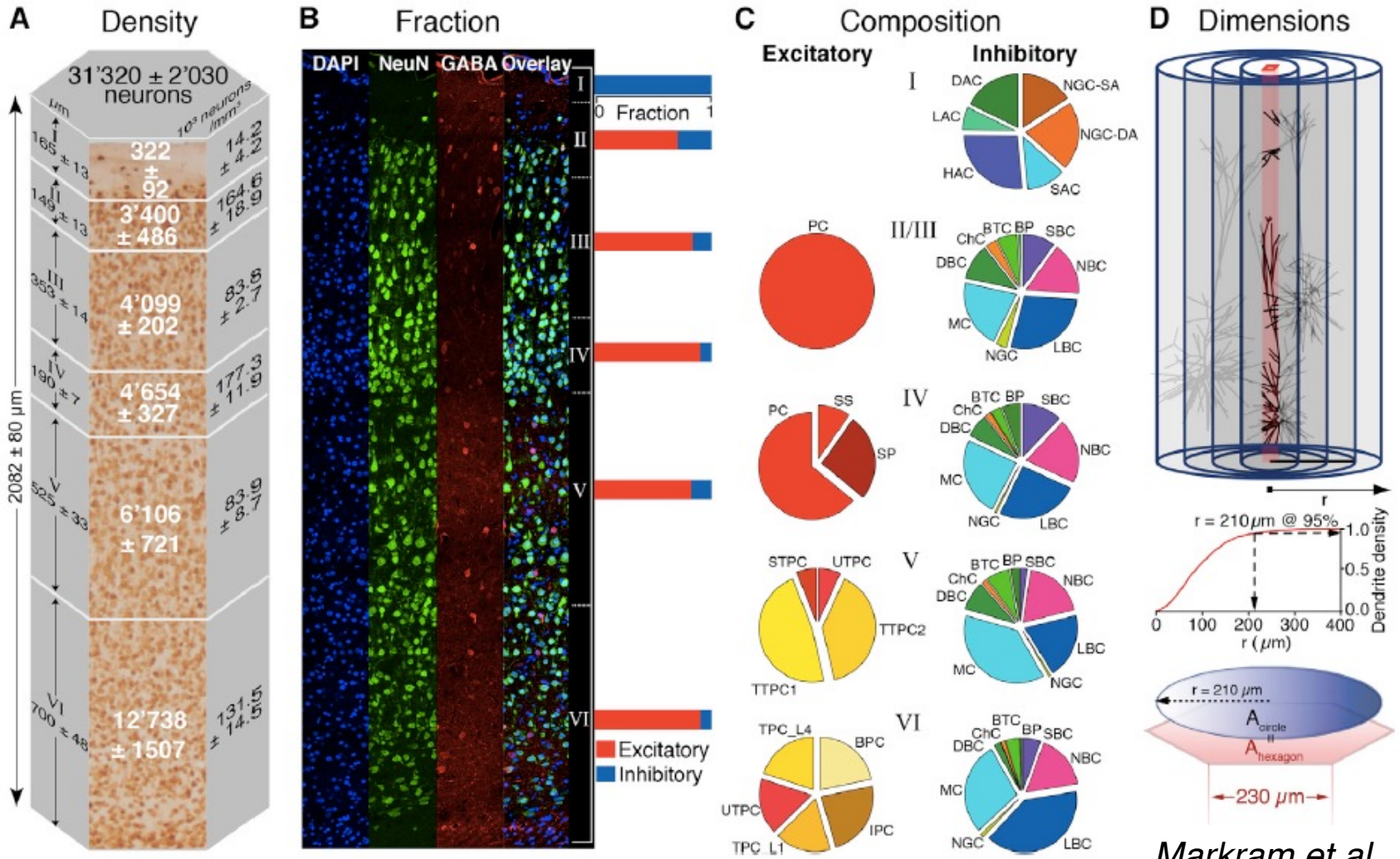
Simplified volume

- SSCx microcircuit
- Layer thicknesses are defined experimentally
- The horizontal dimensions of a microcircuit were estimated by evaluating the density of dendritic fiber at the center of the circuit
- The hexagonal shape was chosen to to facilitate tiling, while minimizing asymmetrical edge effects





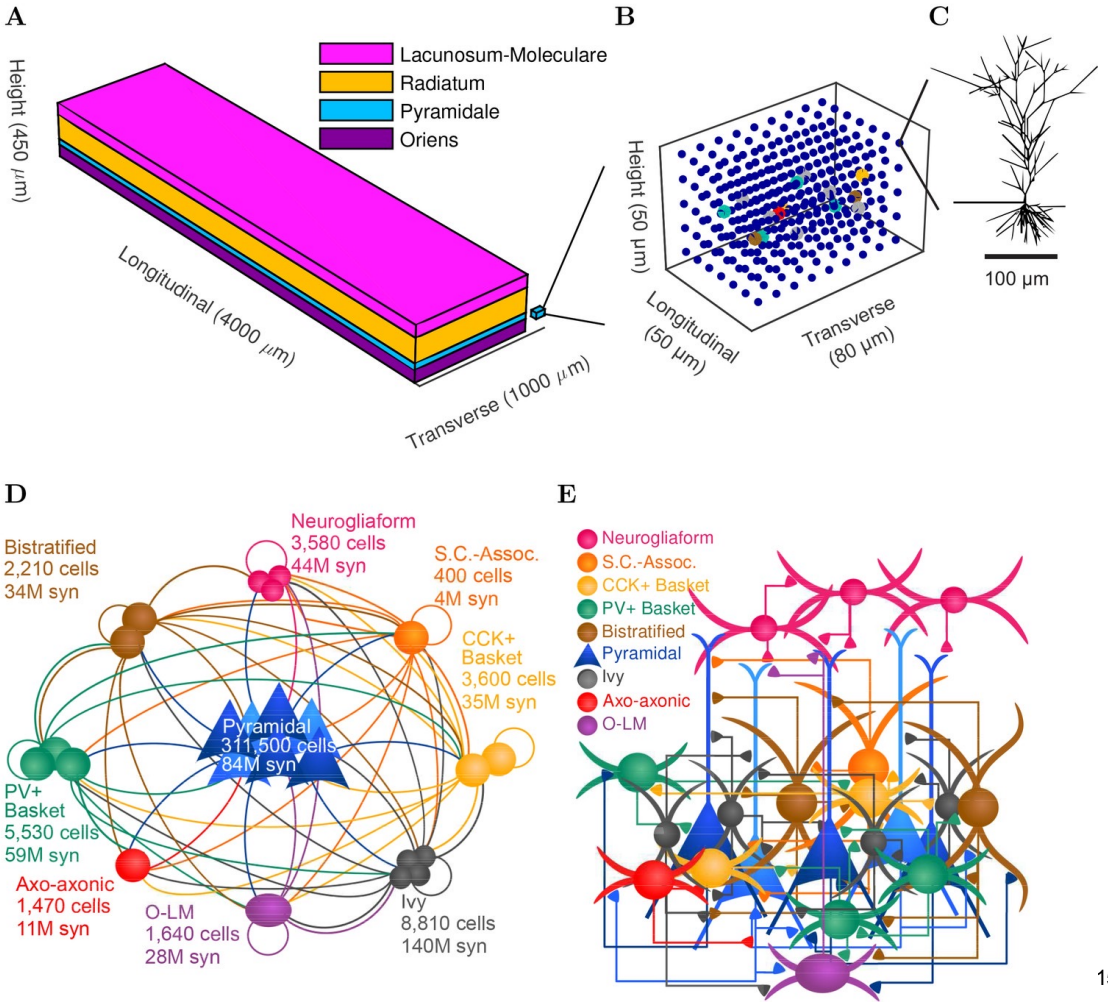
Markram et al., 2015



Markram et al., 2015

Simplified volume

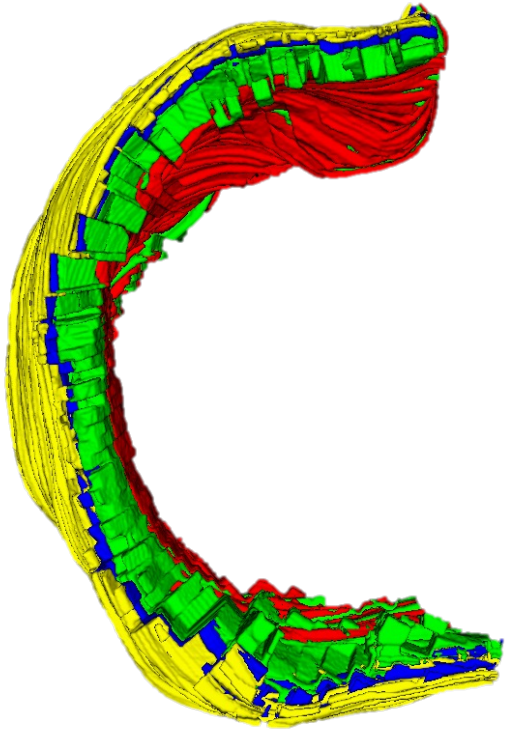
- Rat hippocampus CA1
- Dimensions are constrained experimentally (?)



Bezaire et al., 2016

Atlas

- Rat hippocampus CA1 model (Romani et al., 2023)
- Atlases are quite noisy
- This makes the cell positioning very challenging



Atlas from *Ropireddy et al, 2012*
http://krasnow1.gmu.edu/cn3/hippocampus3d/

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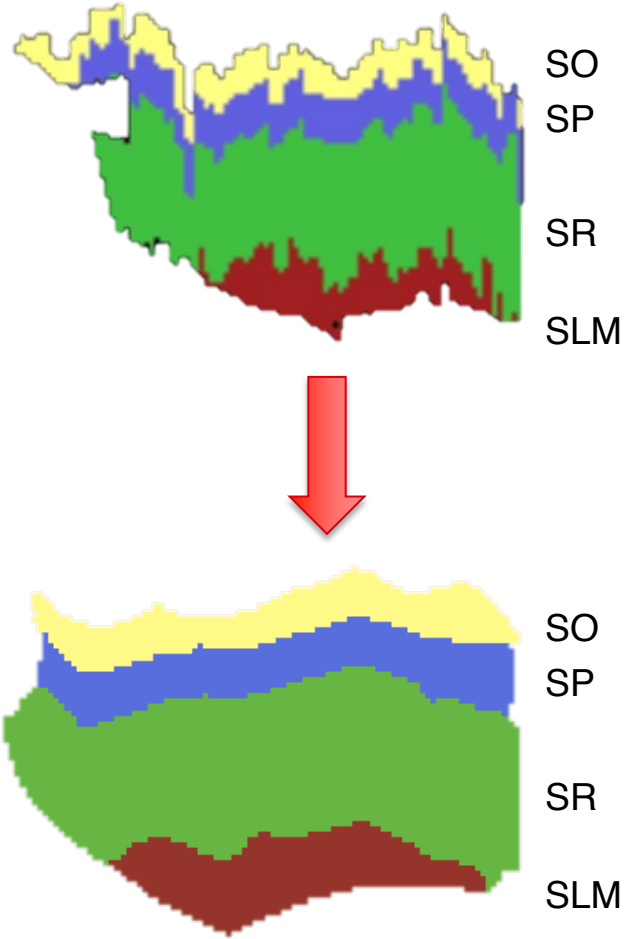
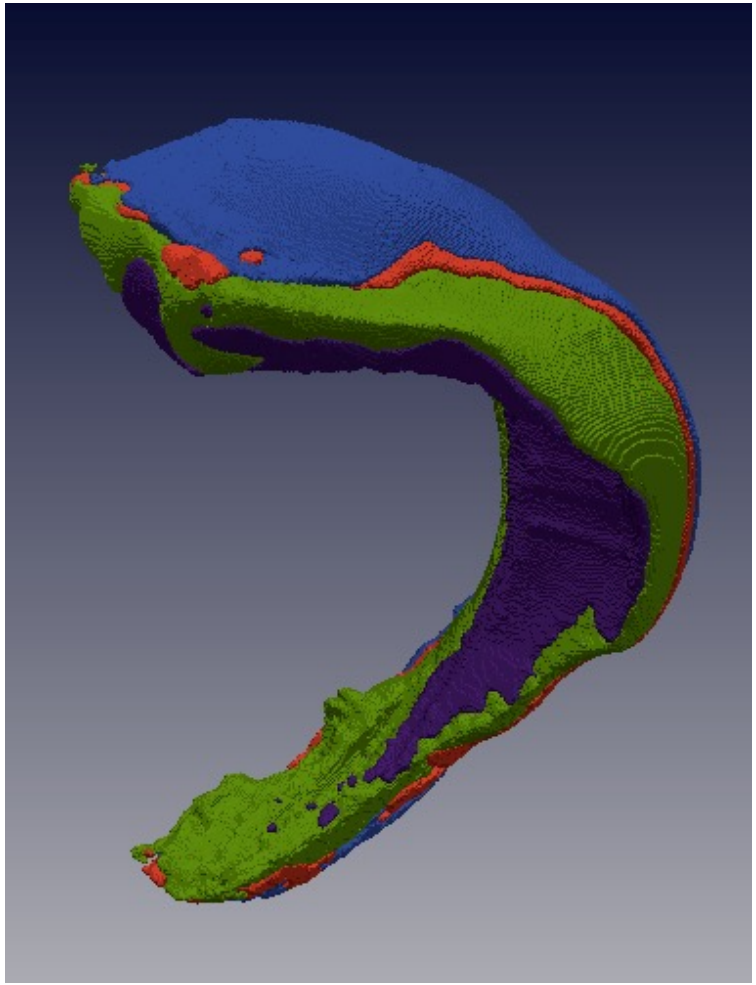
Atlas

- Noisy atlases contain sudden jumps in layer thickness and different kind of discontinuities
- Series of manipulations can be adopted to alleviate those problems



Atlas

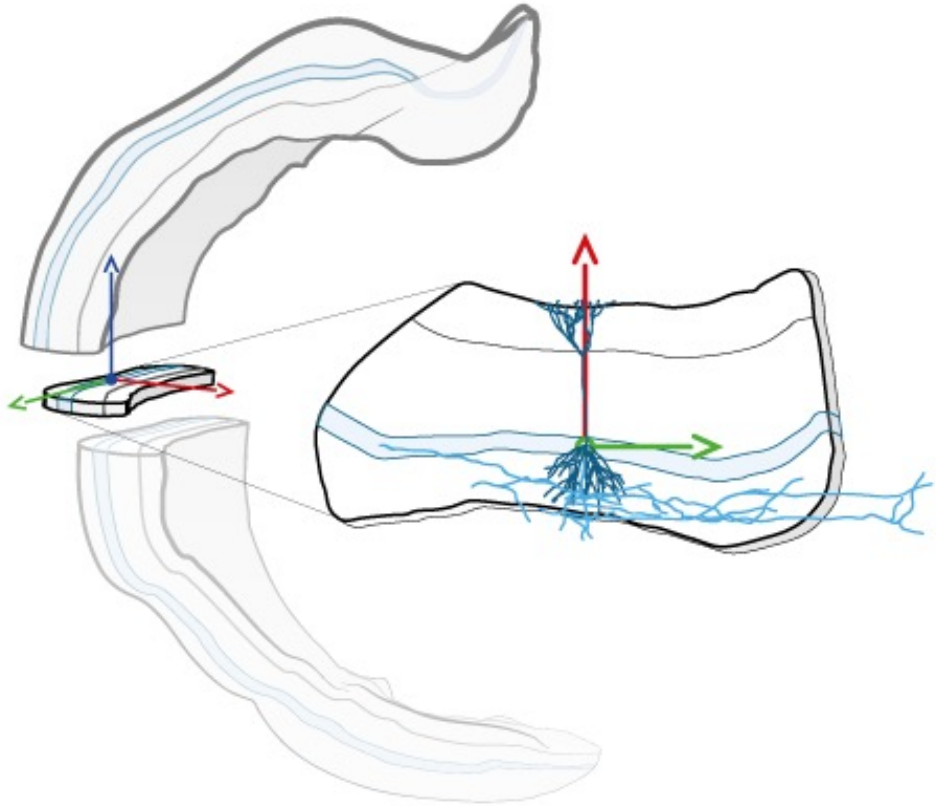
- After smoothing the atlas still contains a series of errors: holes, layers may terminate earlier
- Further manipulations make the volume deviates too much from original data
- We have to accept that the raw data is pretty noisy



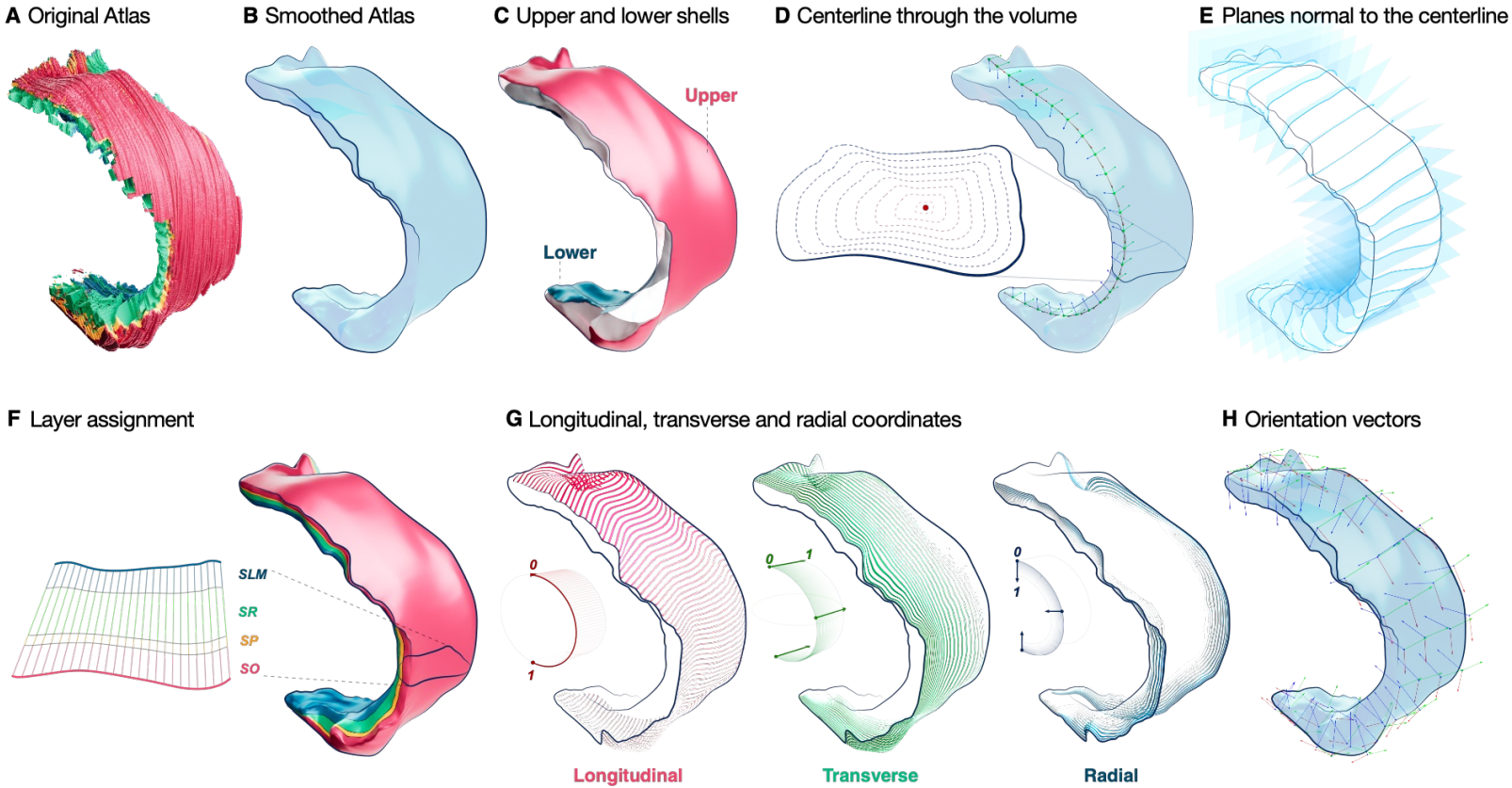
Romani et al.

Cell positioning: follow the curvature

- In regions like cortex and hippocampus, cells have a specific orientation in the volume
- If the region of interest is curved, cells follow this curvature

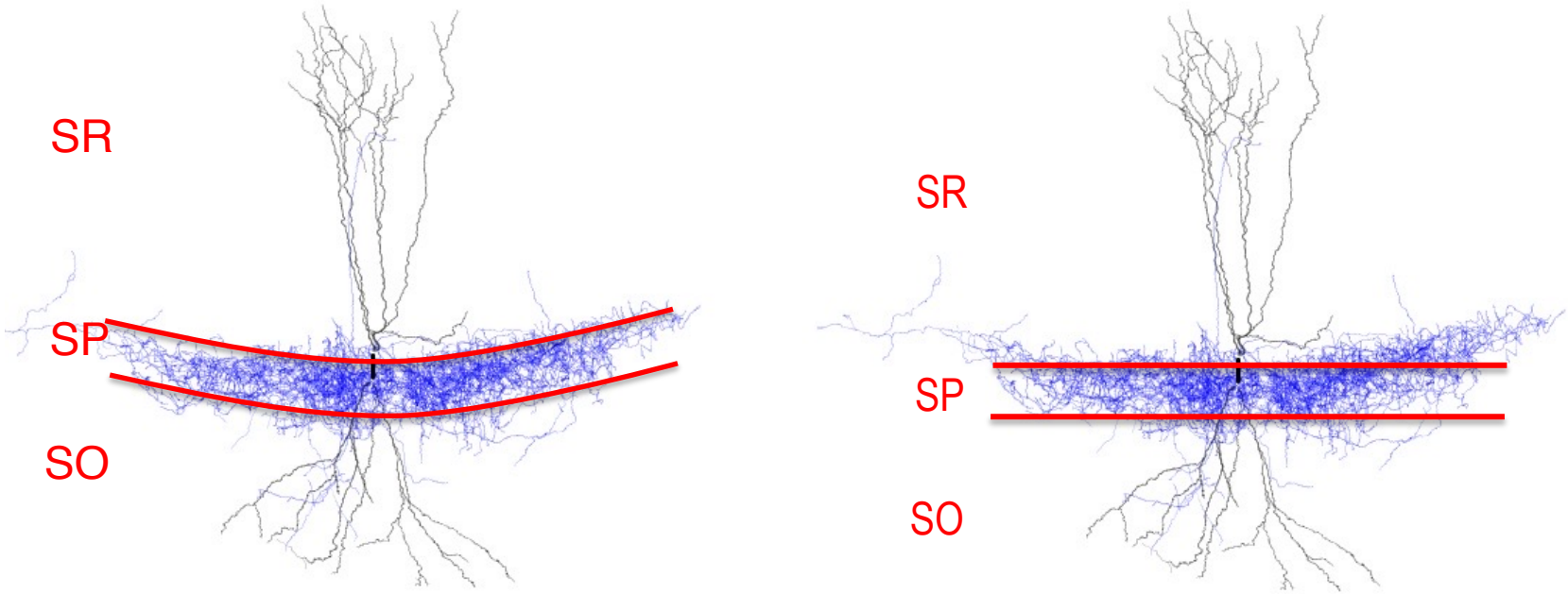


Romani et al., 2024

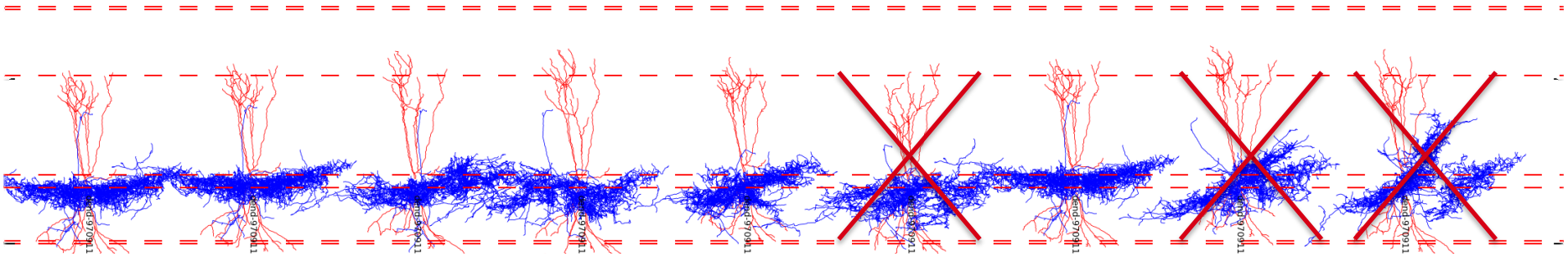


Romani et al., 2024

Cell positioning: respect neurite targeting

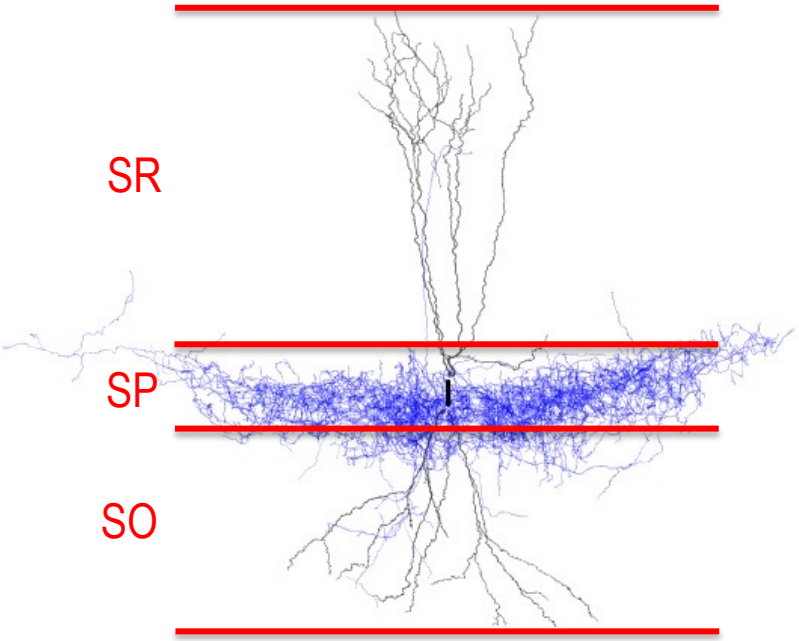


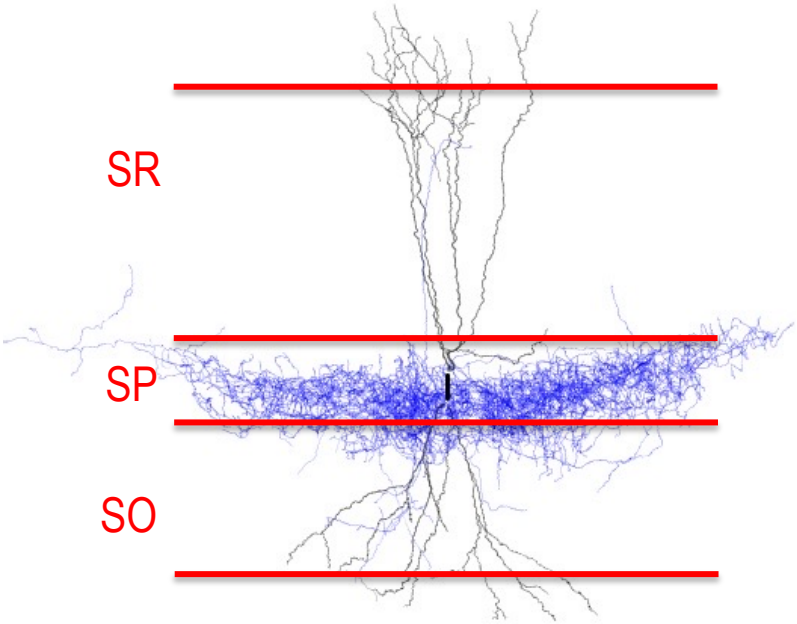
Cell positioning: respect neurite targeting



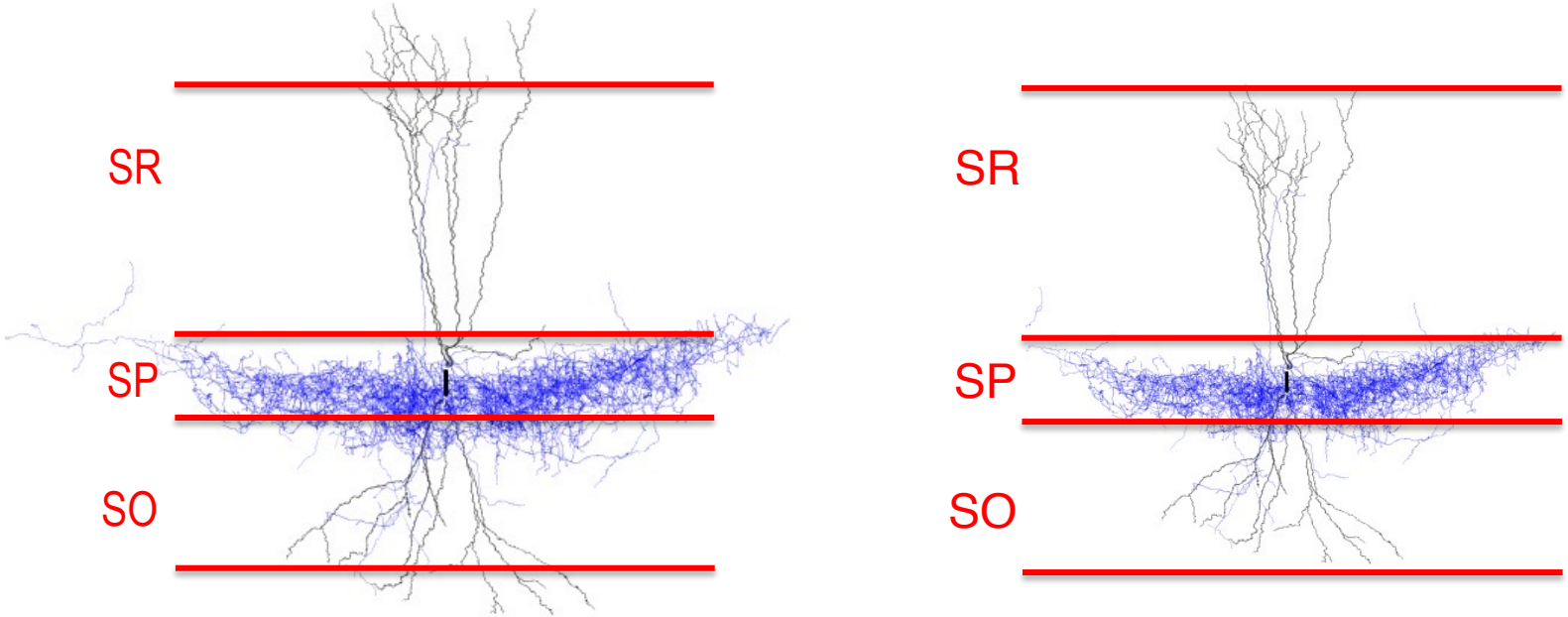
Insert gittering (cloning) and select the most appropriate cell (see later)

Cell positioning: respect neurite targeting



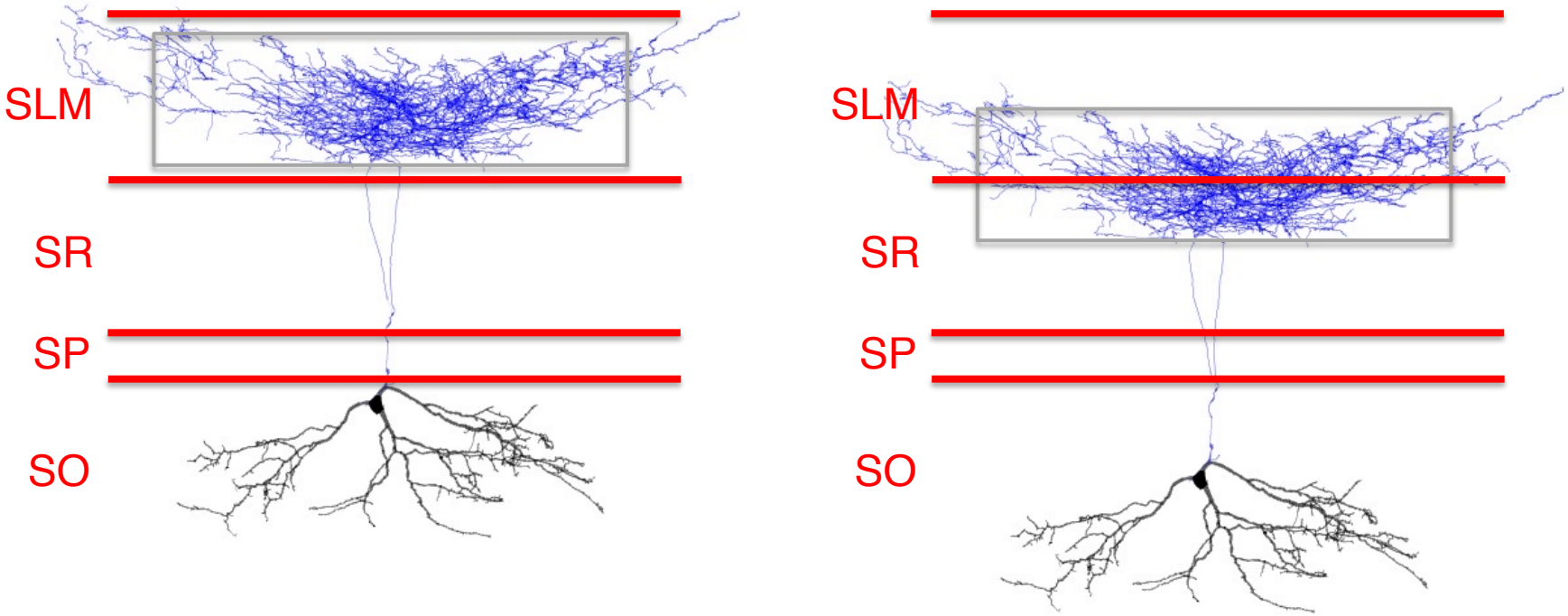


Cell positioning: respect neurite targeting



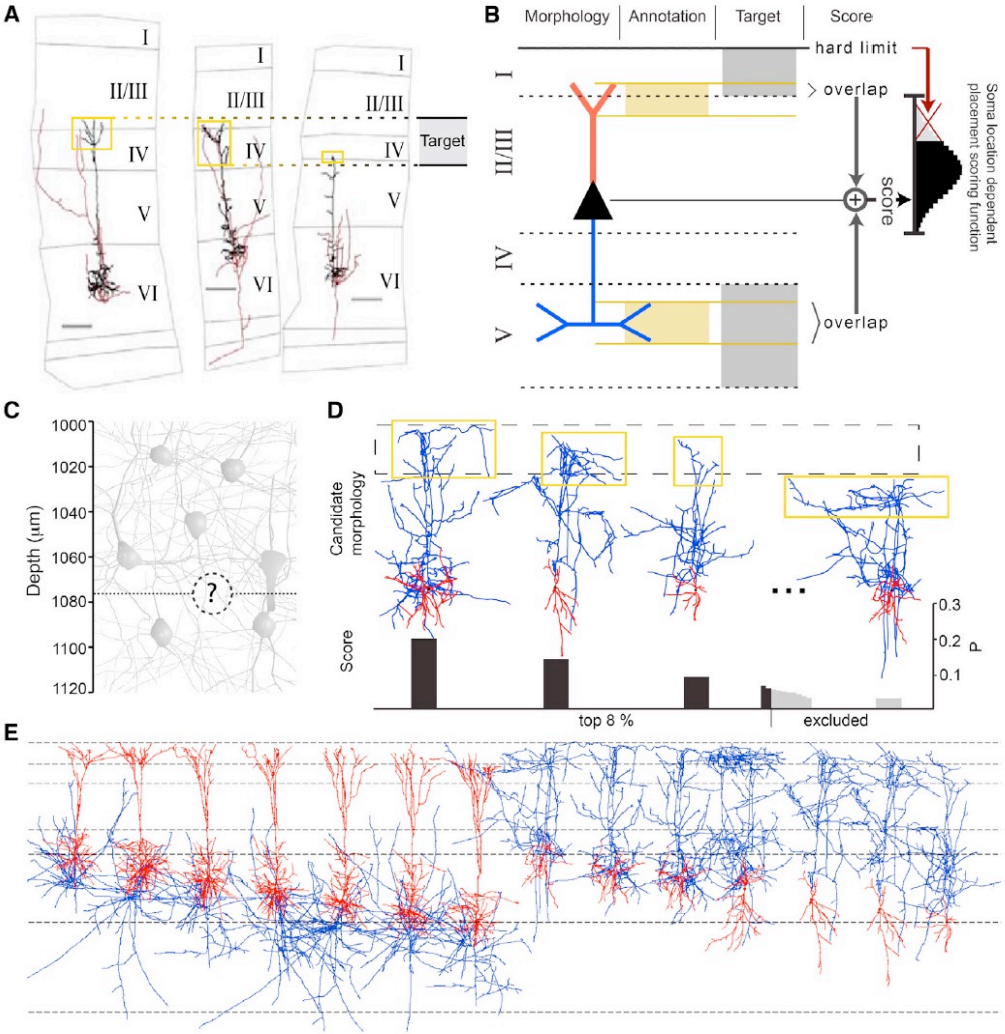
Scaling and select the most appropriate cell (see later)

Cell positioning: respect neurite targeting



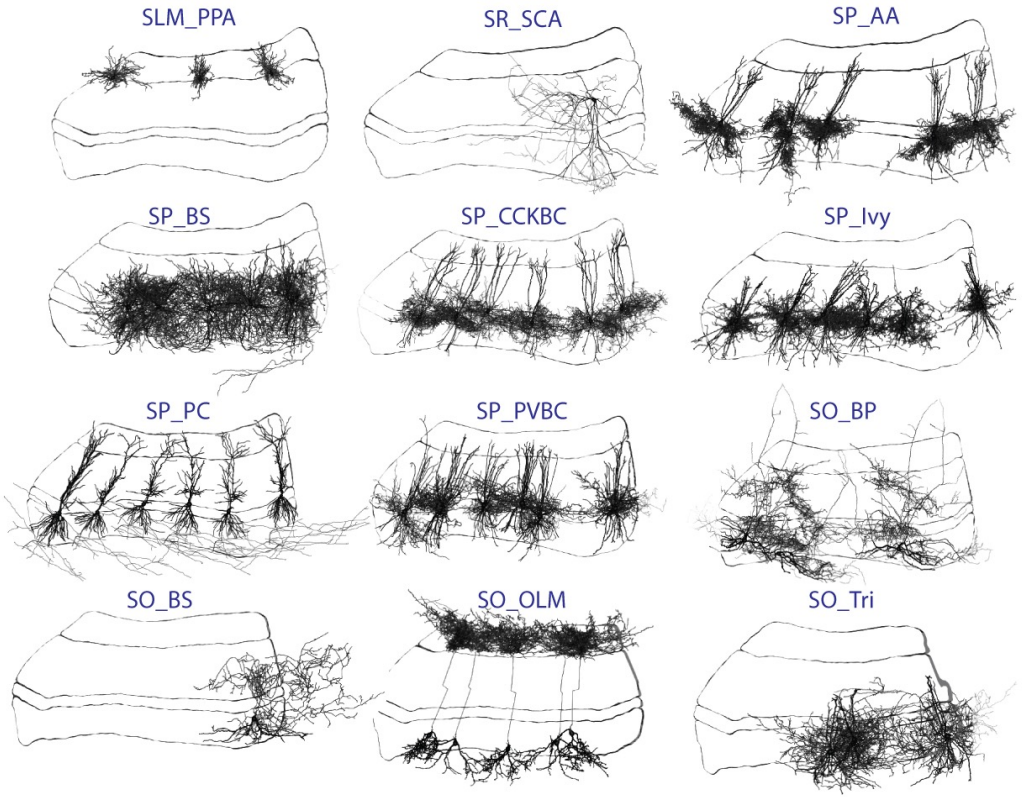
Cloning and scaling, and select the most appropriate cell (see later)

Cell positioning: respect neurite targeting



Markram et al., 2015

Cell positioning



Romani et al., 2024

Morphological synthesis

OPEN ACCESS Freely available online

PLoS COMPUTATIONAL BIOLOGY

One Rule to Grow Them All: A General Theory of Neuronal Branching and Its Practical Application

Hermann Cuntz[1,2]*, Friedrich Forstner[2], Alexander Borst[2], Michael Häusser[1]

1 Wolfson Institute for Biomedical Research and Department of Neuroscience, Physiology and Pharmacology, University College London, London, United Kingdom, **2** Department of Systems and Computational Neurobiology, Max-Planck Institute of Neurobiology, Martinsried, Germany

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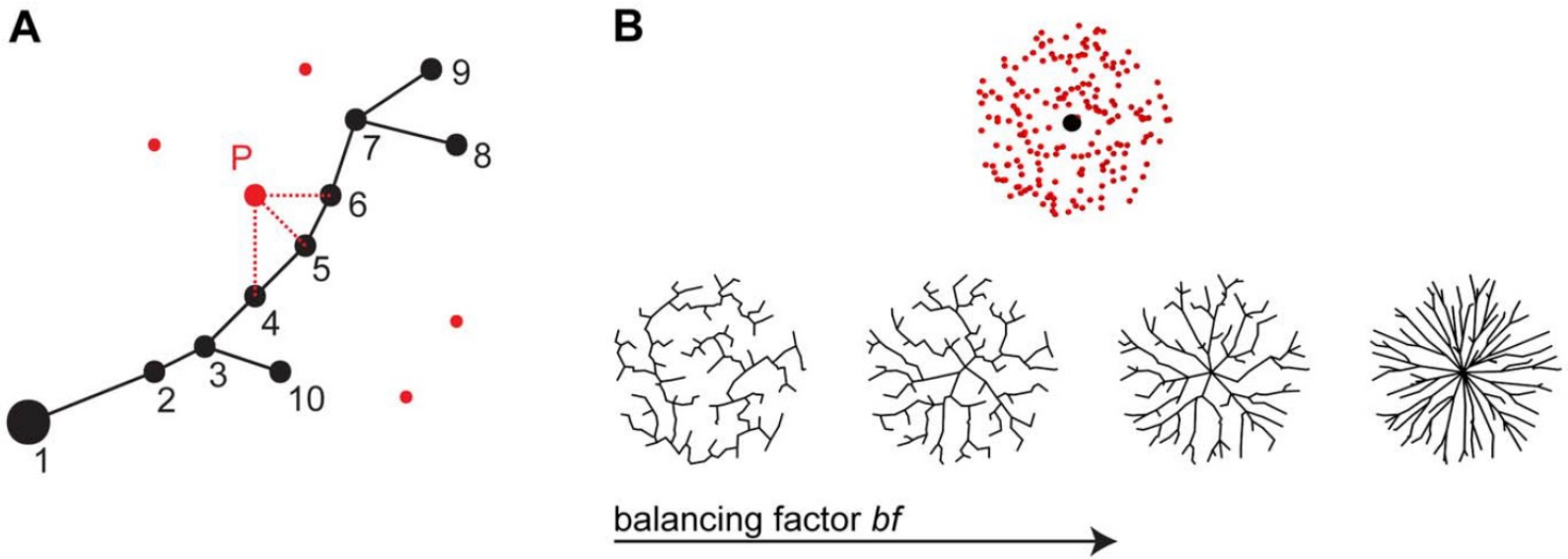
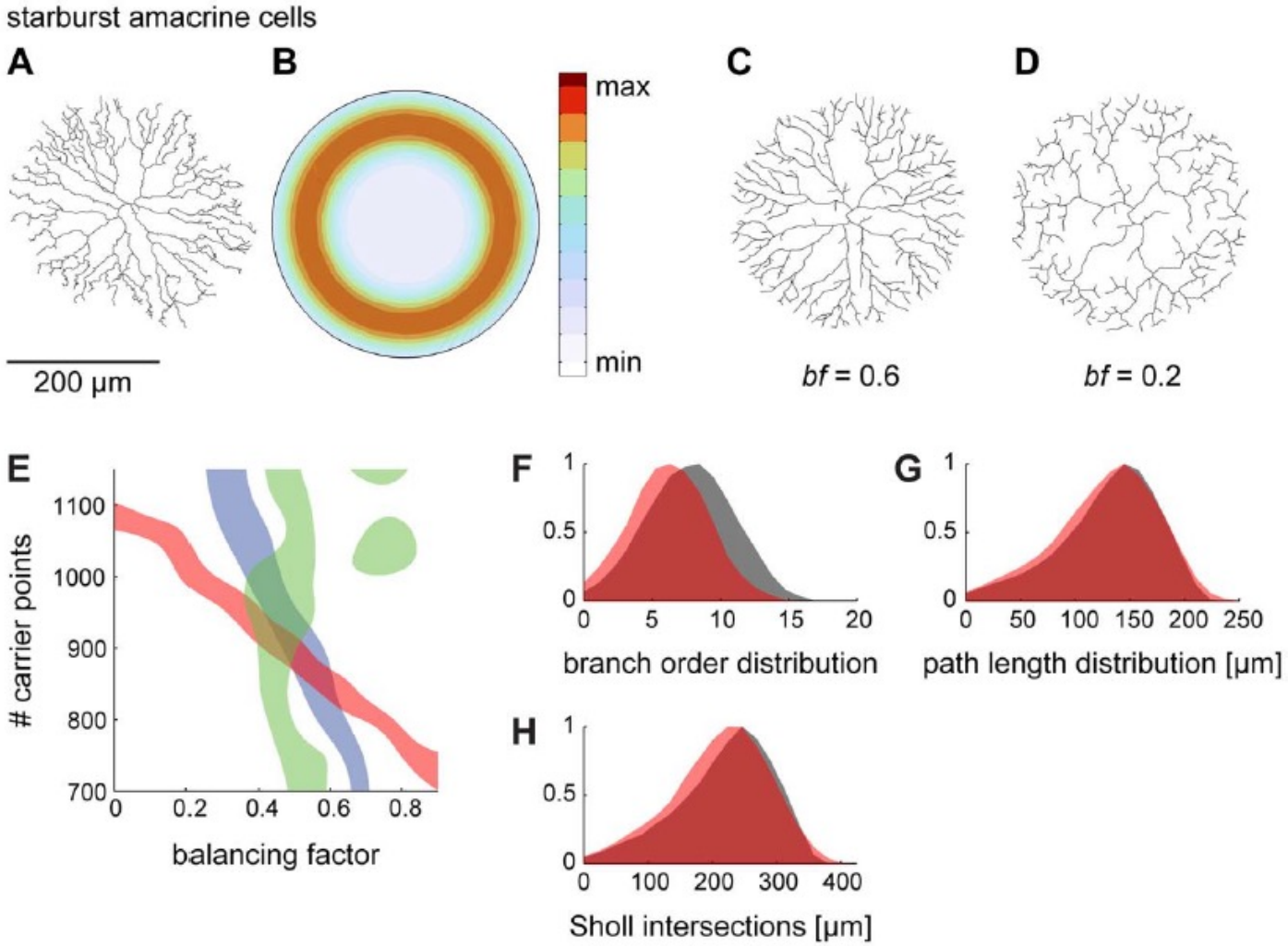
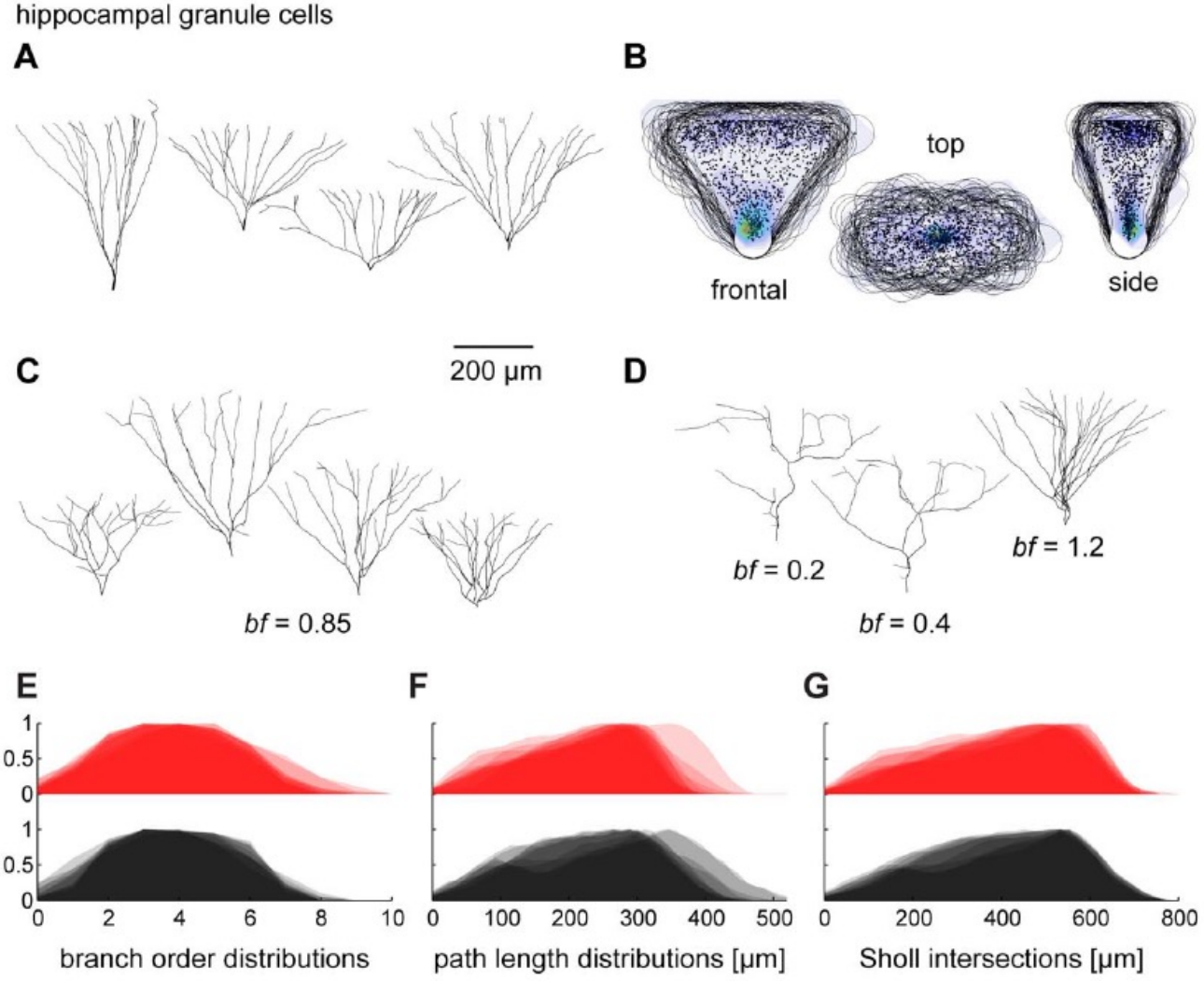


*(total cost) = (wiring cost) + bf * (path length cost)*

wiring cost = Euclidean distance between the carrier point and the node

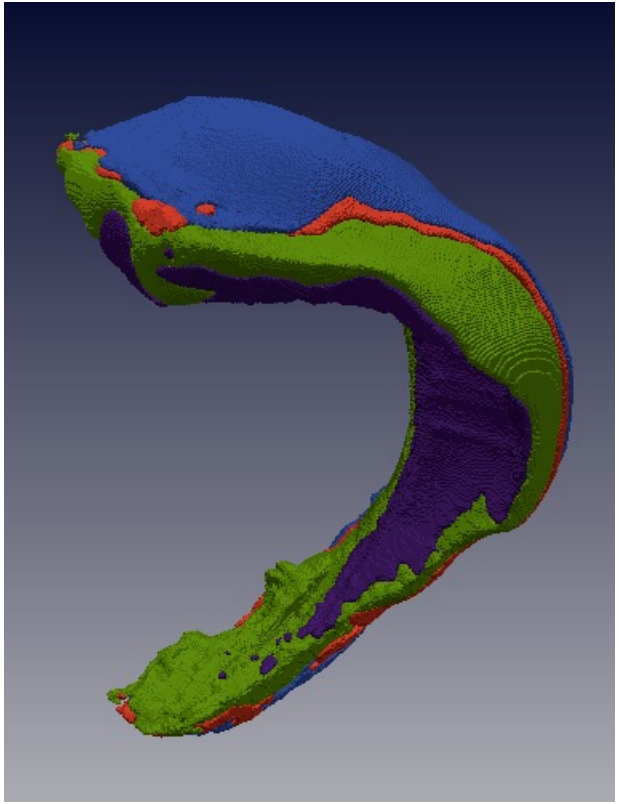
path length cost = path along the tree from the root to the carrier point


starburst amacrine cells
A
B
C
D
max
min
200 µm
bf = 0.6
bf = 0.2
E
carrier points
1100
1000
900
800
700
0
0.2
0.4
0.6
0.8
balancing factor
F
1
0.5
0
0
5
10
15
20
branch order distribution
G
1
0.5
0
0
50
100
150
200
250
path length distribution [µm]
H
1
0.5
0
0
100
200
300
400
Sholl intersections [µm]

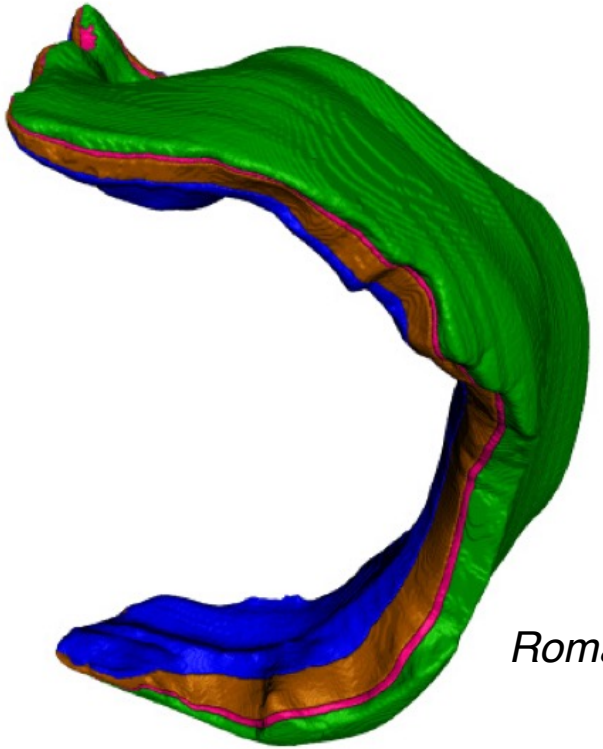

hippocampal granule cells
A
B
top
frontal
side
C
200 µm
D
bf = 0.85
bf = 0.2
bf = 1.2
bf = 0.4
E
F
G
1
0.5
0
1
0.5
0
0 2 4 6 8 10
branch order distributions
0 100 200 300 400 500
path length distributions [µm]
0 200 400 600 800
Sholl intersections [µm]

Intermediate approaches

Smoothed atlas

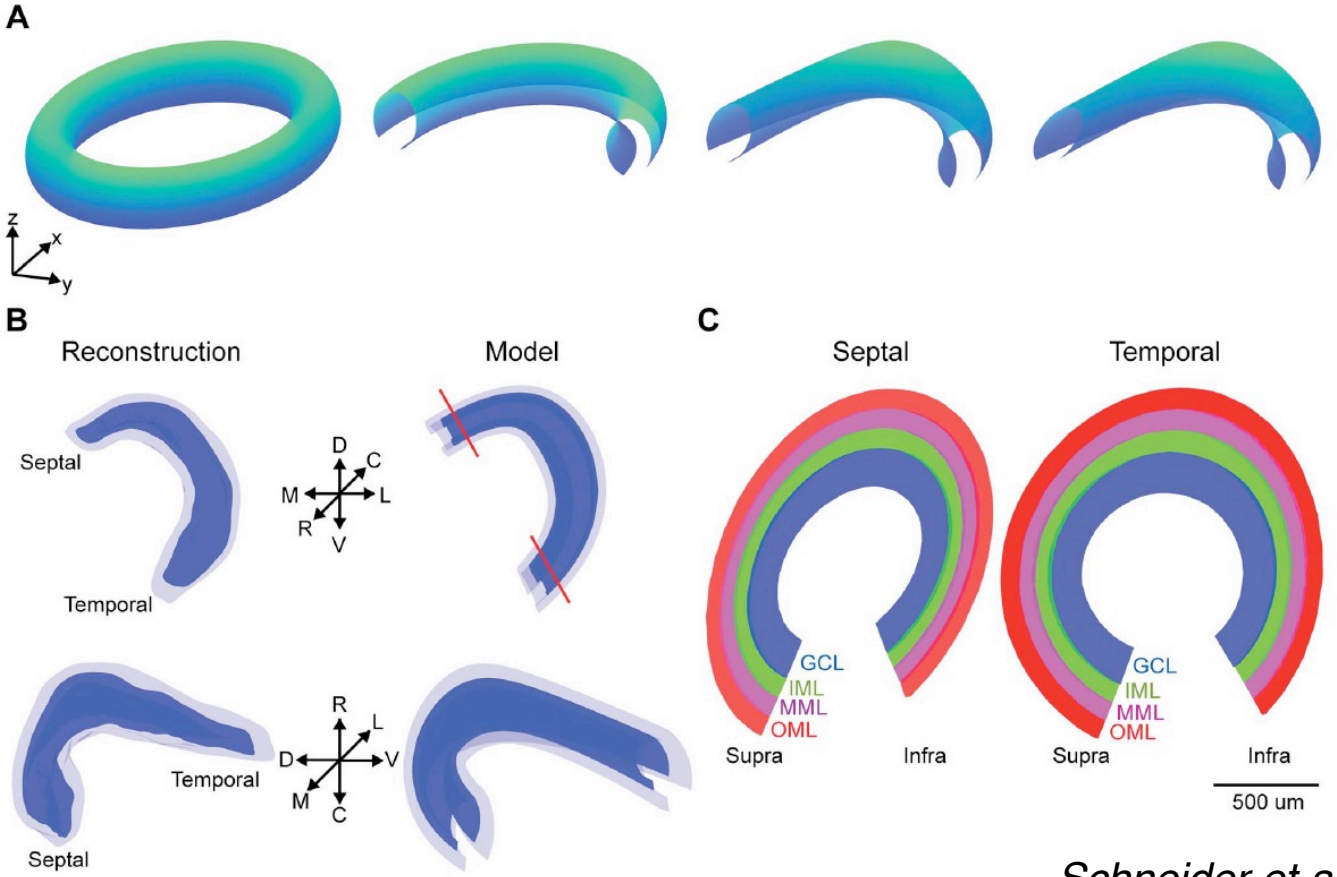


Fixed ratio between layer thicknesses



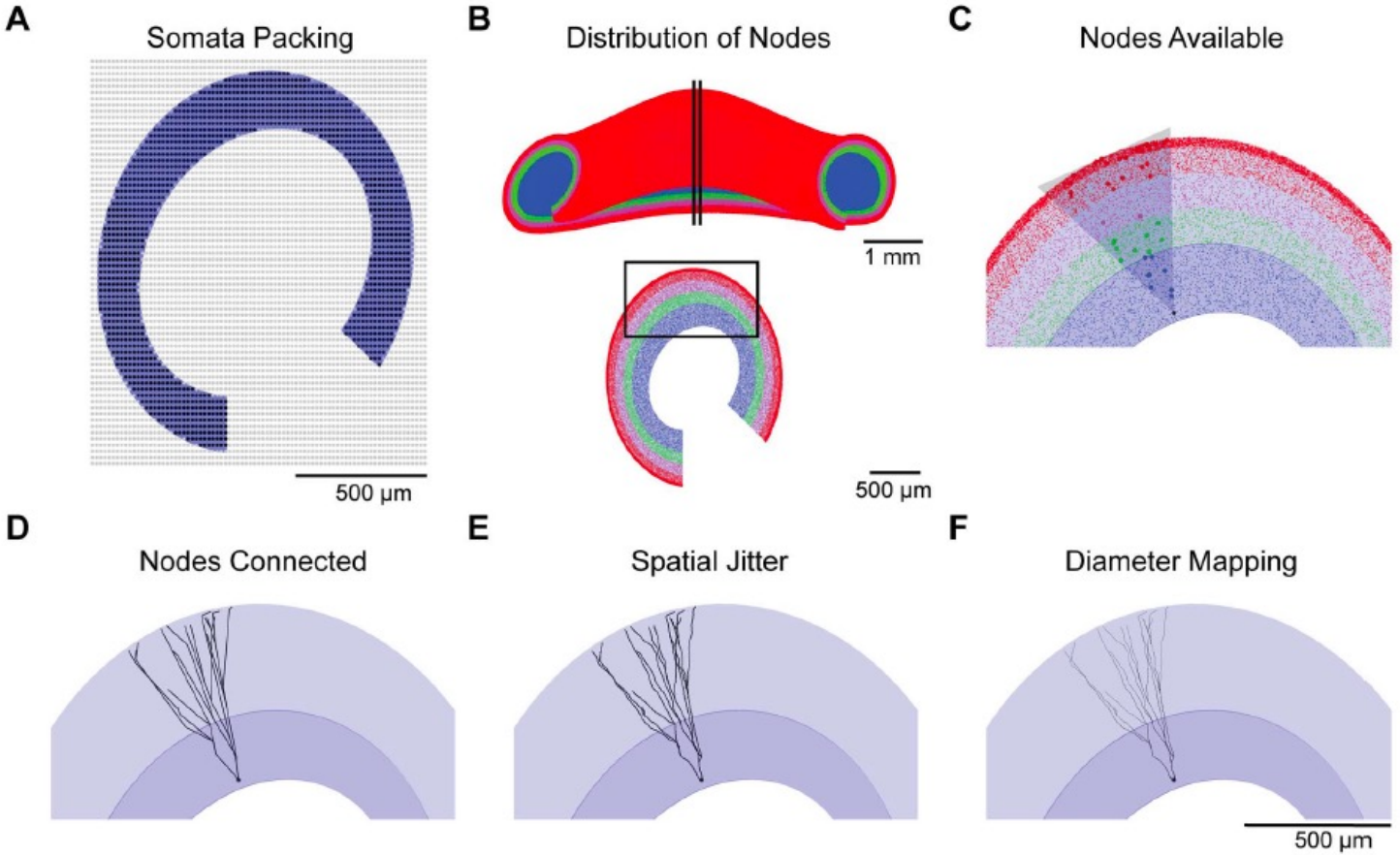
Romani et al.

Intermediate approaches

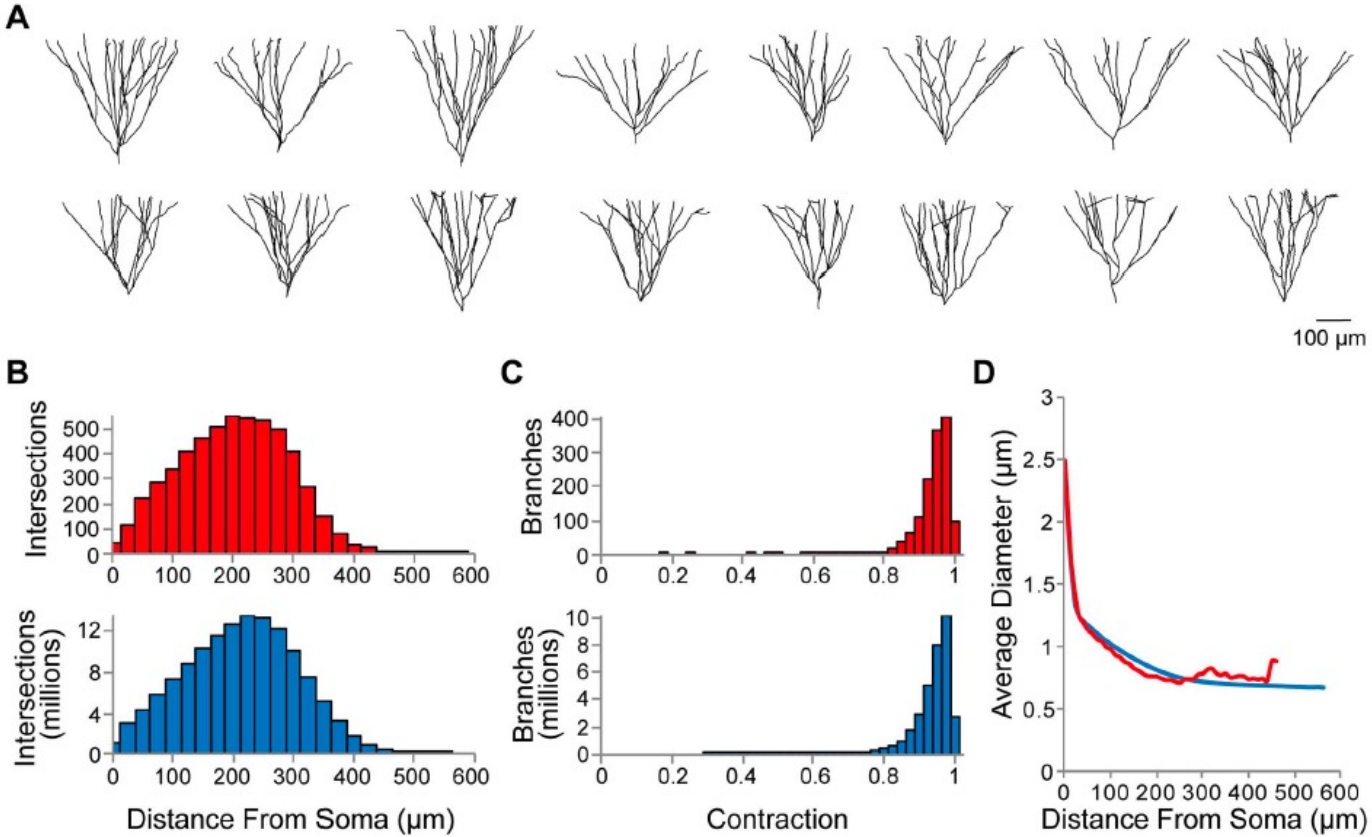


Schneider et al., 2014

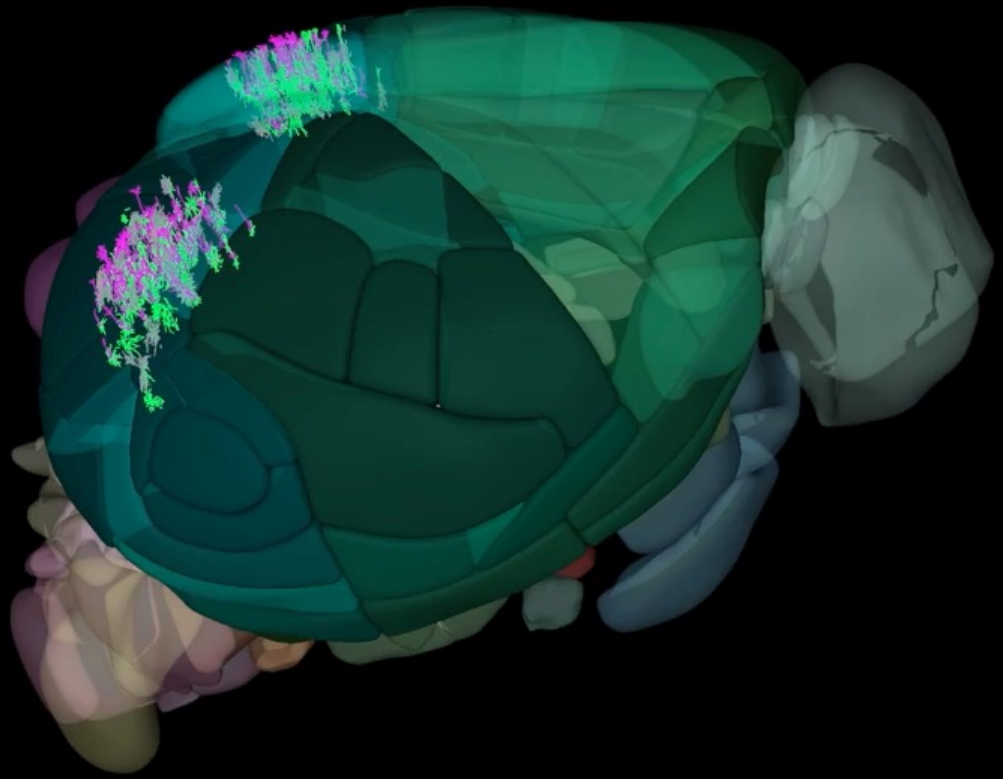
Cell placement: synthetic cells



Cell placement: synthetic cells



ALLEN INSTITUTE for
BRAIN SCIENCE

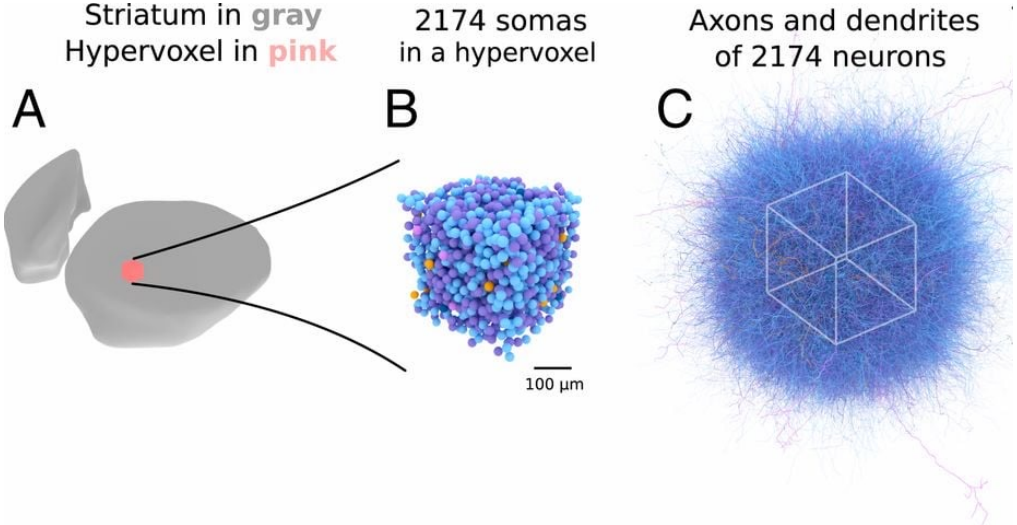


Erö et al., 2018

https://bbp.epfl.ch/nexus/cell-atlas/

Striatum

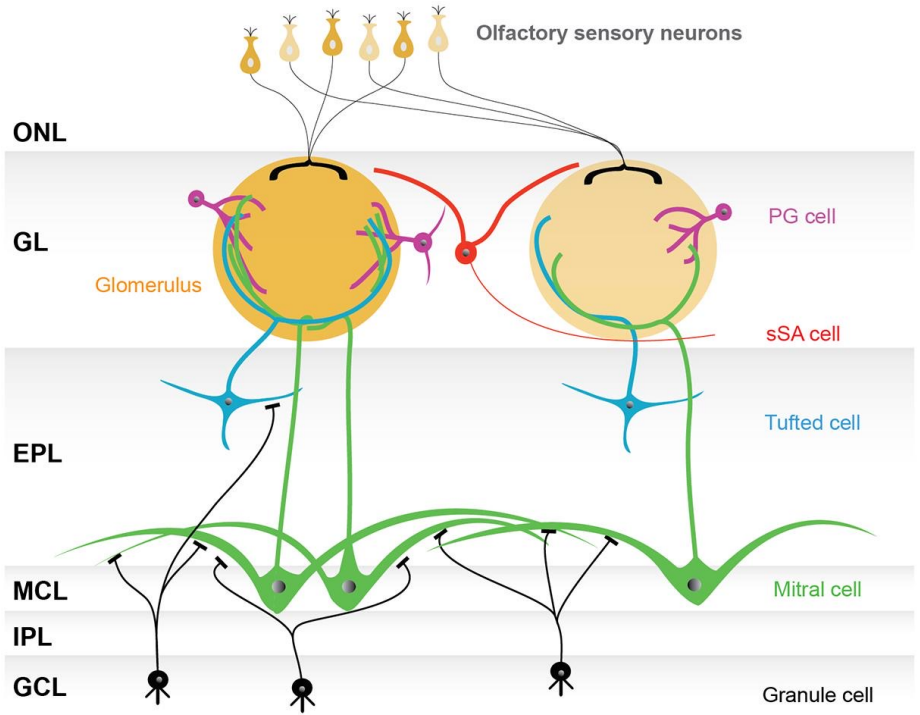
- The simplest cell placement is random orientation
- An example of a network like that is striatum



Hjorth et al., 2020

Olfactory bulb

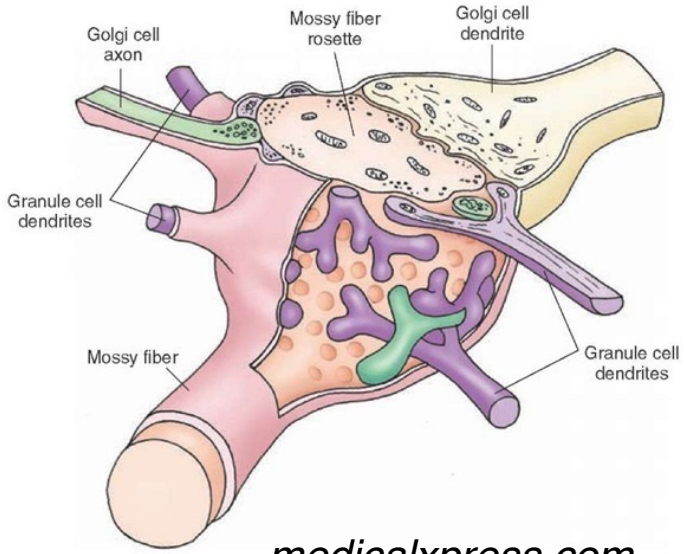
- Glomeruli are specialized structures where a series of dendrites and axons converge and form synapses
- Cell placement has to take this into account



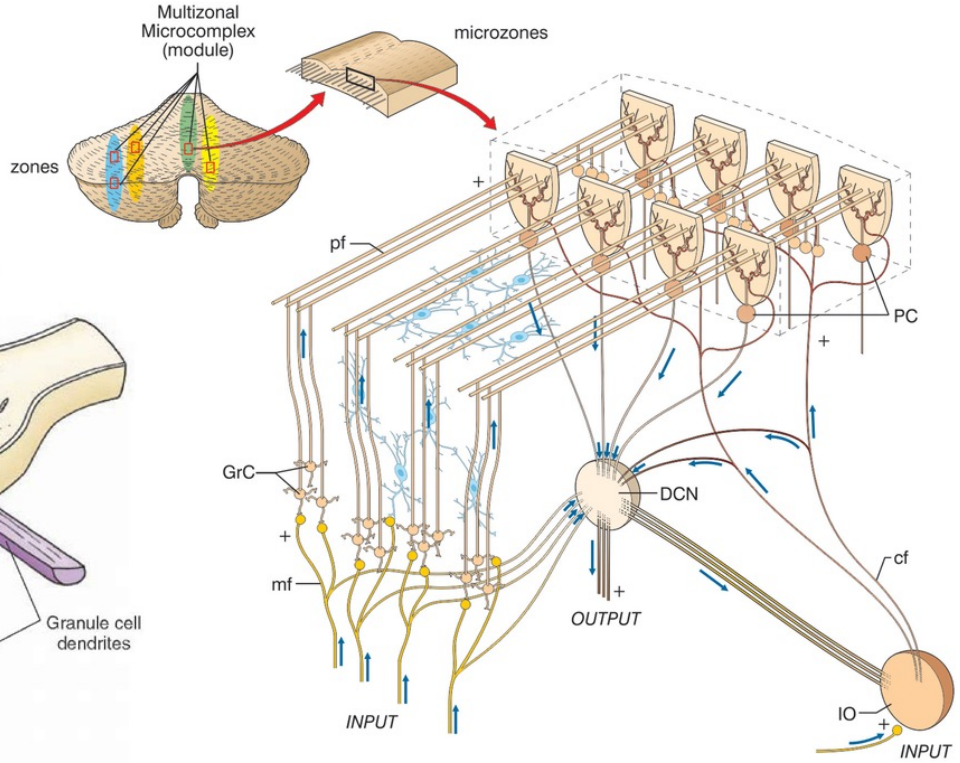
Nagayama et al., 2014

Cerebellum

- Glomeruli
- “semicrystalline” structure



medicalxpress.com



D’Angelo and Casali, 2013

Summary 1

- Find a tradeoff between accuracy and cost
- Atlas-based networks use a standard space
- More reusability
- More and more data will be registered in atlases
- It enables us to move from brain regions to whole brain
- Some intermediate approaches (atlas with fixed layers) keep the cost reasonable while allowing to use a standard space

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Circuit 1
Part 2: dealing with sparse data

Lecture Overview

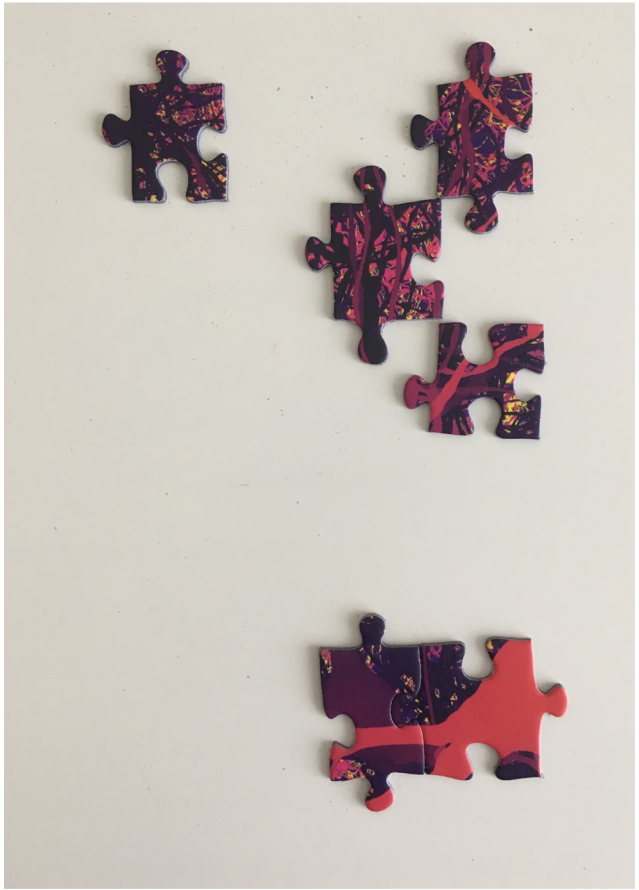
- Scope
- Approaches
- Applications

Lecture Overview

- **Scope**
- Approaches
- Applications

What you would like

The reality



How to overcome sparsity and reproducibility of data?

Examples of some issues with existing data

Cell densities

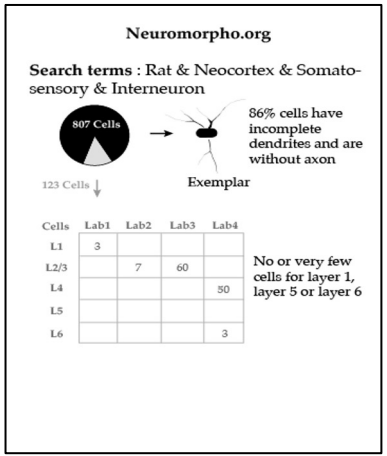
Reference	Species (region, age)	Microcircuit cell count	Microcircuit cell density/mm³
Knox, 1982	Rat (V1, adult)	~15,000	~40,000
Peters et al. 1987	Rat (V1, adult)	~15,000	~75,000
Beaulieu 1992	Rat (mPfC, adult)	~5,000	~36,400
DeFelipe et al. 2002	Rat (S1, adult)	~8,000	~5,000
Garcia et al. 2006	Rat (S1, p14)	~7,000	~52,000
Meyer et al. 2010	Rat (S1, p27)	~20,000	~82,000

~4x variability

~2.5x variability

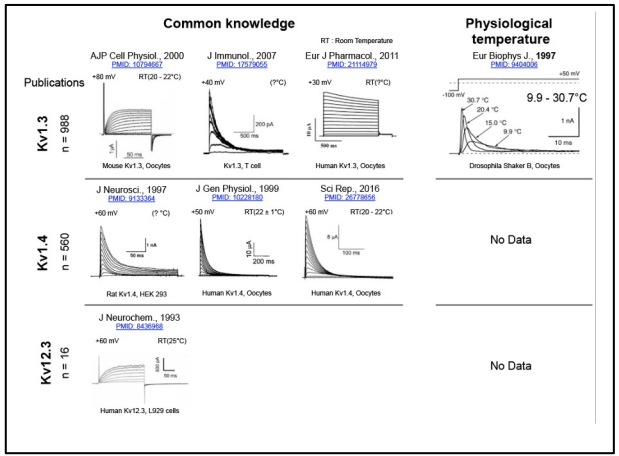
Numbers in literature can **vary** up to **4 fold**

Morphologies



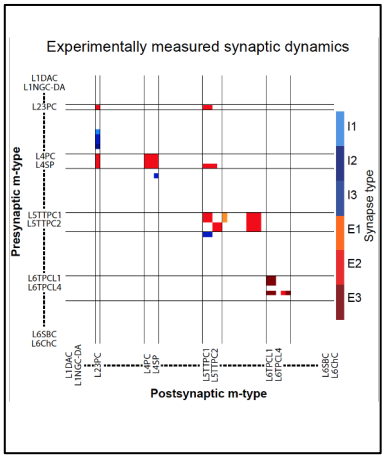
Usually data is **incomplete or missing**

Ion channel kinetics



Data often is **inconsistent** and raw data largely not publicly **available**

Synaptic physiology

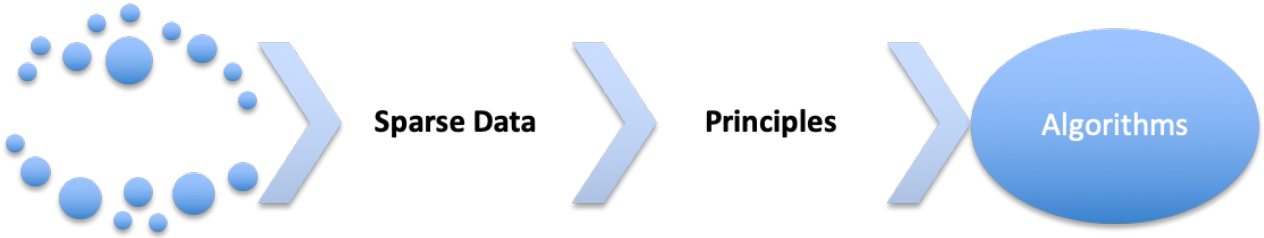


Very few pathways have been characterized. Data can be very **sparse**

Lecture Overview

- Scope
- **Approaches**
- Resources

From Sparse Data to Dense Models



Interconnection of the data

Connectome

- Volume
- Number of cells
- Cell composition
- Cell densities
- Cell positions
- Cell morphologies (neurite lengths, topology…)
- Number of synapses
- Spine morphologies (length…)
- Bouton densities
- Number of synapses per connection
- Connection probabilities
- Synapse location (on soma, dendrite, axon…)
- Divergence, convergence…

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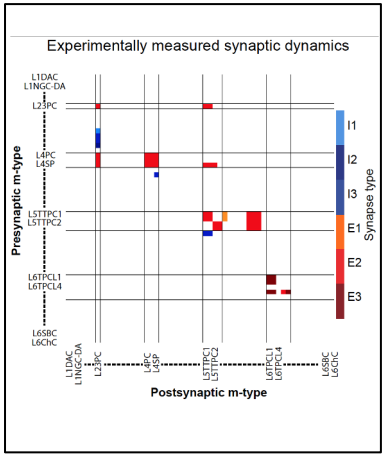
Example 1: predict the connectome

- Connectome (set of connections) is a classical example of sparse data
- N cells form N^2 potential connections and only few of them are well characterized (e.g. number of synapses per connection, connection probability…)
- The figure on the right represent data on synaptic physiology but something similar occurs with synaptic anatomy
- The connectome can be predicted by co-localization of axon and post-synaptic neurons

Synaptic physiology

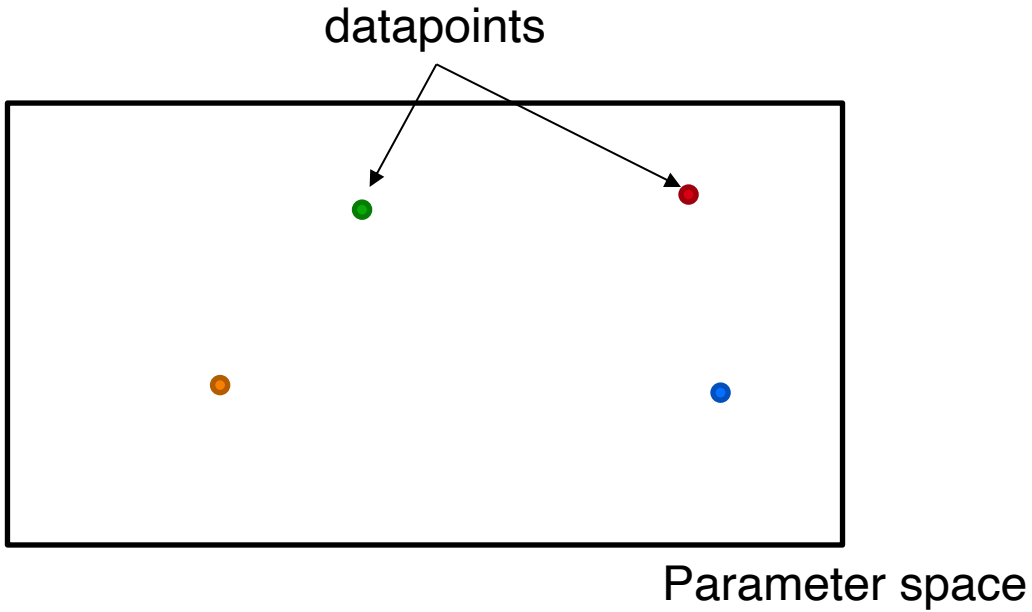


Very few pathways have been characterized. Data can be very **sparse**

Example 2: generalisation

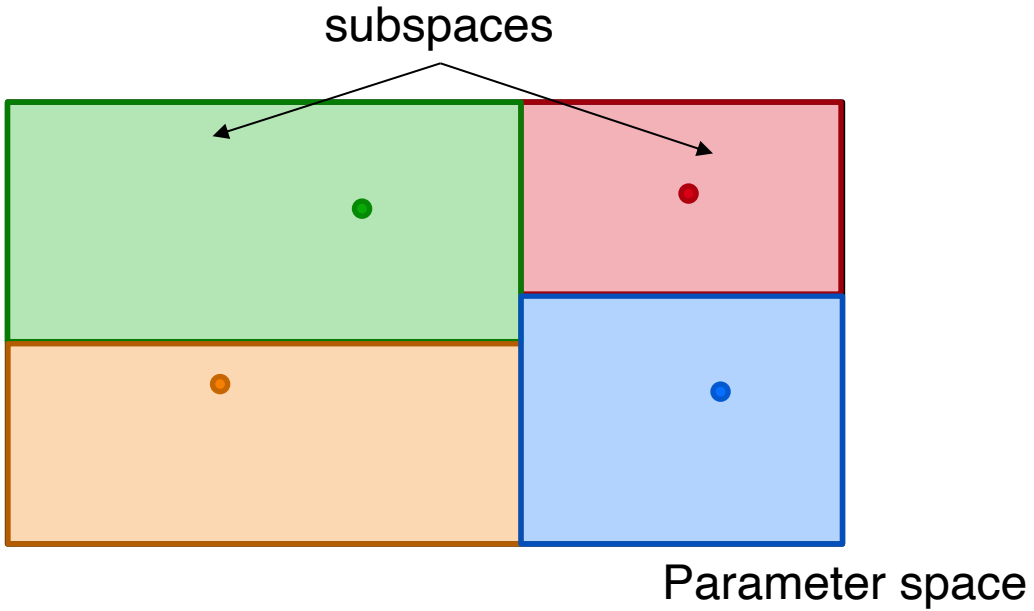
- When we lack data on A, we can use data on B which we assume to be similar to A
- The frequent example is using data from a species to model another species (use rat data to model mouse or vice versa)
- Another example is schematized in the next slides

Generalization



Similar data are located in close proximity

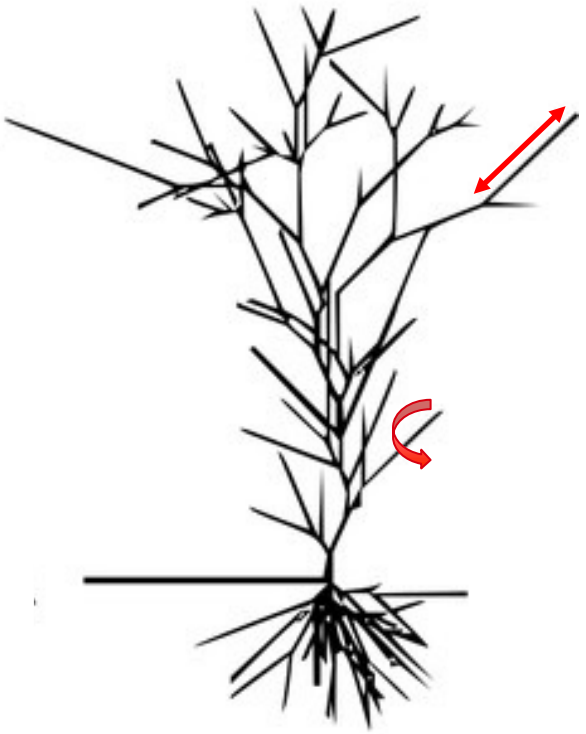
Generalization



1. Divide the space in subspaces
2. Use the datapoints to describe the corresponding subspaces

Example 3: morphologies

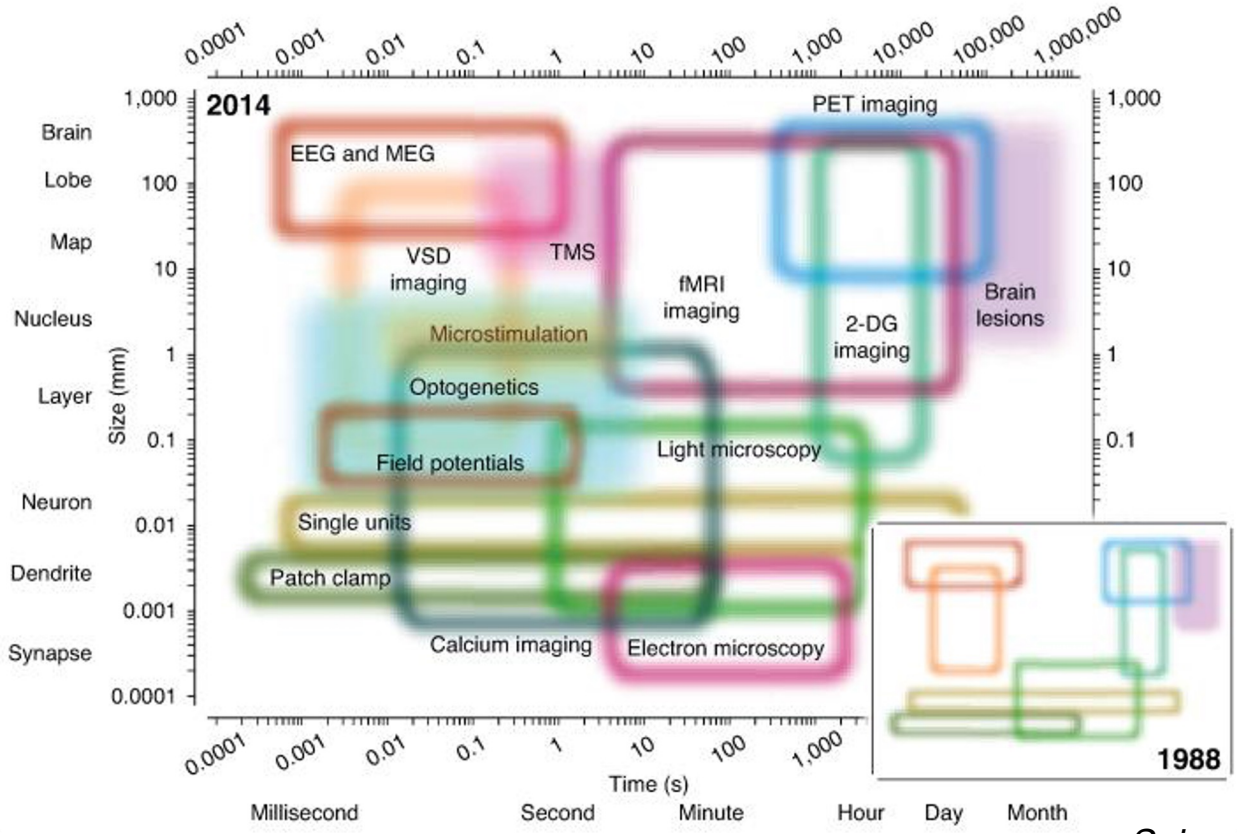
- Morphologies are all unique
- We have only few reconstructions
- How can we restore the biological variability?
- We could inject noise into branch lengths and rotations, leaving the overall branching structure unchanged



Data heterogeneity

- Our sparse data is often heterogeneous
- (Experimental) data are from different animals, experimental conditions, of different quality, scales…
- Data curation homogenizes data and preparers them to be integrated in the model (data integration)

Different scales - Experimental neuroscience

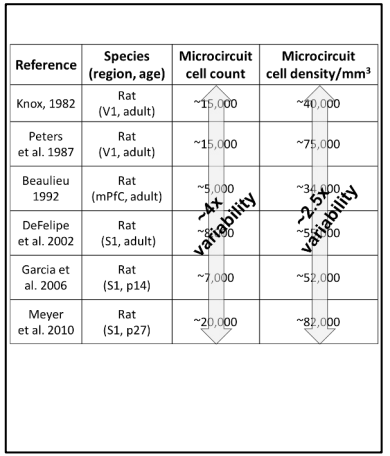


Sejnowski et al., 2014

Data curation

- Select the most appropriate data (e.g. data for the species we are modelling, higher quality data…)
- Working assumptions are often necessary to mitigate heterogeneity (e.g. rat data can be used to model mouse in the lack of specific data, we can ignore the effect of temperature on morphology reconstruction)
- Simple data manipulations can be adopted (e.g. divisive scaling factor of 0.41 to convert mouse data to rat – Attili et al., 2021)
- More sophisticated strategies are necessary in other cases (e.g. kinetics of the channels can be measured at different temperatures, recordings can be made at different bath concentrations of Ca and K)

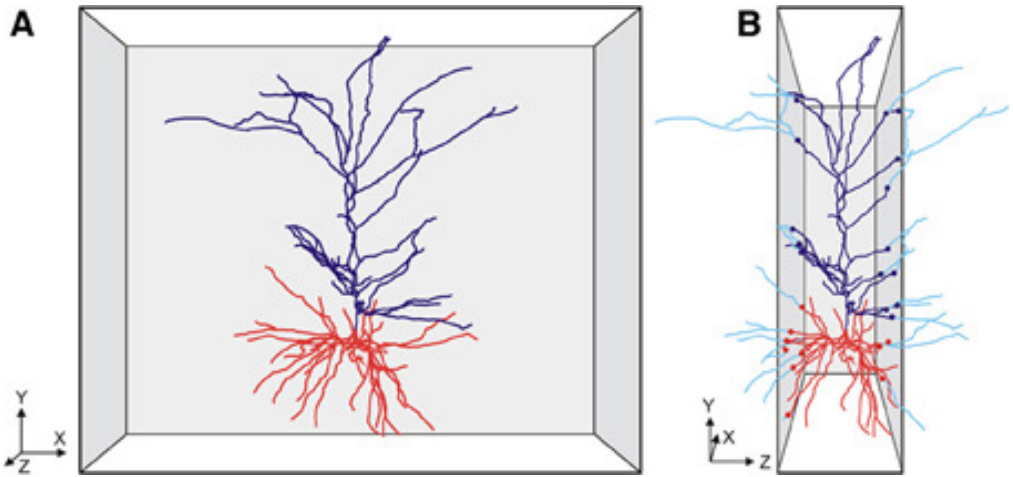
Cell densities



Reference	Species (region, age)	Microcircuit cell count	Microcircuit cell density/mm³
Knox, 1982	Rat (V1, adult)	~15,000	~40,000
Peters et al. 1987	Rat (V1, adult)	~15,000	~75,000
Beaulieu 1992	Rat (mPfC, adult)	~5,000	~34,000
DeFelipe et al. 2002	Rat (S1, adult)	~20,000	~92,000
Garcia et al. 2006	Rat (S1, p14)	~7,000	~52,000
Meyer et al. 2010	Rat (S1, p27)	~20,000	~82,000

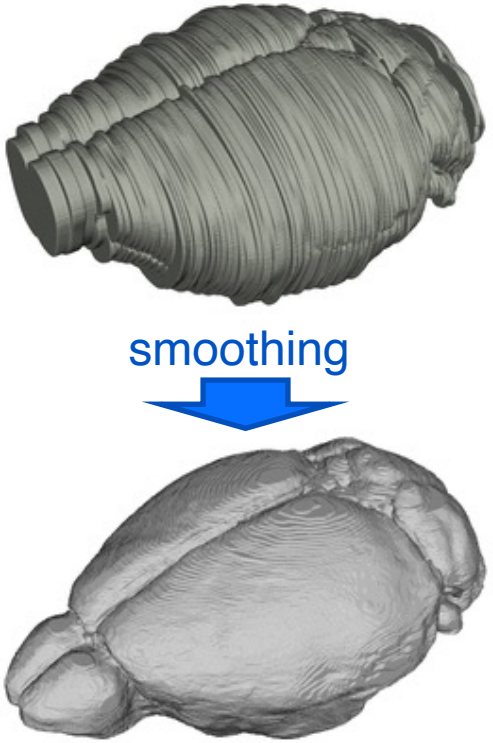
Numbers in literature can **vary** up to **4 fold**

Repair data



van Pelt et al., 2014

Cut repair
(lecture 3)



(lecture 9)

What to do with missing data?

From lecture 6…

• More (novel) experiments	• Possible for few parameters
• Guess parameters and hand-tune	• See next ‘working assumptions’
• Systematic grid search	• Possible for few parameters
• Regularize parameters	• Extrapolation / fit. See next ‘algorithm’
• Infer parameters from other (related) and more easily measurable properties	• See next ‘use similar datasets’
• Parameter Optimization	• Possible but expensive for large networks

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What to do with missing data?

- Working assumptions
- Generalization
- Algorithms

Lecture Overview

- Scope
- Approaches
- **Applications**

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Check for updates

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RESEARCH ARTICLE

Data-driven integration of hippocampal CA1 synaptic physiology *in silico*

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TABLE 2 List of assumptions. All the assumptions that were made to arrive at model parameters from a sparse set of raw data and published values

1	We assume that after all the listed correction in this paper, all parameters coming from different sources can be used together to parameterize the synapse models.
2	When using data from Kohus et al. (2016), we assumed that CCK+ DTIs (dendrite-targeting interneurons) are SCA cells in SR. Furthermore, we assumed that synaptic currents measured in mouse CA3 are representative of similar pathways in rat CA1.
3	In the lack of representative data and our lack of neurogliaform cells, we assumed that all inhibitory synapses are mediated purely by $GABA_A$ receptors.
4	For calculating release probabilities at different $[Ca^{2+}]_o$, we assumed that Hill functions parameterized with cortical data generalize well for hippocampal connections.
5	For modeling synaptic currents, we assumed that all CA1 synapses can be described with biexponential conductances, with vesicle release kinetics governed by the stochastic TM model. When modeling dendritic PSC decays, we assumed a single exponential function, parametrized with a time constant extracted from somatic recording.
6	In the process of calibrating synaptic peak conductances, we simulated only the synapses mediating the given connection and thus we assume that the background activity does not matter.
7	Some of the biggest assumptions are inherited from the network model: In this work, we assumed that the published electrical models of single cells (Migliore et al., 2018) capture the behavior of different neurons in rat CA1. (The fact that unlike experimentalists, we cannot clamp PC models to potentials above −58 mV without blocking sodium channels seems to violate this assumption.) We also assumed that the cell composition and cell density within each layer are homogeneous and the constrained connectivity reflects the connectivity of rat CA1.
8	Kinetic parameters for a given pathway are drawn from a distribution, but since (almost) all experimental data used to derive these parameters are representative for a given connection and not for individual synapses per se, we use the same parameters for all synapses mediating a single connection.
9	The biggest assumption is that one can extrapolate parameters from experimentally characterized pathways, to fill in missing values. When generalizing our parameters for similar, experimentally uncharacterized pathways we group CA1 interneurons based on only one chemical marker. However, cells express many of these and the markers overlap (see hippocampome.org (Wheeler et al., 2015)). By PV+ cells we mean: SP_PVBCs, SP_BS cells, and SP_AA cells. By CCK+ cells we mean: SP_CCKBCs, SR_SCA cells and SLM_PPA cells. The only interneurons in our NOS+ class are SP_Ivy cells. (Neurogliaform cells would belong here as well.) We assume all neurons in SO: SO_OLM cells, SO_BS cells, SO_Tri cells, and SO_BP cells to be SOM+.
10	A usually unspoken, implicit assumption on communication between neurons is used here as well, namely, we model only glutamatergic and GABAergic synapses between presynaptic axons and postsynaptic somata and dendrites. Thus, we leave out cotransmission and neuromodulators acting on different receptors, retrograde messengers, any kind of gap junctions and any axonal receptors.

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Ecker et al., 2020

TABLE 3 Parameters and generalization to nine classes

Pre	Post	$\hat{g}$	τ_{decay}	U_{SE}	D	F	N_{RRP}
			PC to PC (E2)				
PC	PC	0.6 ± 0.1	3 ± 0.2	0.5 ± 0.02[a]	671 ± 17[a]	17 ± 5[a]	2
			PC to SOM+ (E1)				
PC	OLM	0.8 ± 0.05	**1.7 ± 0.14[a]**	**0.09 ± 0.12[a]**	**138 ± 211[a]**	**670 ± 830[a]**	**1**
PC	**SOM+**	**0.8 ± 0.05**	**1.7 ± 0.14[a]**	**0.09 ± 0.12[a]**	**138 ± 211[a]**	**670 ± 830[a]**	**1**
			PC to SOM– (E2)				
PC	PVBC	2 ± 0.05	4.12 ± 0.5	0.23 ± 0.09	410 ± 190	10 ± 11	1
PC	CCKBC	3.5 ± 0.4	**4.12 ± 0.5**	0.23 ± 0.09	410 ± 190	10 ± 11	1
PC	BS	1.65 ± 0.1	**4.12 ± 0.5**	**0.23 ± 0.09**	**410 ± 190**	**10 ± 11**	1
PC	Ivy	6.5 ± 0.5	**4.12 ± 0.5**	**0.23 ± 0.09**	**410 ± 190**	**10 ± 11**	1
PC	**SOM–**	**2.4 ± 0.8**	**4.12 ± 0.5**	**0.23 ± 0.09**	**410 ± 190**	**10 ± 11**	**1**
			PV+ to PC (I2)				
PVBC	PC	2.15 ± 0.2	5.94 ± 0.5	0.16 ± 0.02	965 ± 185	8.6 ± 4.3	6
AA	PC	2.4 ± 0.1	11.2 ± 0.9	0.1 ± 0.01	1,278 ± 760	10 ± 6.7	1
BS	PC	1.6 ± 0.1	16.1 ± 1.1	**0.13 ± 0.03**	**1,122 ± 156**	**9.3 ± 0.7**	1
PV+	**PC**	**2 ± 0.35**	**11.1 ± 4.1**	**0.13 ± 0.03**	**1,122 ± 156**	**9.3 ± 0.7**	**1**
			CCK+ to PC (I3)				
CCKBC	PC	1.8 ± 0.3	9.35 ± 1	0.16 ± 0.04	153 ± 120	12 ± 3.5	1
SCA	PC	2.15 ± 0.3	8.3 ± 0.44	0.15 ± 0.03	185 ± 32	14 ± 5.8	1
CCK+	**PC**	**2 ± 0.15**	**8.8 ± 0.25**	**0.16 ± 0.01**	**168 ± 15**	**13 ± 0.5**	**1**
			SOM+ to PC (I2)				
Tri	PC	1.4 ± 0.3	7.75 ± 0.9	**0.3 ± 0.08[a]**	**1,250 ± 520[a]**	**2 ± 4[a]**	1
SOM+	**PC**	**1.4 ± 0.3**	**8.3 ± 2.2[a]**	**0.3 ± 0.08[a]**	**1,250 ± 520[a]**	**2 ± 4[a]**	**1**
			NOS+ to PC (I3)				
Ivy	PC	0.48 ± 0.05	16± 2.5	0.32 ± 0.14[a]	144 ± 80[a]	62 ± 31[a]	1
			CCK– to CCK– (I2)				
PVBC	PVBC	4.5 ± 0.3	2.67 ± 0.13	0.26 ± 0.05	930 ± 360	1.6 ± 0.6	6
PVBC	AA	**4.5 ± 0.3**	**2.67 ± 0.13**	0.24 ± 0.15	1,730 ± 530	3.5 ± 1.5	1
CCK–	**CCK–**	**4.5 ± 0.3**	**2.67 ± 0.13**	**0.26 ± 0.05**	**930 ± 360**	**1.6 ± 0.6**	**1**
			CCK+ to CCK+ (I1)				
CCKBC	CCKBC	**4.5 ± 0.3**	4.5 ± 0.55	0.11 ± 0.03	115 ± 110	1,542 ± 700	1
CCK+	**CCK+**	**4.5 ± 0.3**	**4.5 ± 0.55**	**0.11 ± 0.03**	**115 ± 110**	**1,542 ± 700**	**1**

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Ecker et al., 2020

Generalization for the hippocampal synapses

			SOM	SOM	SOM	SOM	PV	PV	PV	NOS	CCK	CCK	CCK
	pre\post	**SP_PC**	**SO_OLM**	**SO_BS**	**SO_Tri**	**SO_BP**	**SP_PVBC**	**SP_BS**	**SP_AA**	**SP_Ivy**	**SP_CCKBC**	**SR_SCA**	**SLM_PPA**
	SP_PC	x	x				xx	x		x	x		
SOM	**SO_OLM**												
SOM	**SO_BS**												
SOM	**SO_Tri**	x											
SOM	**SO_BP**												
PV	**SP_PVBC**	xx					xx						
PV	**SP_BS**	x											
PV	**SP_AA**	x											
NOS	**SP_Ivy**	x											
CCK	**SP_CCKBC**	xx									xx		
CCK	**SR_SCA**	xx											
CCK	**SLM_PPA**												

xx complete parameters

x partial parameters

E1	E2	E3	I1	I2	I3

Morphologies

Examples of strategies used to recover missing information at the level of morphologies:

- Assumptions
  - Generic / simplified / ball-and-stick morphologies
- Generalizations
  - Apply a morphology from a species/age/region to another
- Algorithms
  - Cloning, scaling, and synthesis can recover missing information

Connectome

Examples of strategies used to recover missing information at the level of connectome:

- No axon, no space approaches
- No axon, space approaches

Less predictive
We have to set all the parameters
We can use generalization

- Axon, space approaches

More predictive

A -> *

Cell	Axonal: Extent (mm)	Axonal: Length (μm)	Axonal: Density (/100 μm)	Classical Boutons: Total	Classical Boutons: Syn.s/conn	Laminar Distribution (%): SO	SP	SR	SLM	Divergence: Fraction (%): Pyr.	Inrn.	Connections: Total	Pyr.	Inrn.
Ivy	ML: 0.75[a] RC: 1.31[a]	176,760[a,b]	41.7[b,c,d,e]	16,200[b]	10[c,f]	40	2	50	8[a,b,g]	92	8[c]	1,620	1,490	130
Neuroglia form	ML: 0.5[h] ST: 1.2[h]	144,000[b]	41.7[b,c,d,e]	13,200[b]	10[c,f]	0	0	17	83[b]	92	8[c]	1,320	1,214	106
O-LM	ML: 0.50[i] ST: 0.84[i]	62,490[i]	26.6[i]	16,370[b,i]	10[j]	7	0	0	93[b,i]	89	11[b,k]	1,637	1,457	180
Double proj.				6,080[c,l]	10[j]	58	0	42	0[b,c,i]	92	8[b,m,n]	608	559	49
Oriens retrohipp.				6,080[c,l]	10[j]	58	0	42	0[b,c,i]	96	4[m]	608	584	24
Trilaminar	ML: 2.45[i] ST: 2.60[i]	54,740[i]	28.2[i]	15,440[b,i]	10[j]	13	17	70	0[b,i]	40	60[o]	1,544	618	926
Back proj.		24,540[l]	24.8[l]	6,080[l]	10[j]	58	0	42	0[b,c,i]	92	8[c]	608	559	49
PV+ basket	ML: 1.04[i] ST: 1.19[i]	46,180[i]	22.6[i]	10,440[i]	pyr.: 11[p] inrn.: 1[i]					99	1[b,i]	1,014	943	71
Bistrati fied	ML: 2.09[i] ST: 1.86[i]	76,040[i]	21.0[b]	15,970[b,i]	10[q]	51	7	42	0[b,i,r]	92	8[c]	1,597	1,469	128
Axo-axonic	0.60[s] 0.85[s]			7,200[b,c,s]	6[b,s]	0	100	0	0[c]	100	0[s,t]	1,200	1,200	0
CCK+ basket	PD: 1[u]			10,000[b,u]	8[p]	19	60	20	1[r]	92	8[c]	1,250	1,150	100
SCA	PD: 1.1[u]			12,000[b,c,u]	6[u]	10	4	82	4[b,g,u]	92	8[c]	2,000	1,840	160
PPA				8,000[b,c,u]	6[u]	0	0	0	100[c]	92	8[c]	1,333	1,227	106

Bezaire and Soltesz, 2013 (Bezaire et al., 2016)

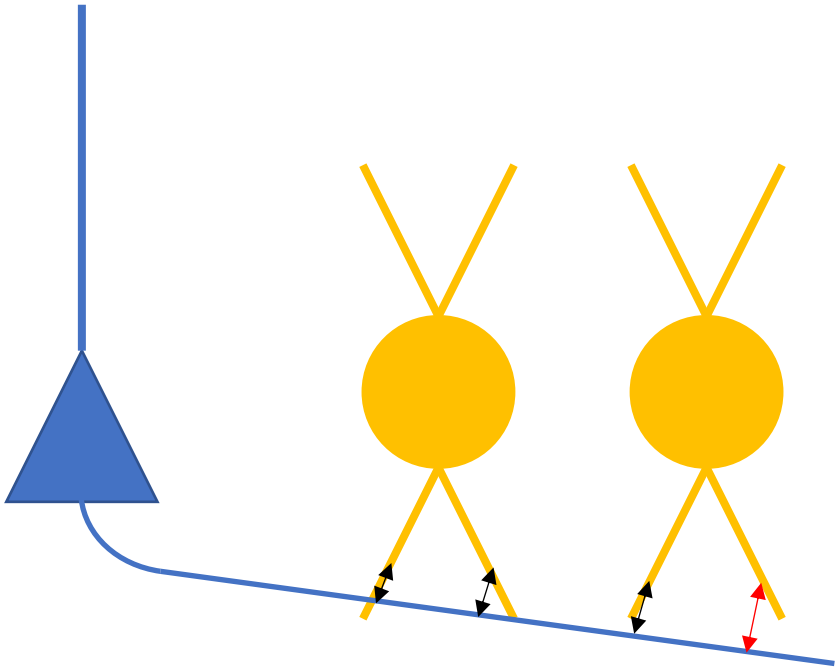
The "density" column gives the average bouton density of the axon. Total axonal length and bouton counts refer to local (CA1 area) only. The Divergence: Connections columns are all calculated from other data in the table.

[a]Fuentealba et al. (2008a).
[b]Further calculations applied to assumed or referenced data.
[c]Assumed.
[d]Szabadics and Soltesz (2009).
[e]Armstrong et al. (2011).
[f]Tamas et al. (2003).
[g]Szabo et al. (2012).
[h]Fuentealba et al. (2010).
[i]Sik et al. (1995).
[j]Maccaferri et al. (2000).
[k]Katona et al. (1999a).
[l]Sik et al. (1994).
[m]Jinno et al. (2007).
[n]Takacs et al. (2008).
[o]Ferraguti et al. (2004).
[p]Foldy et al. (2010).
[q]Klausberger et al. (2004).
[r]Pawelzik et al. (2002).
[s]Li et al. (1992).
[t]Buhl et al. (1994b).
[u]Vida et al. (1998).

ML: mediolateral, ST: septotemporal, PD: proximodistal, RC: rostrocaudal. Proj: projection.

Bezaire and Soltesz, 2013 (Bezaire et al., 2016)

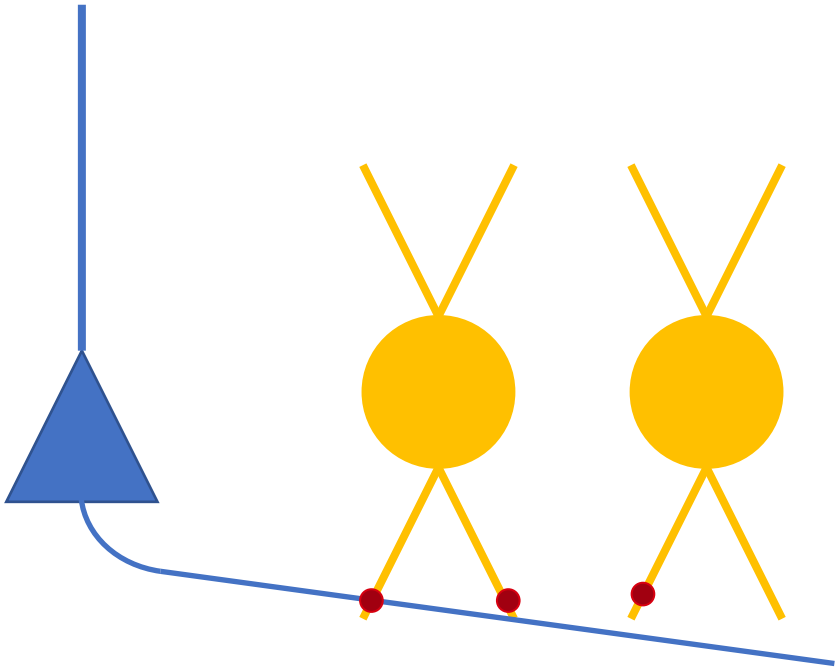
Recap: axon-based approaches



Below threshold

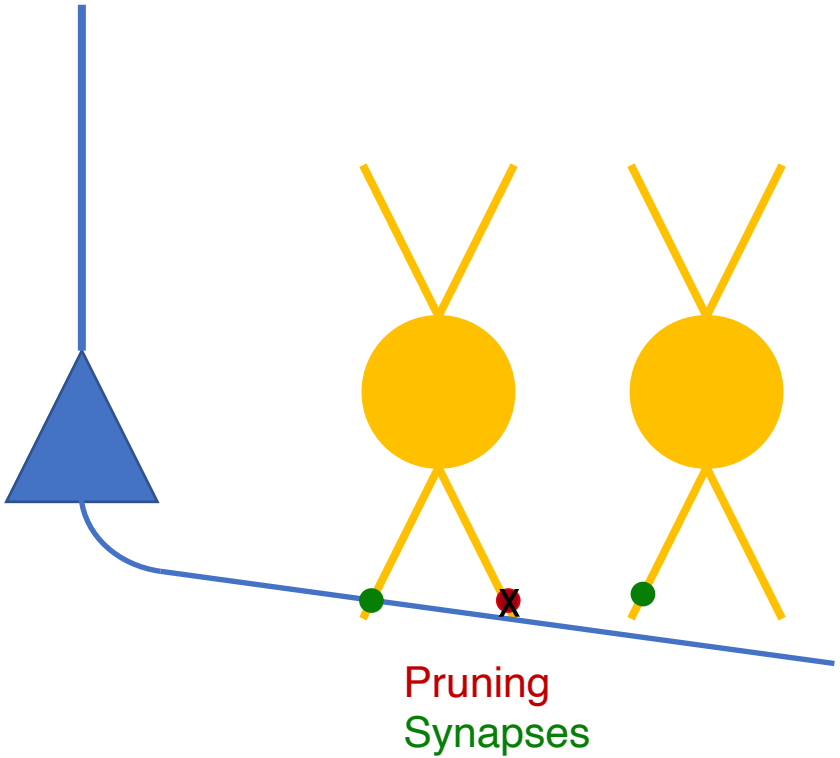
Above threshold

Recap: axon-based approaches

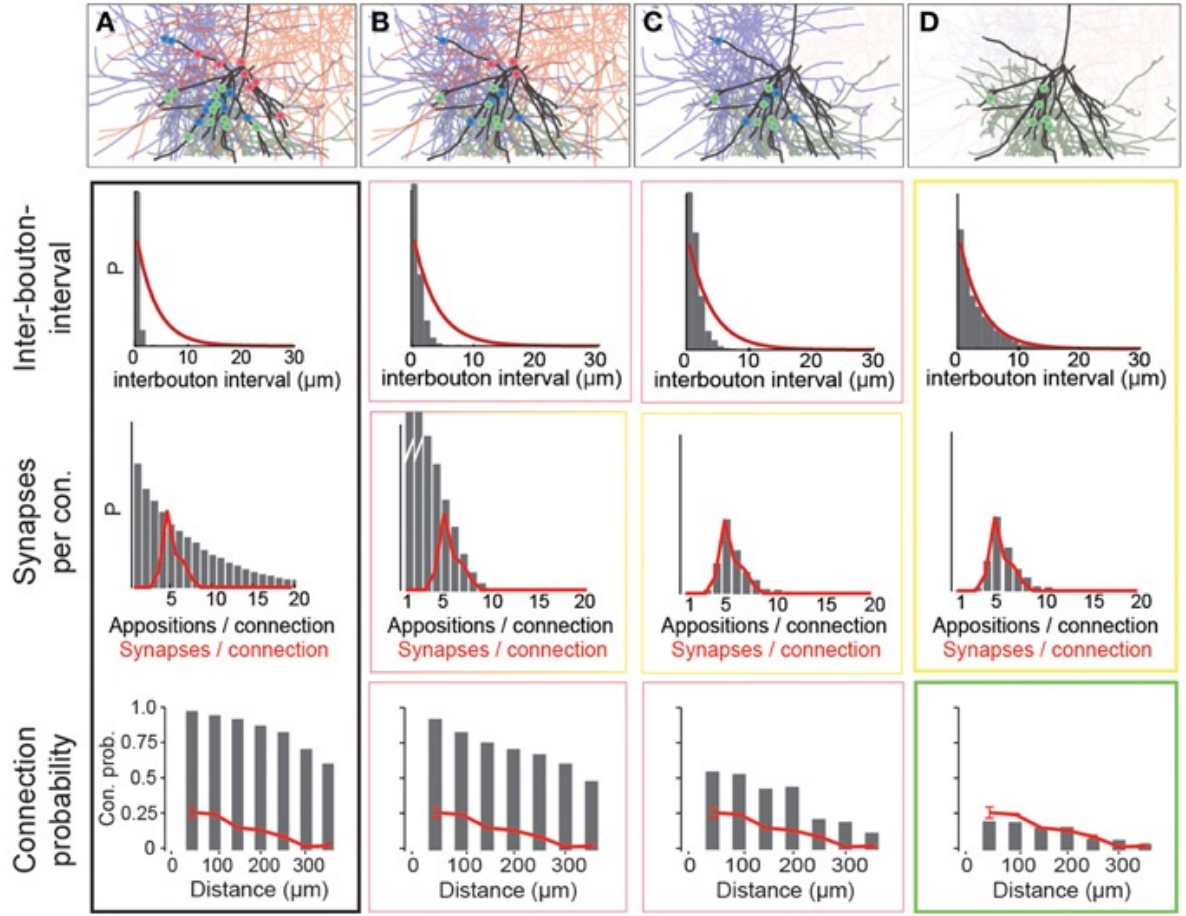


Potential synapses
Appositions
Touches

Recap: axon-based approaches



Reimann et al., 2015



Reimann et al., 2015

1. Tabula rasa rule: virtually all neurons within a layer of a microcircuit are potentially connected
2. Synapse location rule: location of synapses is established by the incidental appositions of semi-randomly placed neurons
3. Fractional conversion rule: while each apposition is a potential synapse, actual synapses form at only a fraction of them
4. Multi-synapse rule: connections always involve multiple synapses
5. Plasticity reserve rule: only a fraction of potential multi-synapse connections are functionally realized

Touch Detector

→ Pruning #1

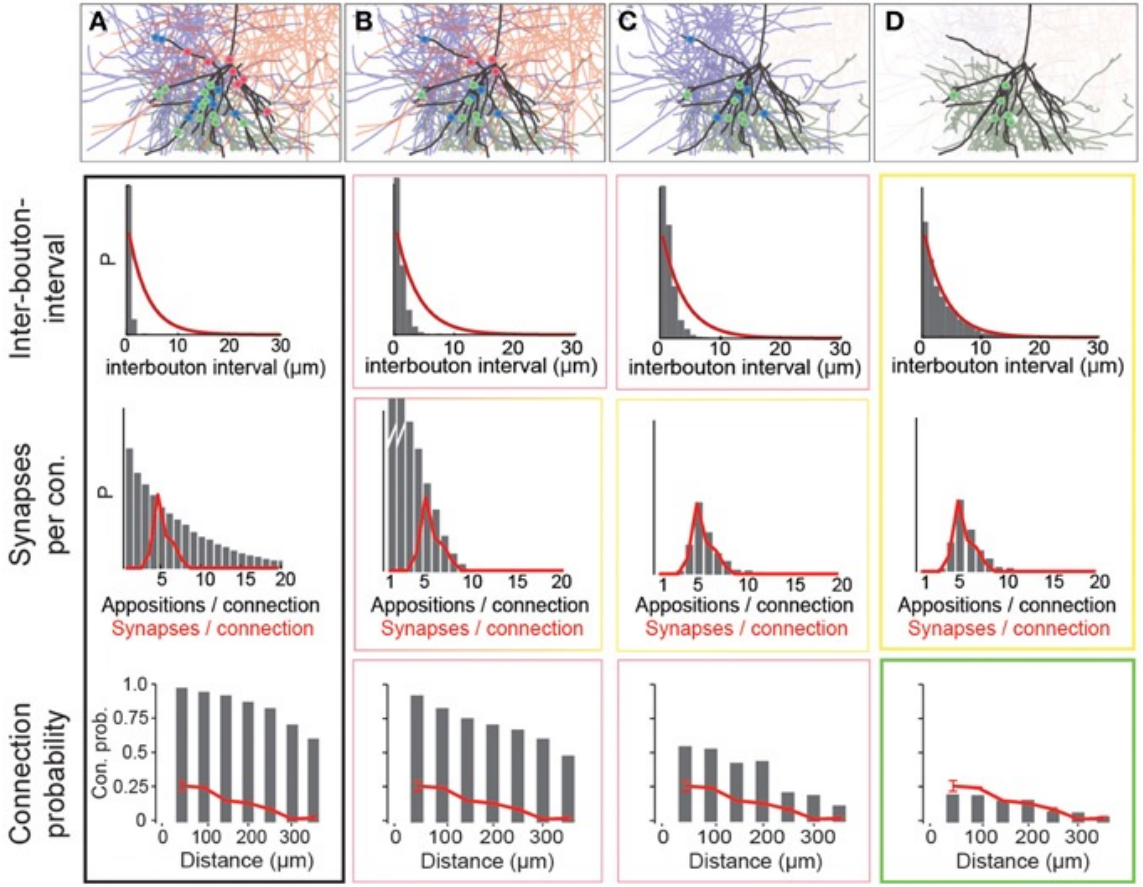
→ Pruning #2

→ Pruning #3

A -> B: general pruning

B -> C: multi-synaptic pruning

C -> D: plasticity-reserve pruning



Reimann et al., 2015

Digital Reconstruction of Neocortical Microcircuitry

Human Brain Project | Blue Brain Project

Home | Microcircuit | Literature Consistency | Experimental Data | Videos | Images | Tools | Downloads | About | Sign In

The Neocortical Microcircuit Collaboration Portal

This portal provides an online public resource of the Blue Brain Project's first release of a digital reconstruction of the microcircuitry of juvenile Rat somatosensory cortex, access to experimental data sets used in the reconstruction, and the resulting models. The following functionality is provided through this portal to support community engagement to use and refine the reconstruction.

- **Neocortical Microcircuit** - an interactive browser of the anatomical and physiological properties of the reconstructed microcircuit, which includes facts and figures, detailed analyses, simulation videos, model and data downloads.
- **Literature Consistency** - a database of published experimental papers that were used either to constrain parameters of the reconstruction directly, or against which the reconstruction was assessed to be quantitatively or qualitatively consistent. This is intended to be an active list that can be discussed and extended by the community.
- **Videos** - a collection of computer generated visualizations of *in silico* experiments.
- **Images** - a collection of images illustrating the various steps in the reconstruction process.
- **Experimental Data** - experimental data sets used in the reconstruction process.
- **Tools** - tools and documentation for reconstructing, simulating and analyzing the reconstruction.
- **Downloads** - downloadable models from the reconstruction.

A quick guide to navigating the portal

Glossary of terms, and abbreviations

For the associated scientific papers, please refer to the following links:

1. The Blue Brain Project Consortium (2015), *Reconstruction and*

Ramaswamy et al., 2015

Summary 2

- Even for a small part of the brain, data are sparse and heterogeneous
- Depending on the approaches used to build our model, we have to specify more or less parameters (e.g. connectivity based on axon or not)
- In any case, we have to make several assumptions
- Be explicit with the assumptions, and list them
- When the model is failing in some validations, it will be easier to revise the assumptions and identify the one that is problematic
- Use validations to verify the assumptions and the resulting model

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Lecture Summary

- Once we build all the blocks of a network, we have to assemble them
- It is not necessarily true that if the building blocks are correct, the assembled artifact is correct as well (see next lecture when we simulate the network)
- Our building blocks are assembled in a space, and defining the space is yet another issue that affects our result
- The problem of data sparseness is even more evident at this stage
- We have to deal with this problem, but strategies exit
- Reconstructing a brain region or the entire brain is now a feasible problem

What you have learn

- Different approaches to consider the volume
- Challenges related to the volume and the cell placement
- Possible strategies to mitigate these challenges. Morphology synthesis
- Generalization and other strategies to fill the gaps