WHAT IS A FLAGSHIP OF ENTERPRISE AND TECHNOLOGY?

Future and Emerging Technology Flagships (FET)

Are ambitious large-scale, informatics-driven, research Initiatives that aim to achieve a visionary goal.

The scientific advance should provide a strong and broad Basis for future technological innovation and economic Exploitation in a variety of areas, as well as novel benefits for society.

The research is collaborative, internally non-competitive, inter- and trans-disciplinary, driven by a commonly agreed road-map

EUROPEAN COMMISSION

FET FLAGSHIPS

BLUE BRAIN PROJECT + NEUROIMAGING COMMUNITY

THE IMPACT OF INFORMATION & COMPUTING TECHNOLOGY

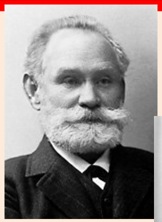
VON NEUMANN MACHINES

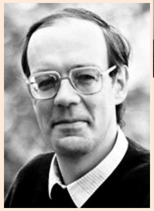
MOORE'S LAW	SUPERCOMPUTING
ENERGY LIMITATIONS	BEYOND EXASCALE
INTERNET	BANDWIDTH & ROUTING [**HTML5, Cisco**]
DATABASE MANAGEMENT	DISTRIBUTED [**Oracle**]
CLOUD ENVIRONMENT	SECURITY [**Amazon, Dropbox, iCloud**]
DATABASE QUERYING & ADDRESSING	LOCAL [**Google**] vs REMOTE [**EPFL**]
REAL-TIME VISUALISATION	FOR SUPERCOMPUTING [**IBM, CRAY**]

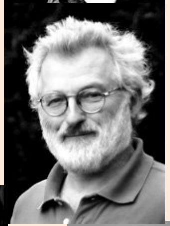
NEUROMORPHIC COMPUTING

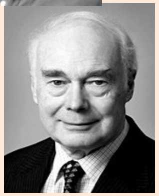
EUROPEAN NOBEL CONTRIBUTIONS TO NEUROSCIENCE

NEUROANATOMY	Golgi & Ramon y Cajal
NEUROPHYSIOLOGY	Pavlov
	Barany
	Sherrington & Adrian
	Von Bekesy
	Eccles, Hodgkin & Huxley, Weisel
	Neher & Sakmann
NEUROPHARMACOLOGY	Dale & Loewi
	Katz & von Euler
	Black
	Carlsson
NEUROIMAGING	Josephson
	Hounsfield
	Mansfield
NEUROSURGERY	Moniz
SOCIAL & COGNITIVE NEUROSCIENCE	Von Frisch, Lorenz & Tinbergen
	Kahneman
GENETICS	*Crick & Wilkins*
	Sanger
	Sulston
IMMUNOLOGY	*Jerne, Milstein & Kohler*
CELL BIOLOGY	*Levi-Montalcini*
	Evans

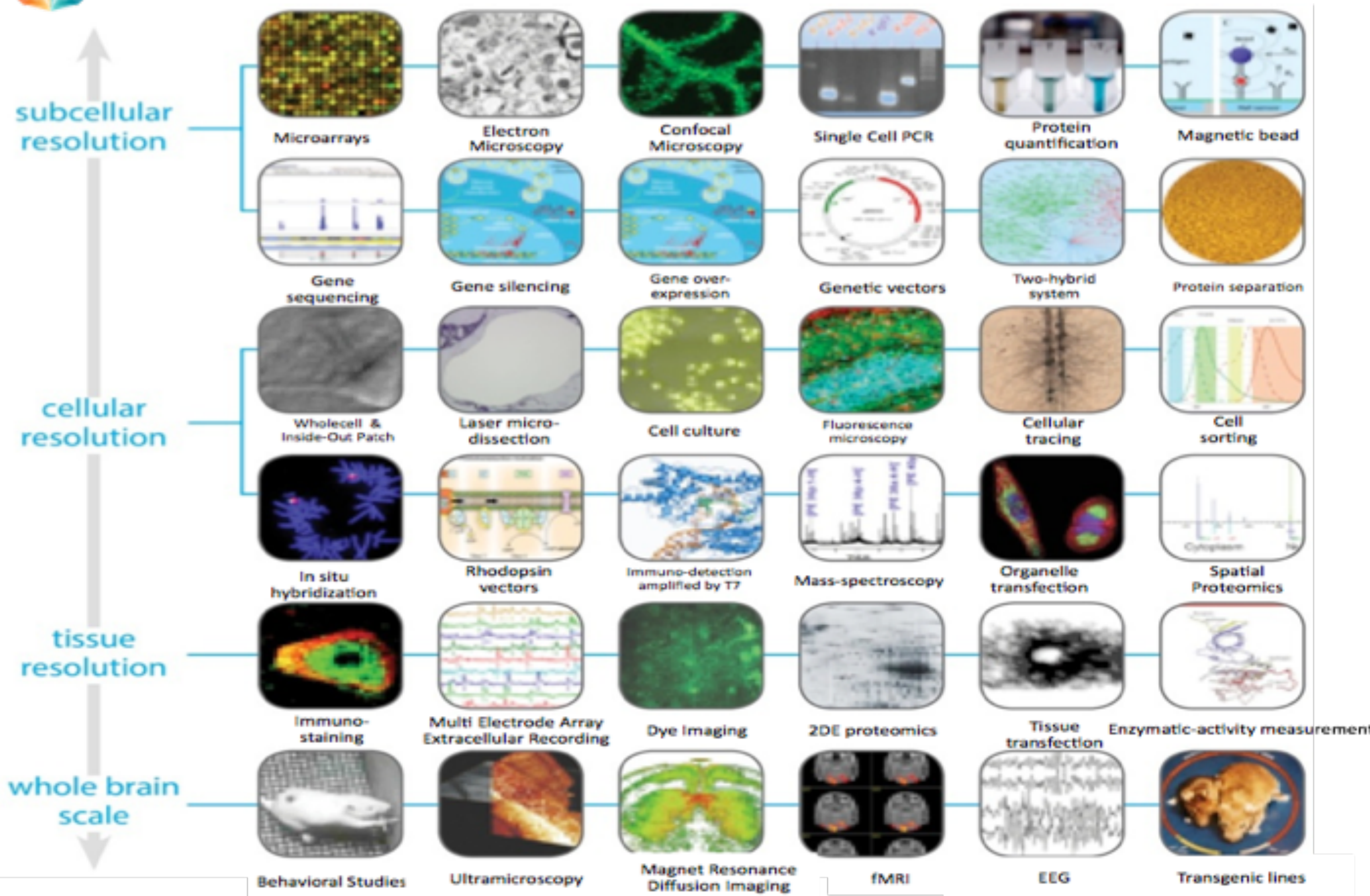






NEUROSCIENCE METHODS



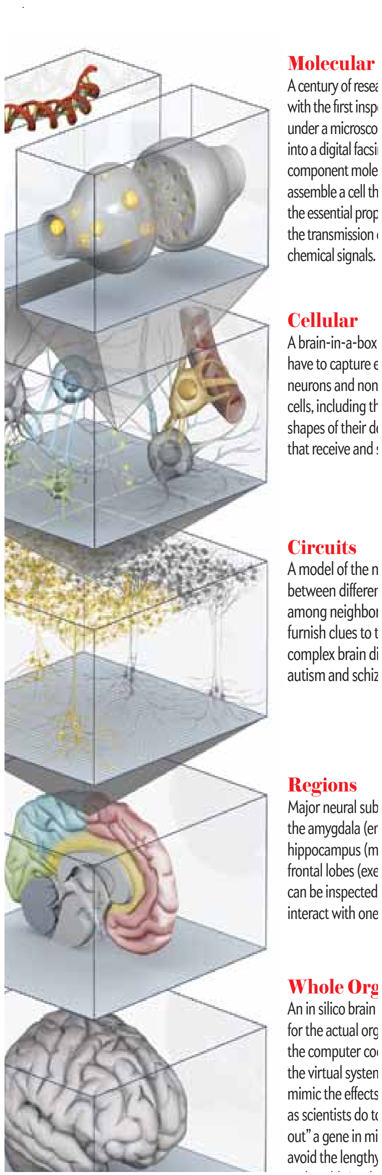
MOTIVATION 1 – DATA DELUGE - FEDERATION & INTEGRATION

The facts:

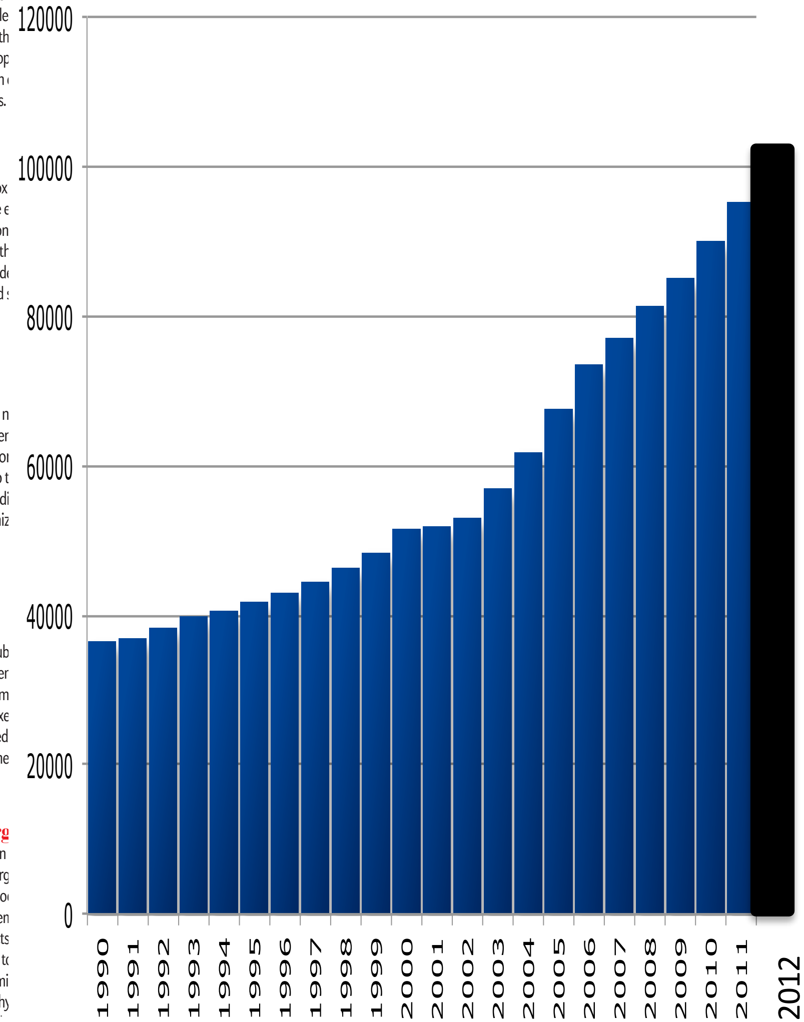
1. Data and knowledge is **growing** exponentially
2. Data and knowledge are increasingly **fragmented**
3. Benefits for society seem to be **decreasing**
4. Economic burden increasing to **unsustainable** levels

The causes:

1. No integration plan
2. No data curation plan
3. No plan to link across levels
4. No plan to transfer knowledge from animal model to human
5. No plan to go beyond traditional classification of diseases



Number of Peer Reviewed Publications on the brain /yr



SIMULATION TO DERIVE A BLUEPRINT OF THE BRAIN AT ALL SPATIAL SCALES FROM GENES TO COGNITION

GOAL

DEVELOP INFORMATICS TECHNOLOGY TO UNIFY OUR UNDERSTANDING OF THE HUMAN BRAIN

CONFRONTING PARADIGMS

CARTESIAN MODEL (TOP DOWN)

Mentally generated hypothesis
Mathematically expressed in a model
Confrontation with "relevant" data
Parameterisation and optimisation of model

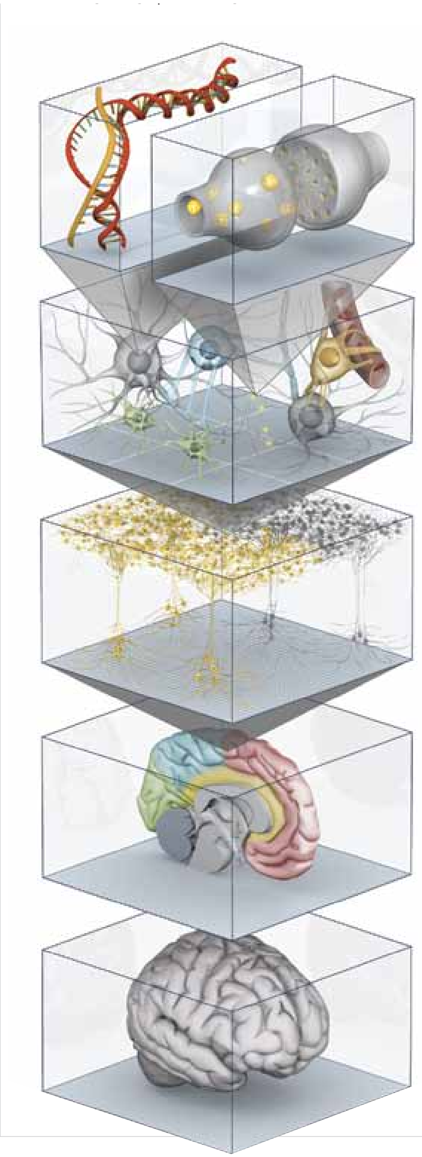
Correlations (non-causal)

SIMULATION MODEL (BOTTOM UP)

Multimodal and multivariate data
Exhaustive mining to demonstrate coherent models
Exploration of these mathematical models as generated hypotheses
Investigation of hypotheses – clinical, mechanistic, prognostic, therapeutic

Knowledge (& causes)

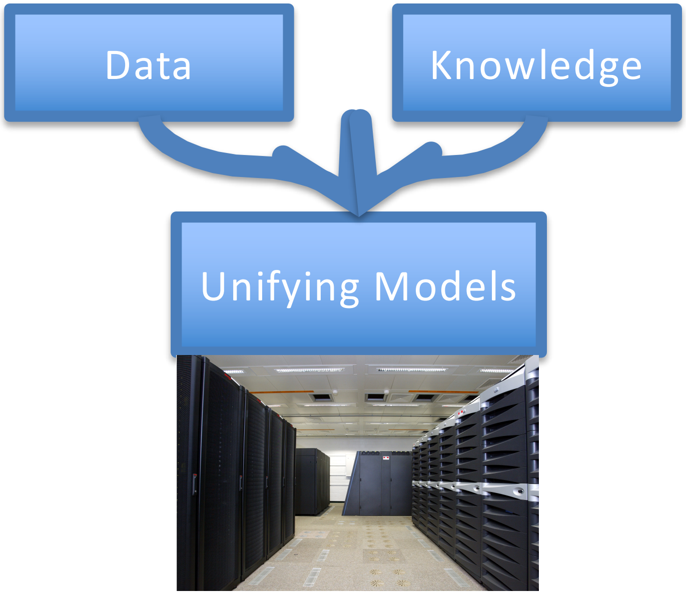
BRAIN SIMULATION

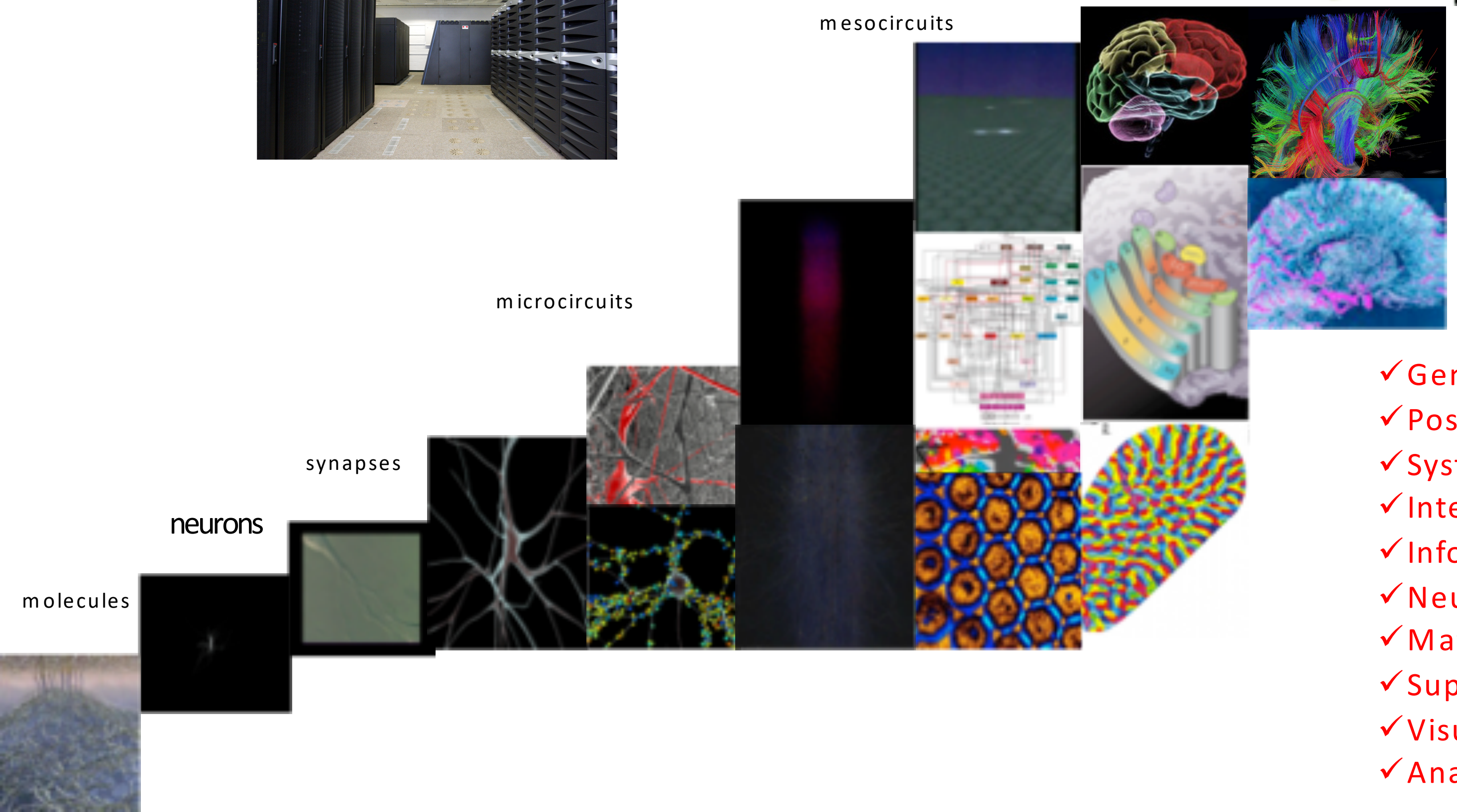


PROVIDE A THEORETICAL FRAMEWORK FOR HUMAN BRAIN ORGANISATION AND FUNCTION

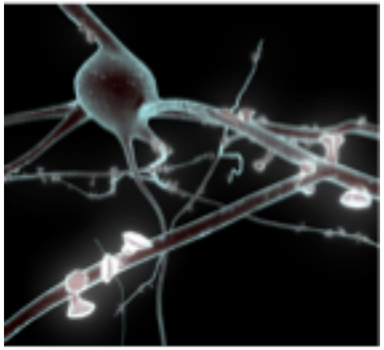
1. Increase the value of all past and future experiments
2. Gather and organize all fragments of data and knowledge on the brain
3. Provide open accessible brain atlases
4. Fill knowledge gaps using novel ICT tools
5. Generate strategically selected missing data that will not be generated otherwise
6. Prioritize, optimize and accelerate biological experiments

Simulation-Based Brain Research





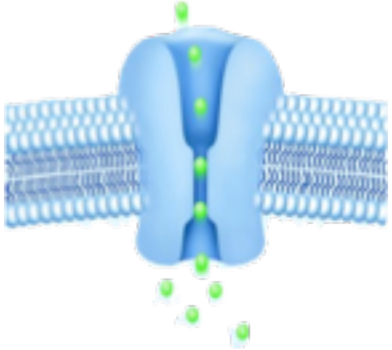
- ✓Genomics
- ✓Post-Genomics…
- ✓Systems Biology…
- ✓Integrative Biology…
- ✓Informatics…
- ✓Neuroscience…
- ✓Mathematical Modeling…
- ✓Supercomputer Simulation …
- ✓Visualization…
- ✓Analysis…



NEURONS

10,000 neurons

~ 4,000,000
Electrical compartments
(Rall Equations)



ION CHANNELS

80,000,000 Ion Channels

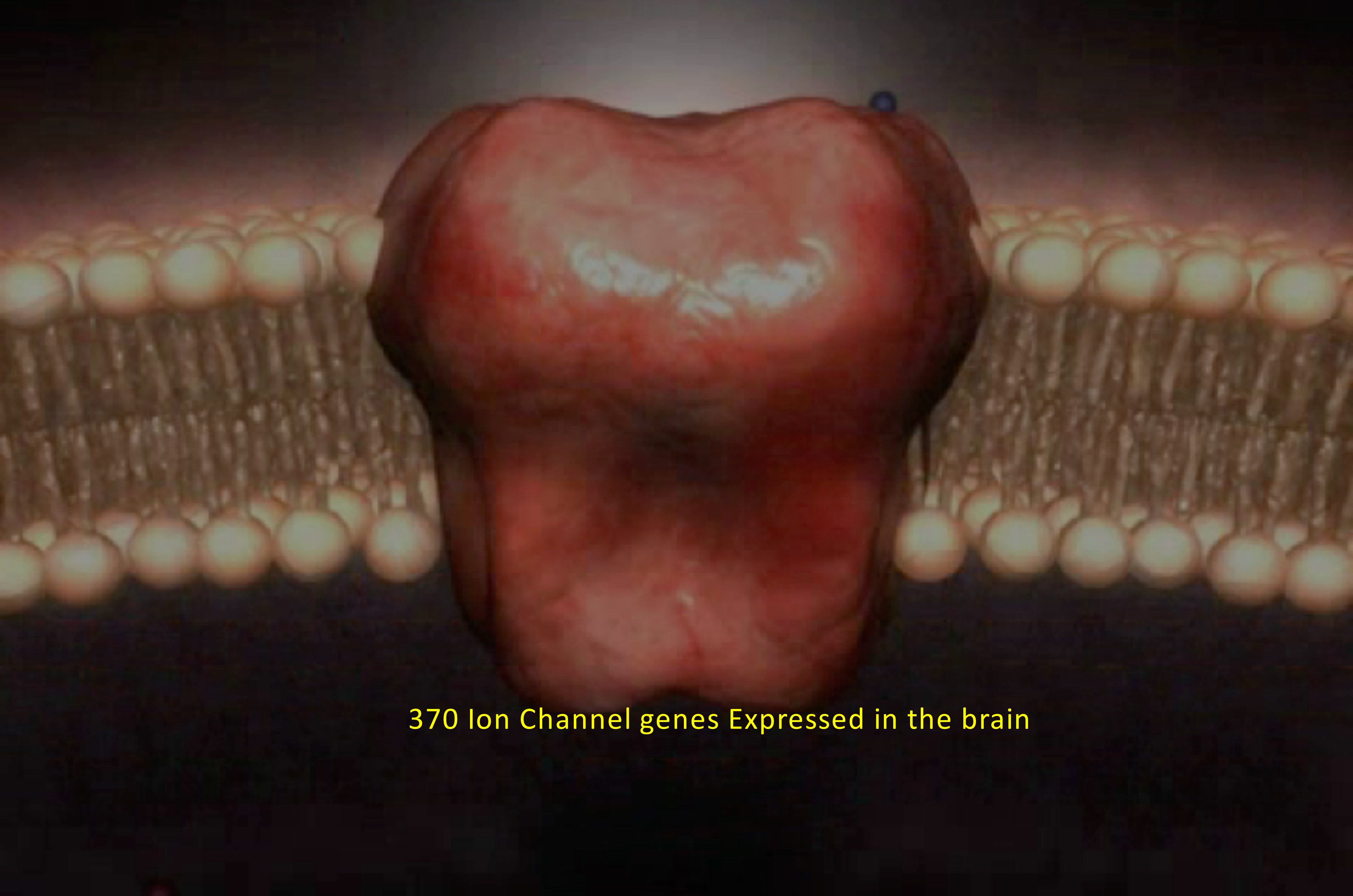
(Hodgkin-Huxley Equations)

SYNAPSES

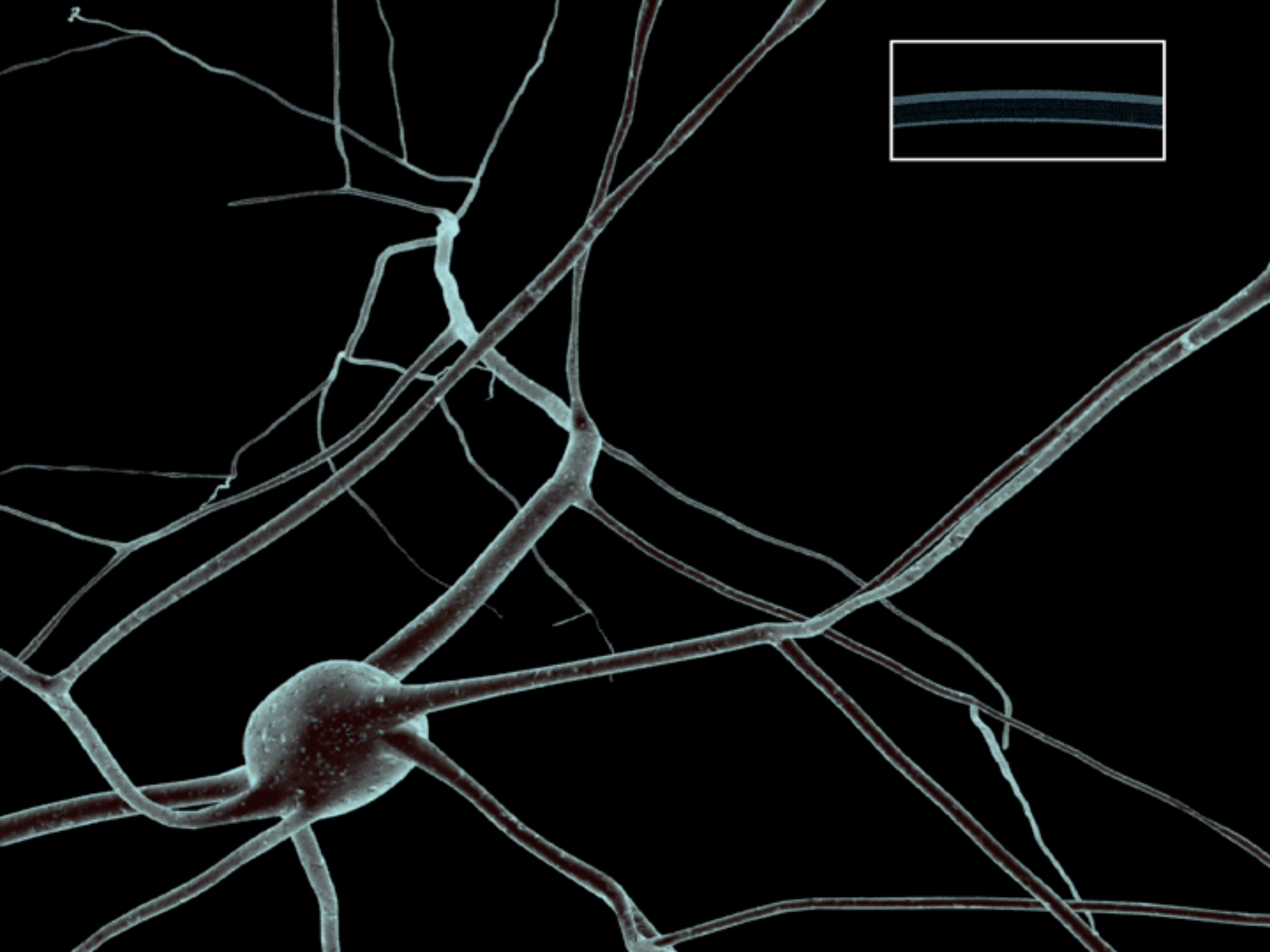
10,000,000 Synapses

(Tsodyks-Markram Equations)

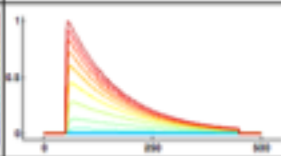
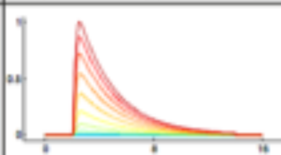
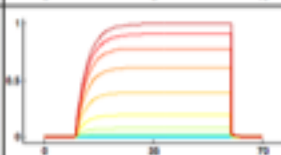
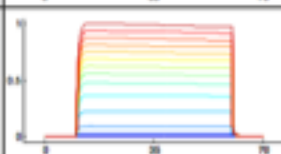
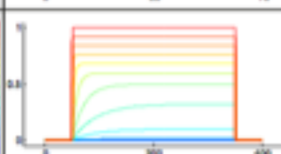
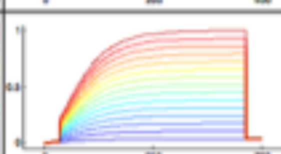
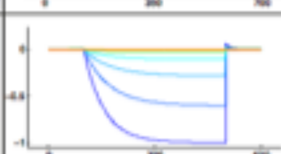
Combination of ion channels determines the electrical phenotype

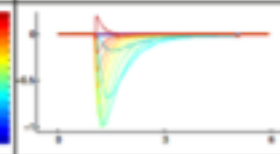
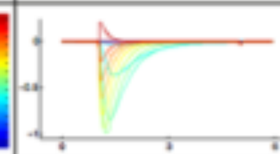
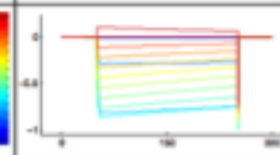
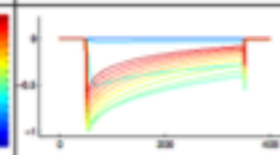
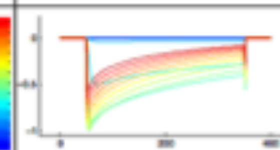
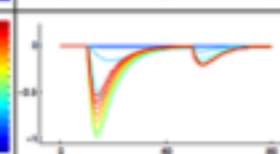


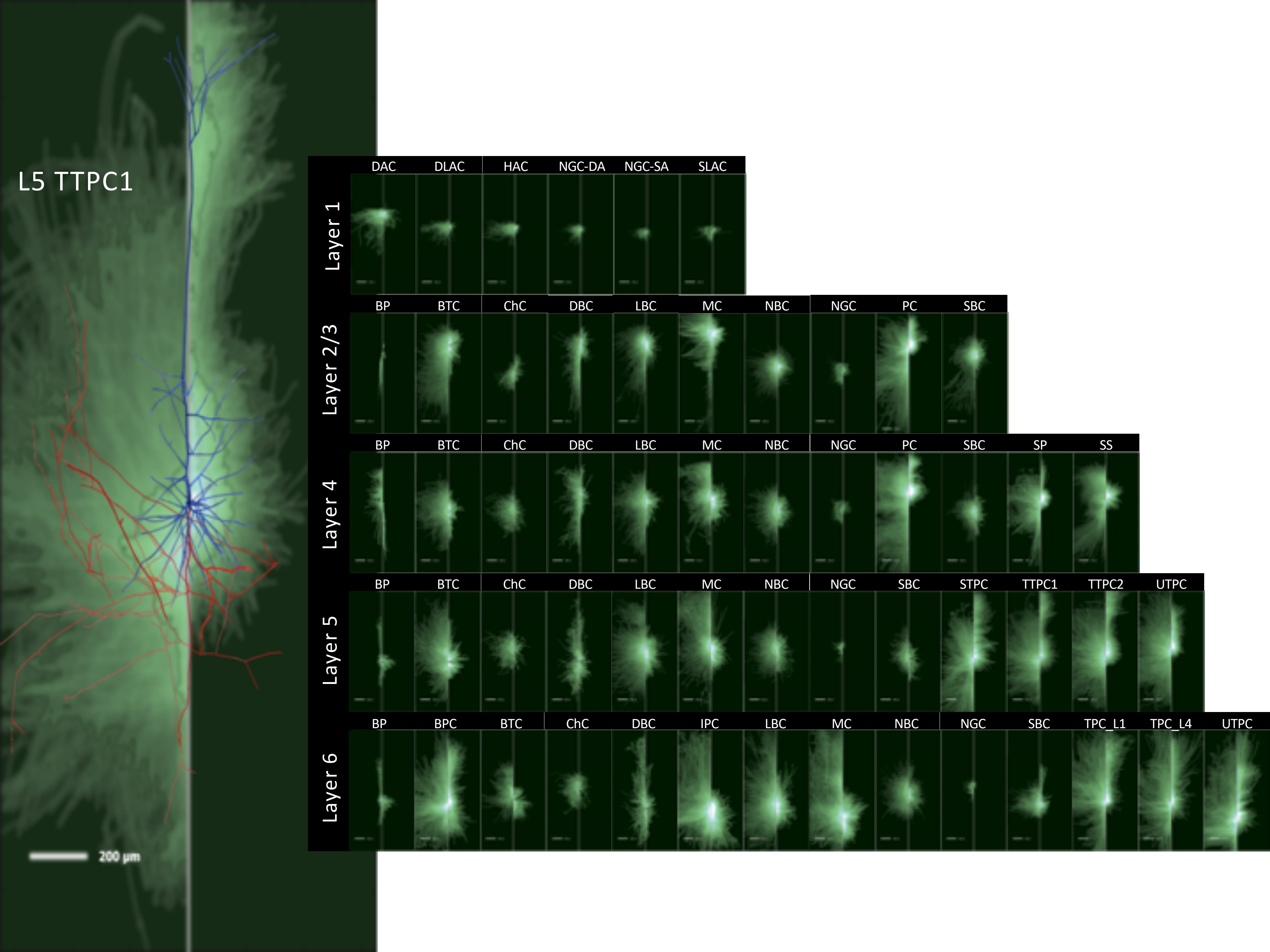
370 Ion Channel genes Expressed in the brain



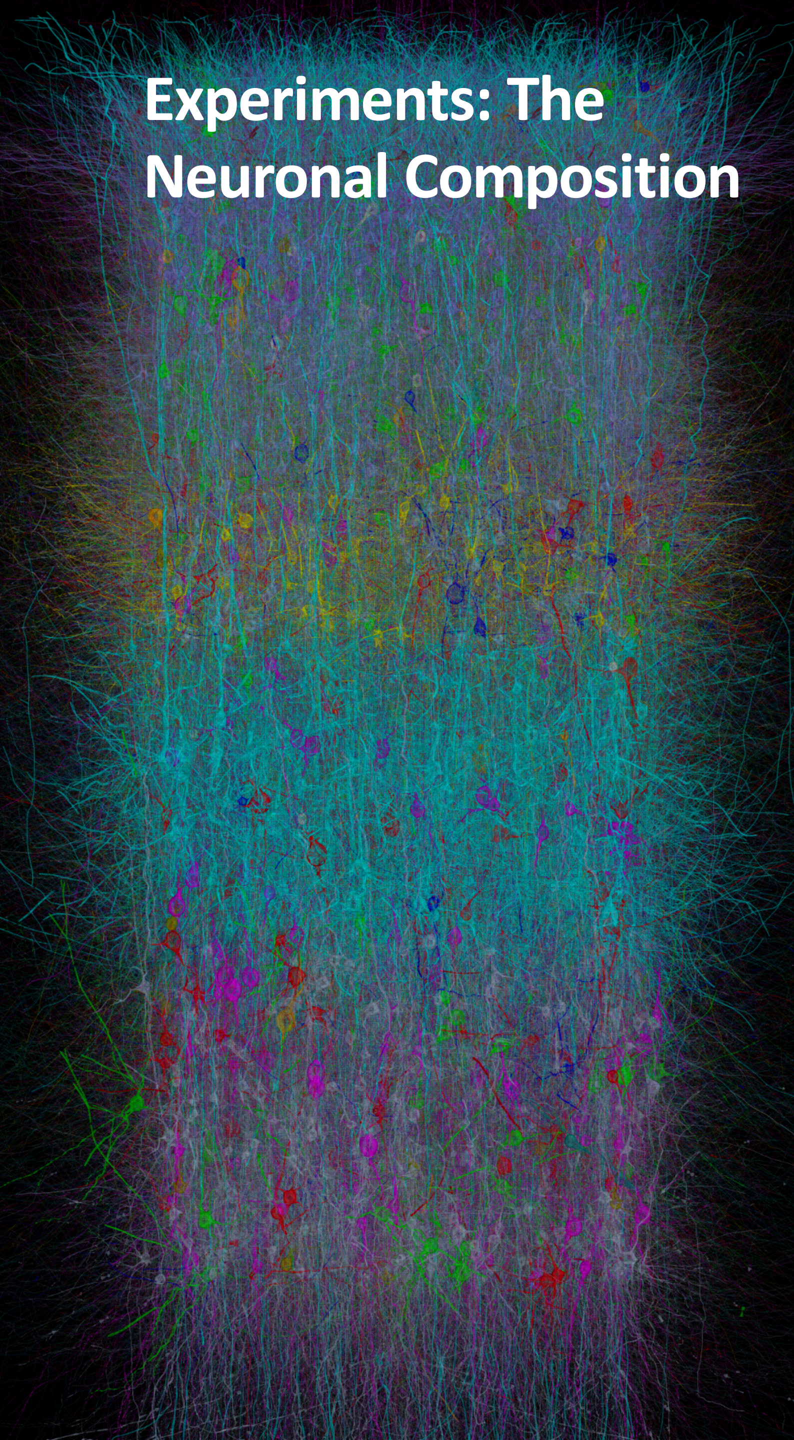
HH Ion Channel Models

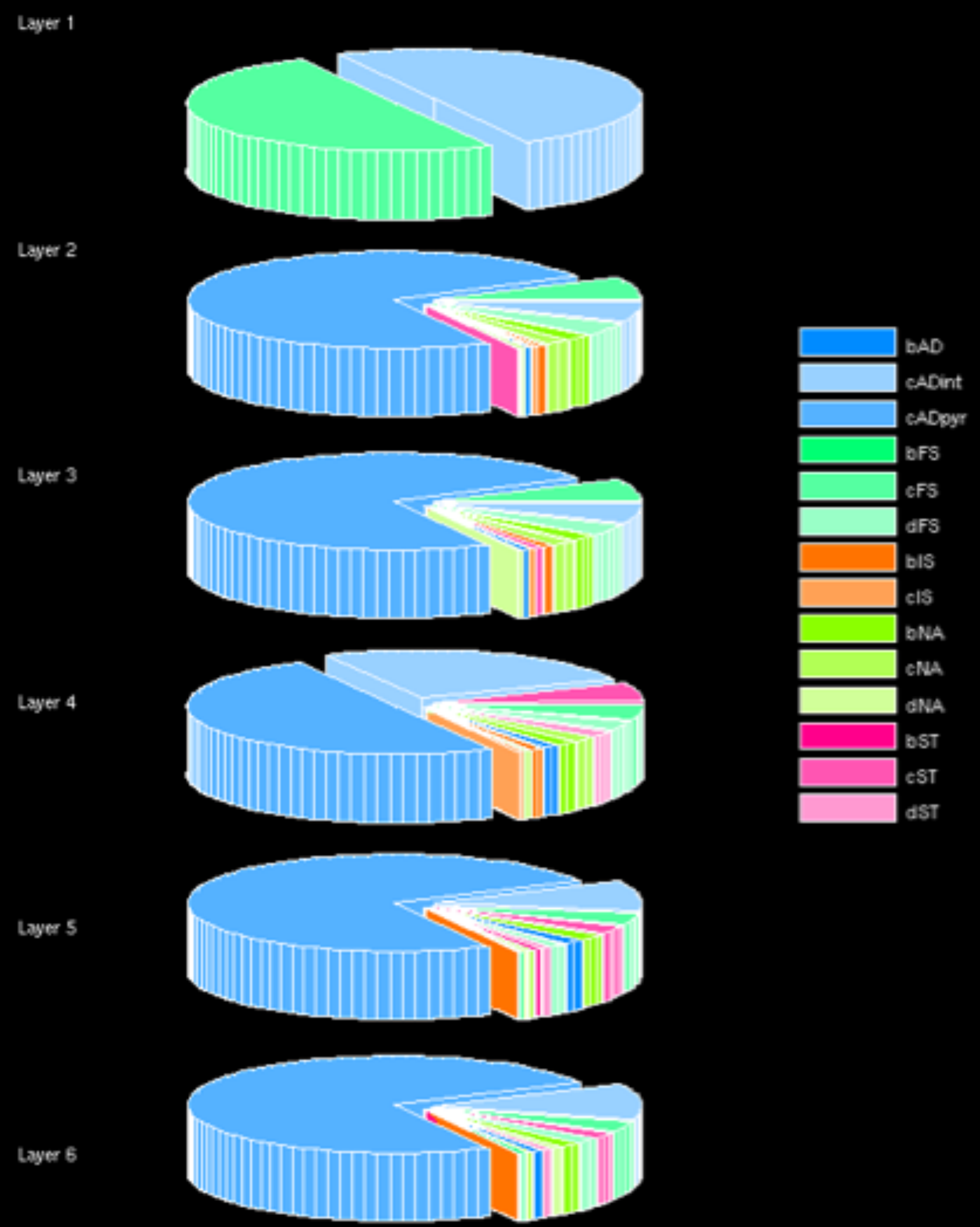
Ion channels	Kinetics	Parameters
Slow potassium (Kp) Ref: Details:		Ion = K^+ Rev = -85mV $g=m^2h$ $m_\infty=(1/(1+\exp(-(v+1)/12)))$ m_τ=if (v < -50) : $(1.25+175.03*\exp(-v*-0.026))/qt$ else : $((1.25+13*\exp(-v*0.026)))/qt$ $h_\infty=1/(1+\exp(-(v+54)/-11))$ $h_\tau=(360+(1010+24*(v+55))*\exp(-((v+75)/48)^2))/qt$
Fast potassium (Kt) Ref: Details:		Ion = K^+ Rev = -85mV $g=m^4h$ $m_\infty=1/(1+\exp(-(v+0)/19))$ $m_\tau=(0.34+0.92*\exp(-((v+71)/59)^2))/qt$ $h_\infty=1/(1+\exp(-(v+66)/-10))$ $h_\tau=(8+49*\exp(-((v+73)/23)^2))/qt$
Kv3.1 potassium (Kv3.1) Ref: Details:		Ion = K^+ Rev = -85mV $g=m$ $m_\infty=1/(1+\exp(((v-(18.700))/(-9.700))))$ $m_\tau=0.2*20.00/(1+\exp(((v-(-46.560))/(-44.140))))$
Delayed potassium (Kd) Ref: Details:		Ion = K^+ Rev = -85mV $g=mh$ $m_\infty=1-1/(1+\exp((v--43)/8))$ $m_\tau=0.6$ $h_\infty=1/(1+\exp((v--67)/7.3))$ $h_\tau=1500$
m current (Im) Ref: Details:		Ion = K^+ Rev = -85mV $g=m$ $m_\infty=m_\alpha/(m_\alpha+m_\beta)$ $m_\tau=1.0/(m_\alpha+m_\beta)$ $m_\alpha=3.3e-3*\exp(2.5*0.04*(v--35))$ $m_\beta=3.3e-3*\exp(-2.5*0.04*(v--35))$
Small conductance (Sk) Ref: Details:		Ion = K^+ Rev = -85mV $g=m$ $m_\infty=1.0/(1.0+(0.00043/ca)^{4.8})$ $m_\tau=1.0$
Hyperpolarization activated(Ih) Ref: Details:		Ion = K^+ Rev = -85mV $g=m$ $m_\infty=m_\alpha/(m_\alpha+m_\beta)$ $m_\tau=1.0/(m_\alpha+m_\beta)$ $m_\alpha=0.001*6.43*(v+154.9)/(\exp((v+154.9)/11.9)-1))$ $m_\beta=0.001*193*\exp(v/33.1))$

Ion channels	Kinetics	Parameters
Fast sodium (NaTa) Ref: Details:		Ion = K^+ Rev = -85mV $g=m^3h$ $m_\infty=m_\alpha/(m_\alpha+m_\beta)$ $m_\tau=1.0/(m_\alpha+m_\beta)$ $h_\infty=h_\alpha/(h_\alpha+h_\beta)$ $h_\tau=1.0/(h_\alpha+h_\beta)$ $m_\alpha=(0.182*(v--38))/(1-(\exp(-(v--38)/6)))$ $m_\beta=(0.124*(-v-38))/(1-(\exp(-(-v-38)/6)))$ $h_\alpha=(-0.015*(v--66))/(1-(\exp((v--66)/6)))$ $h_\beta=(-0.015*(-v-66))/(1-(\exp((-v-66)/6)))$
Fast sodium (Nats) Ref: Details:		Ion = K^+ Rev = -85mV $g=m^3h$ $m_\infty=m_\alpha/(m_\alpha+m_\beta)$ $m_\tau=1.0/(m_\alpha+m_\beta)$ $h_\infty=h_\alpha/(h_\alpha+h_\beta)$ $h_\tau=1.0/(h_\alpha+h_\beta)$ $m_\alpha=(0.182*(v--32))/(1-(\exp(-(v--32)/6)))$ $m_\beta=(0.124*(-v-32))/(1-(\exp(-(-v-32)/6)))$ $h_\alpha=(-0.015*(v--60))/(1-(\exp((v--60)/6)))$ $h_\beta=(-0.015*(-v-60))/(1-(\exp((-v-60)/6)))$
Persistent sodium (Nap) Ref: Details:		Ion = K^+ Rev = -85mV $g=m^3h$ $m_\infty=1.0/(1+\exp((v--52.6)/-4.6))$ $h_\infty=1.0/(1+\exp((v--48.8)/10))$ $m_\tau=6.0/(m_\alpha+m_\beta)$ $h_\tau=1.0/(h_\alpha+h_\beta)$ $m_\alpha=(0.182*(v--38))/(1-(\exp(-(v--38)/6)))$ $m_\beta=(0.124*(-v-38))/(1-(\exp(-(-v-38)/6)))$ $h_\alpha=-2.88e-6*(v+17)/(1-\exp((v+17)/4.63))$ $h_\beta=6.94e-6*(v+64.4)/(1-\exp(-(v+64.4)/2.63))$
Generic Calcium (Ca) Ref: Details:		Ion = K^+ Rev = -85mV $g=m^2h$ $m_\infty=m_\alpha/(m_\alpha+m_\beta)$ $m_\tau=1.0/(m_\alpha+m_\beta)$ $h_\infty=h_\alpha/(h_\alpha+h_\beta)$ $h_\tau=1.0/(h_\alpha+h_\beta)$ $m_\alpha=(0.055*(-27-v))/(\exp((-27-v)/3.8)-1)$ $m_\beta=(0.94*\exp((-75-v)/17))$ $h_\alpha=(0.000457*\exp((-13-v)/50))$ $h_\beta=(0.0065/(\exp((-v-15)/28)+1))$
High voltage activated (CaHVA) Ref: Details:		Ion = K^+ Rev = -85mV $g=m^2h$ $m_\infty=m_\alpha/(m_\alpha+m_\beta)$ $m_\tau=1.0/(m_\alpha+m_\beta)$ $h_\infty=h_\alpha/(h_\alpha+h_\beta)$ $h_\tau=1.0/(h_\alpha+h_\beta)$ $m_\alpha=(0.055*(-27-v))/(\exp((-27-v)/3.8)-1)$ $m_\beta=(0.94*\exp((-75-v)/17))$ $h_\alpha=(0.000457*\exp((-13-v)/50))$ $h_\beta=(0.0065/(\exp((-v-15)/28)+1))$
Low voltage activated (CaLVA) Ref: Details:		Ion = K^+ Rev = -85mV $g=m^2h$ $m_\infty=1.0/(1+\exp((v--30.0)/-6))$ $m_\tau=(5.0+20.0/(1+\exp((v--25.0)/5)))/qt$ $h_\infty=1.0/(1+\exp((v--80.0)/6.4))$ $h_\tau=(20.0+50.0/(1+\exp((v--40.0)/7)))/qt$
Stochastic potassium (IK) Ref: Details:		

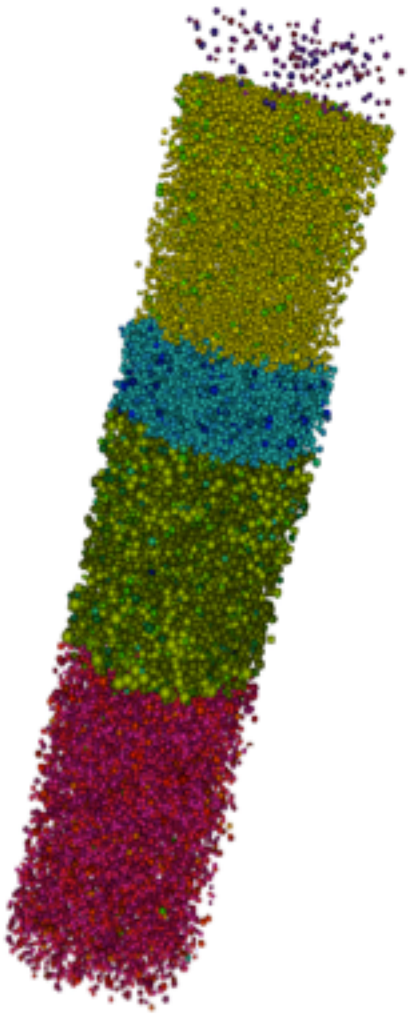

L5 TTPC1
200 µm
Layer 1
DAC DLAC HAC NGC-DA NGC-SA SLAC
Layer 2/3
BP BTC ChC DBC LBC MC NBC NGC PC SBC
Layer 4
BP BTC ChC DBC LBC MC NBC NGC PC SBC SP SS
Layer 5
BP BTC ChC DBC LBC MC NBC NGC SBC STPC TTPC1 TTPC2 UTPC
Layer 6
BP BPC BTC ChC DBC IPC LBC MC NBC NGC SBC TPC_L1 TPC_L4 UTPC

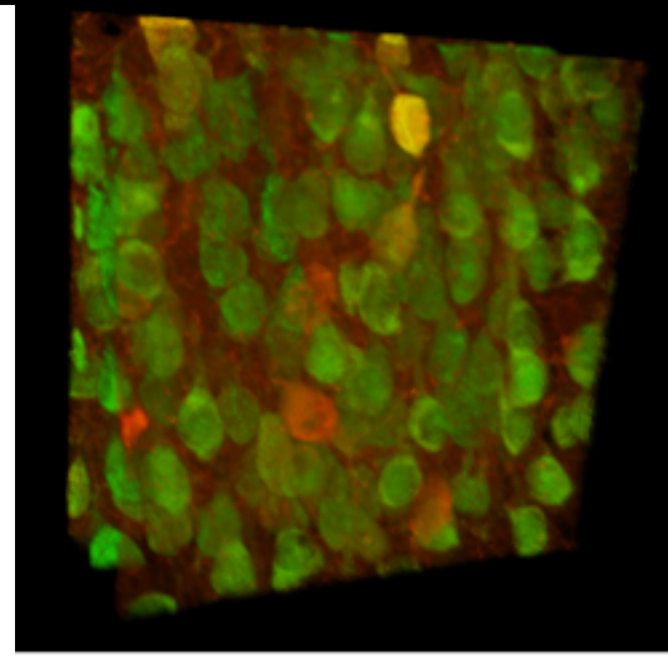
Experiments: The Neuronal Composition



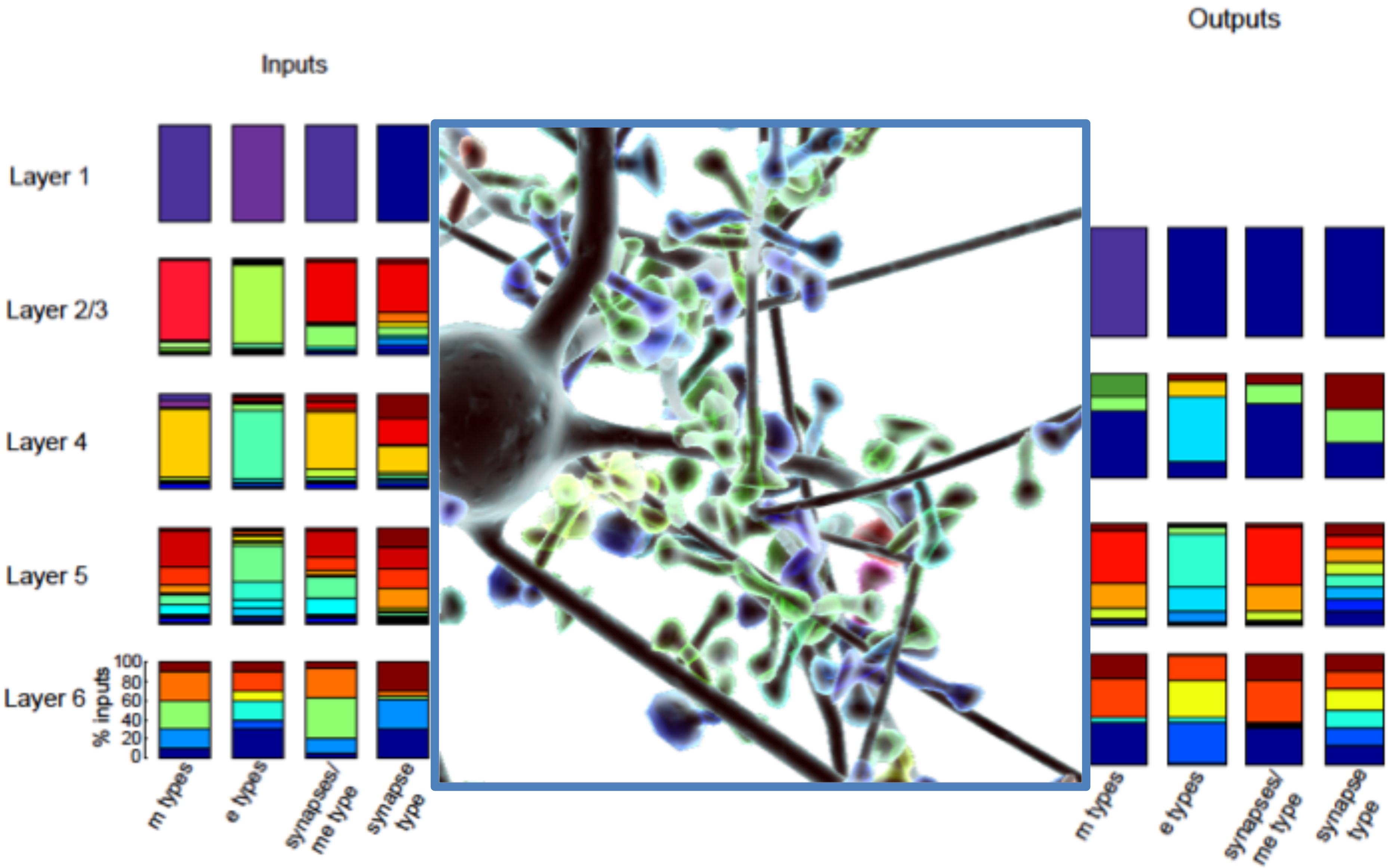


Neuronal Densities and E:I Proportions



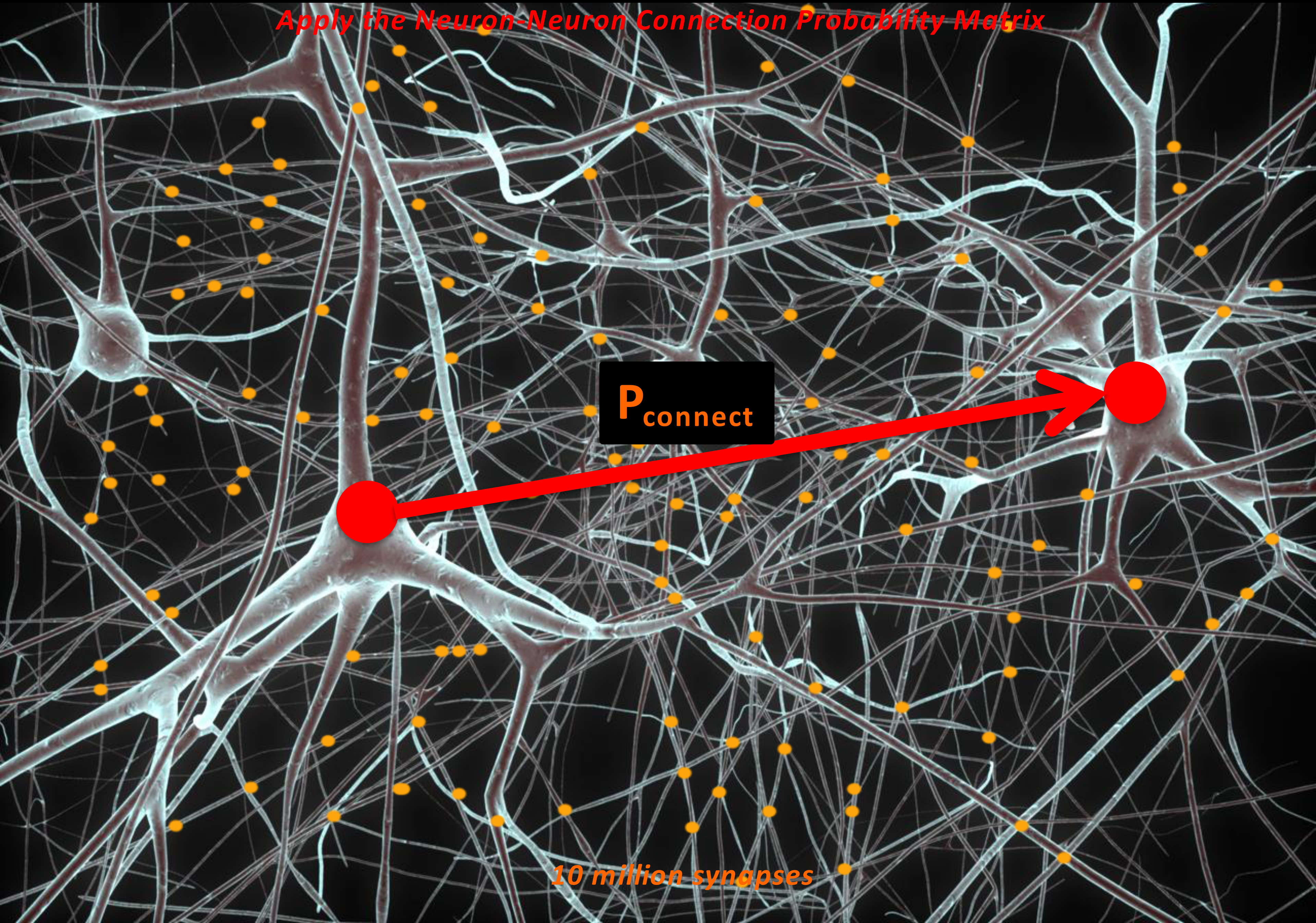


Predicting extrinsic connectivity

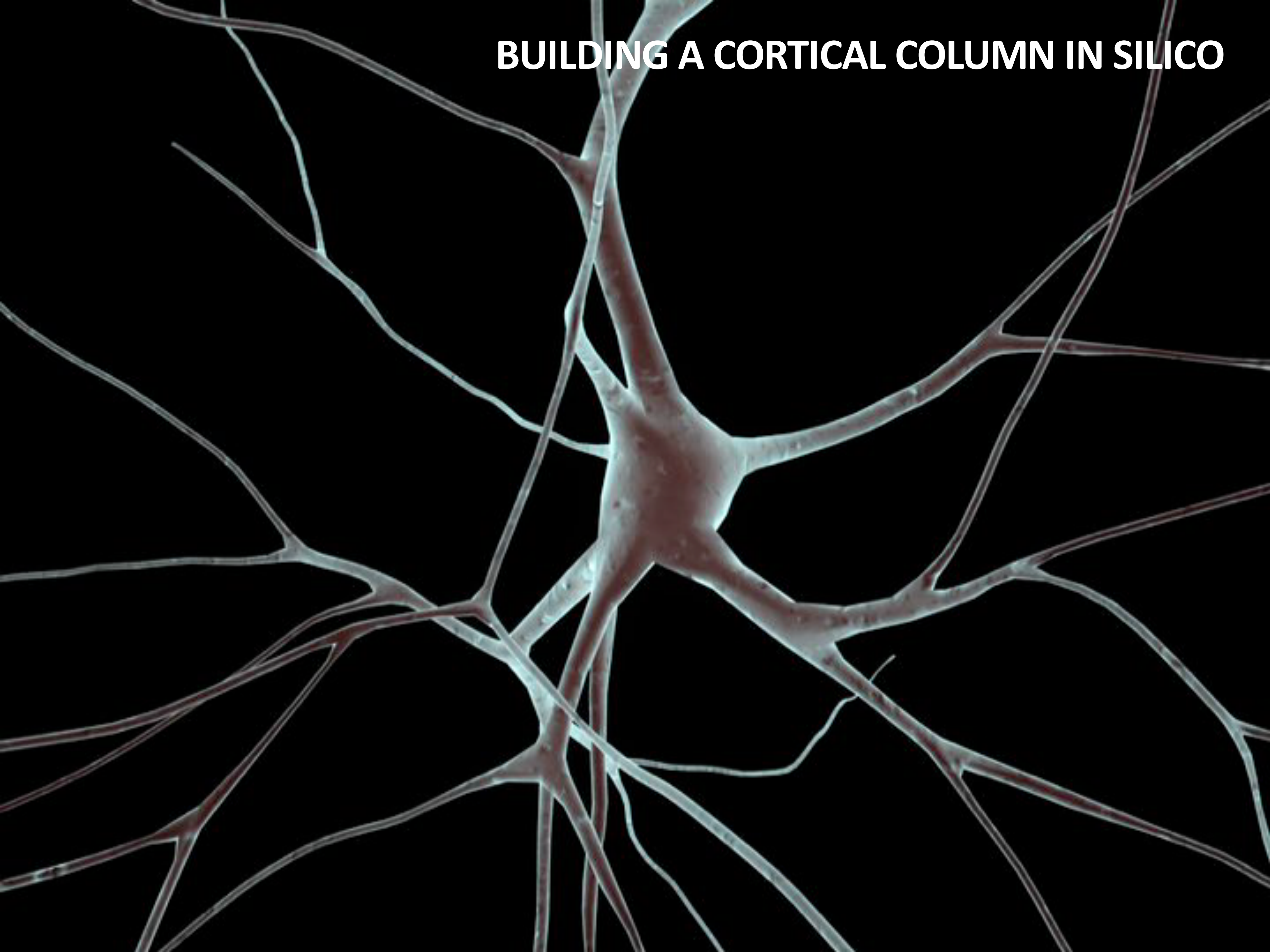


Building: the structural connectome

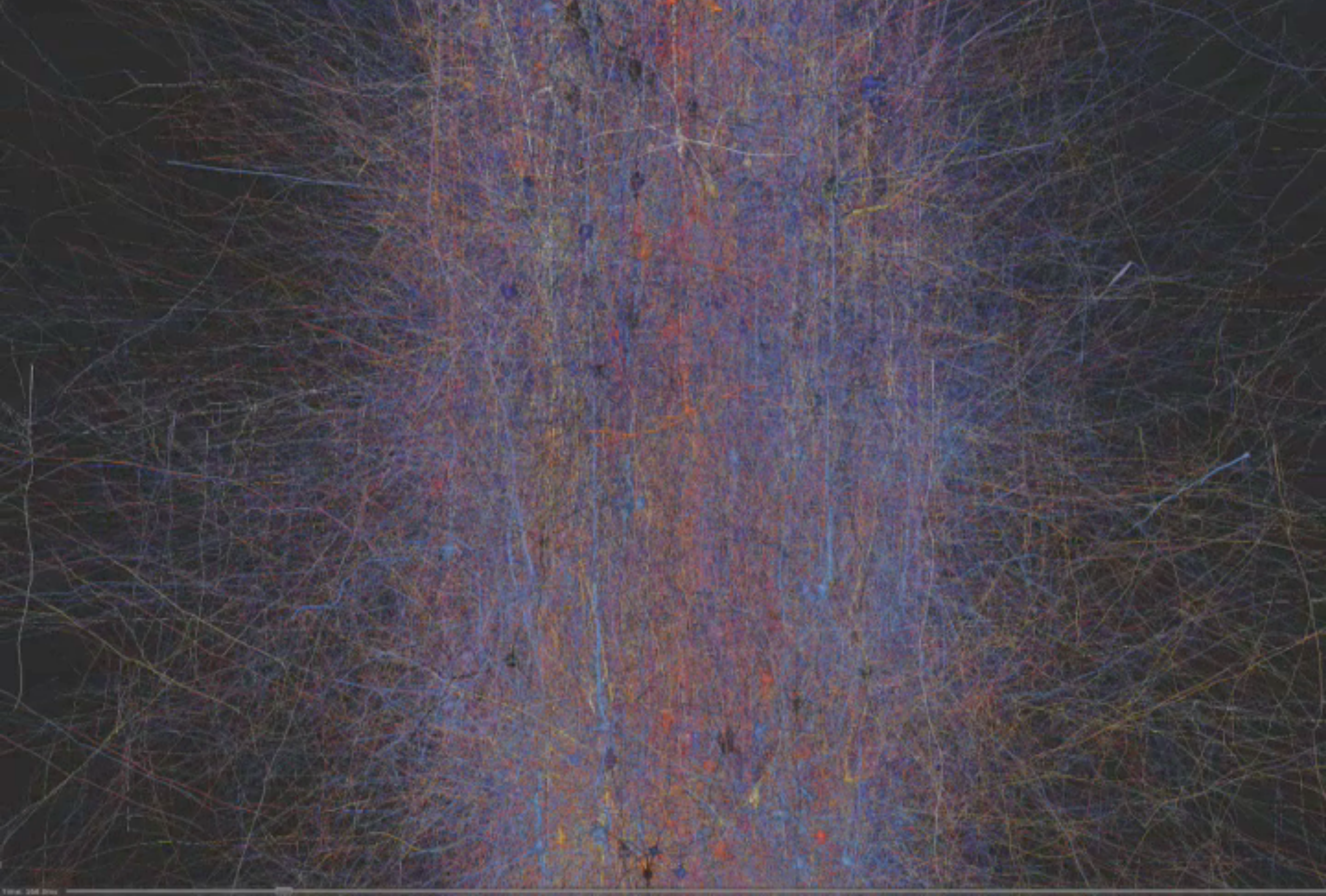
Building: the functional connectome

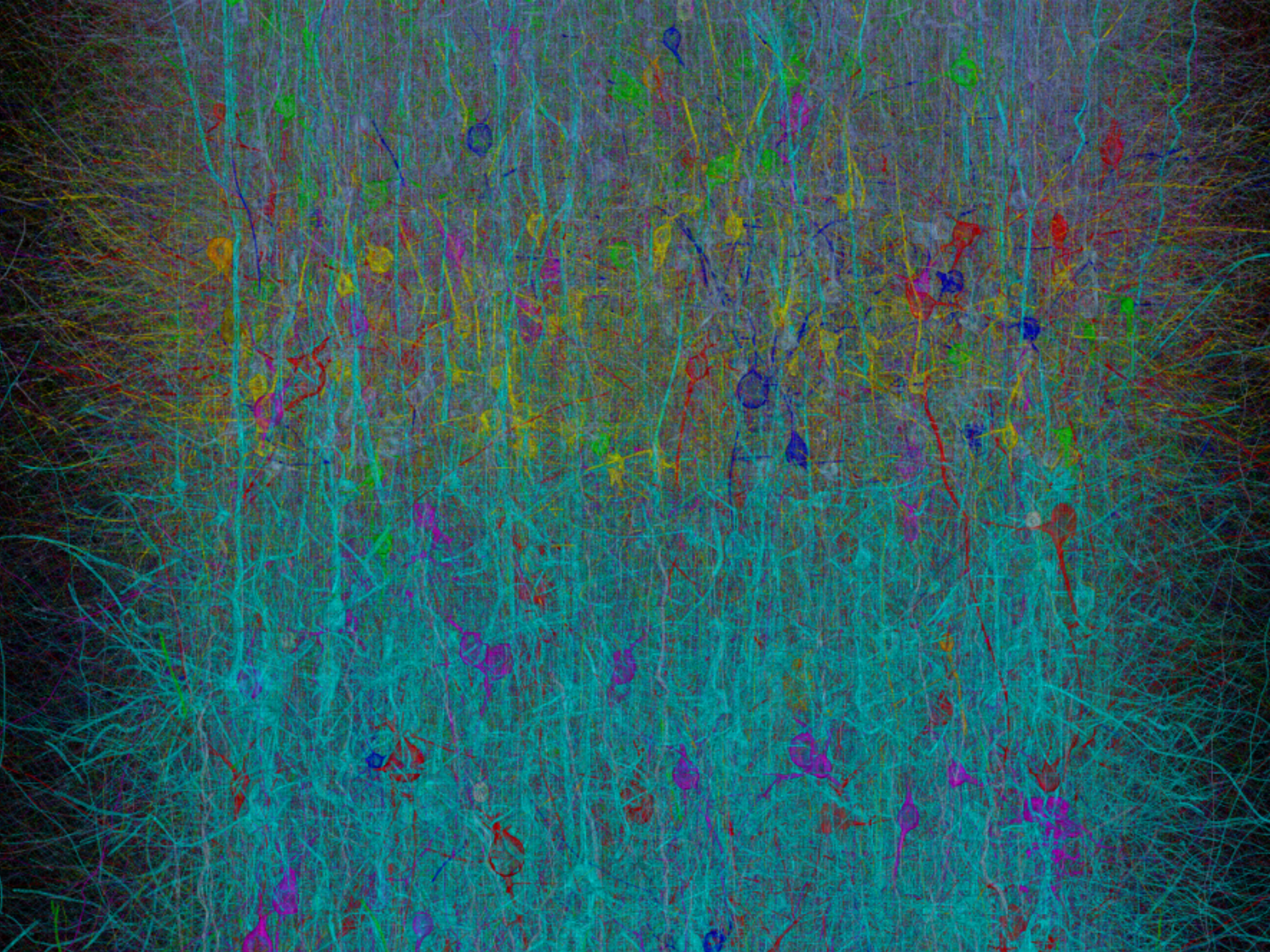


BUILDING A CORTICAL COLUMN IN SILICO

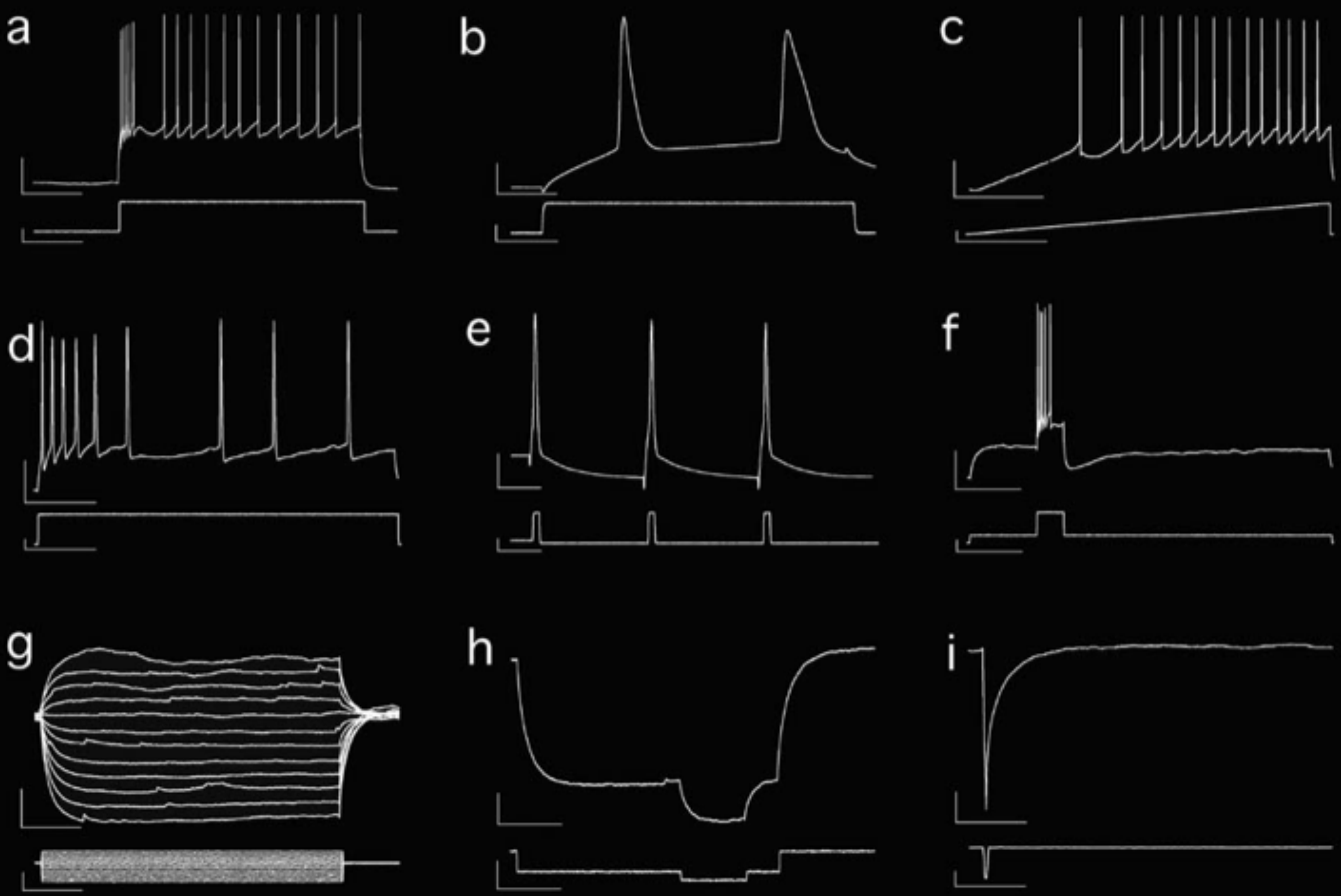


A SIMULATED CORTICAL COLUMN

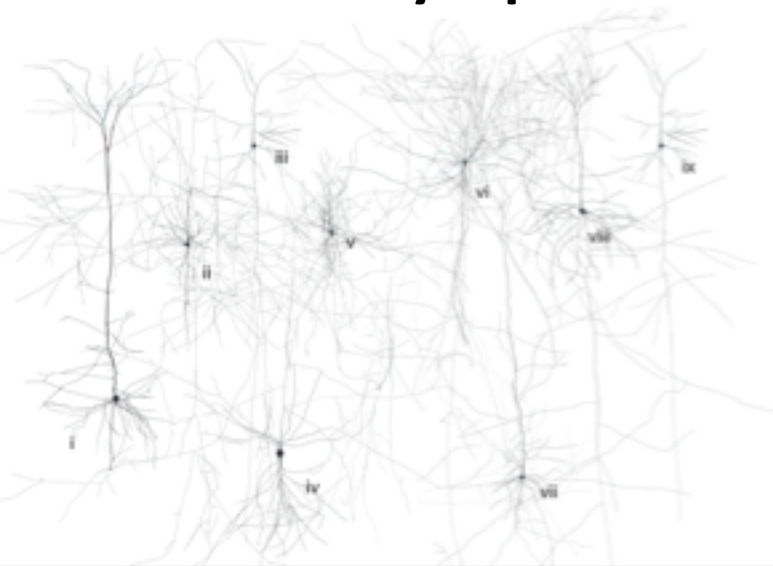


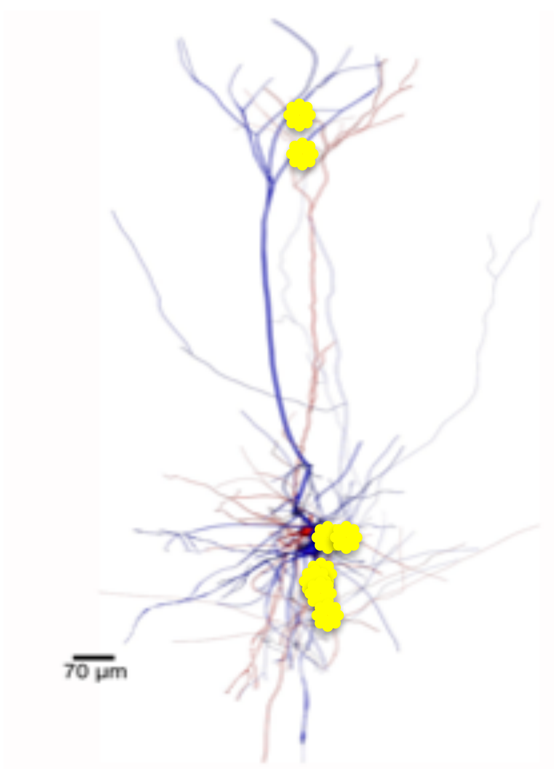


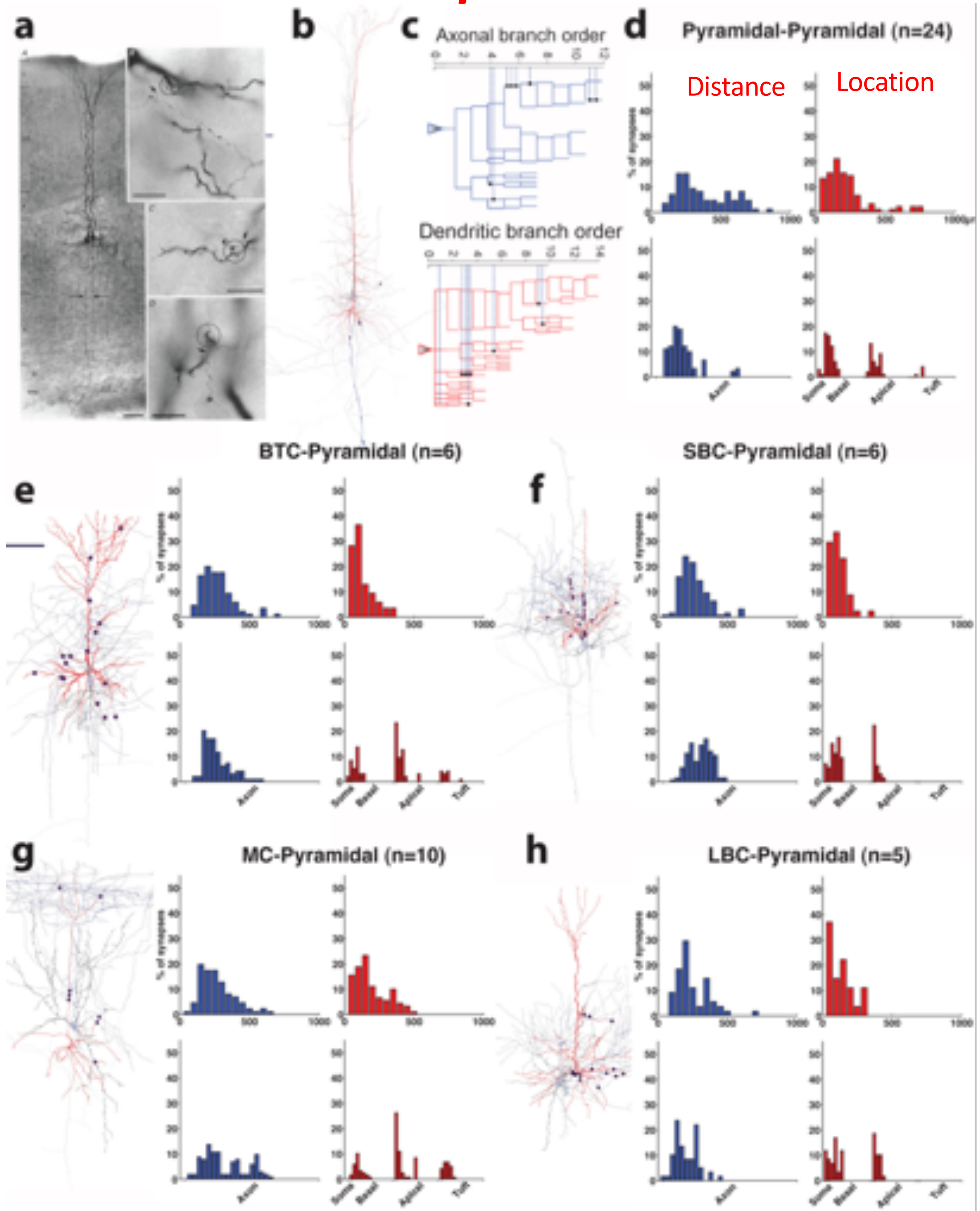
The Neurons: probing the eTypes



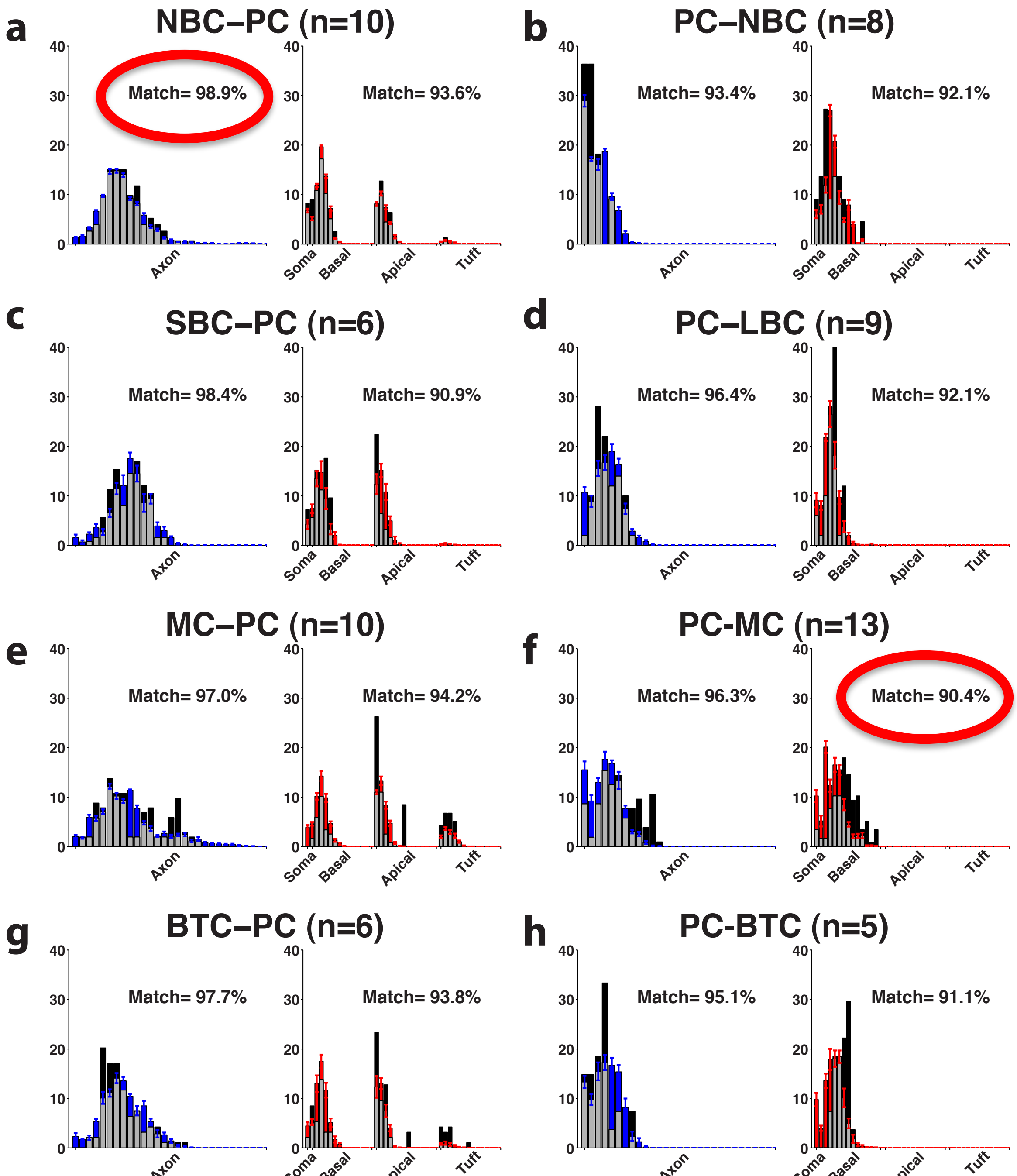
Synaptic Numbers & Locations - *Experiments*





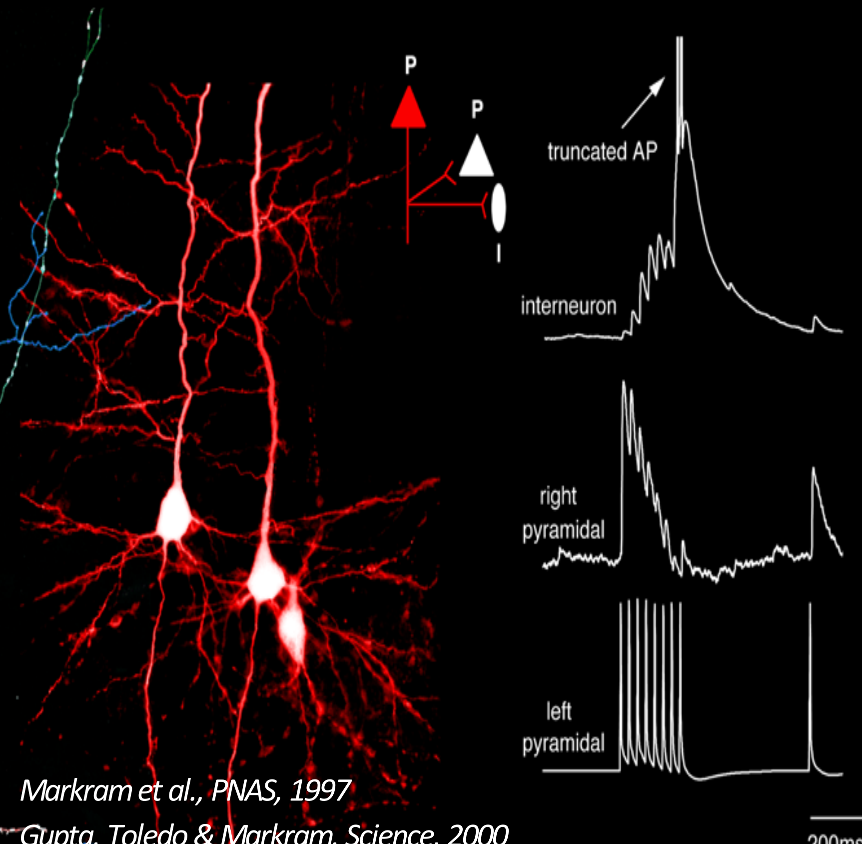


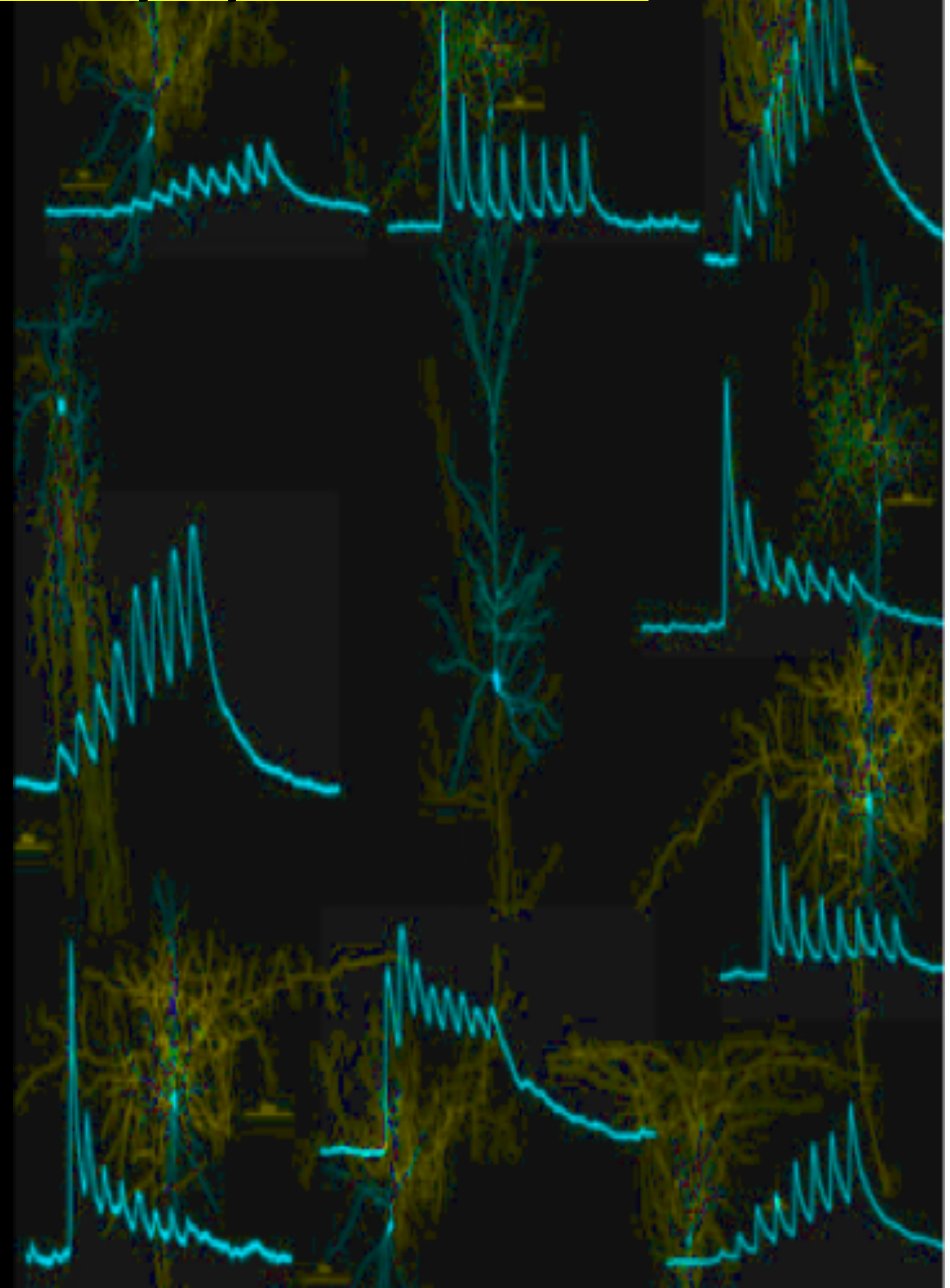
Discovery: Synaptic Positions in the Model MATCH those in Experiments



Hill et al., 2011

Experiments: Dynamic Synaptic Transmission





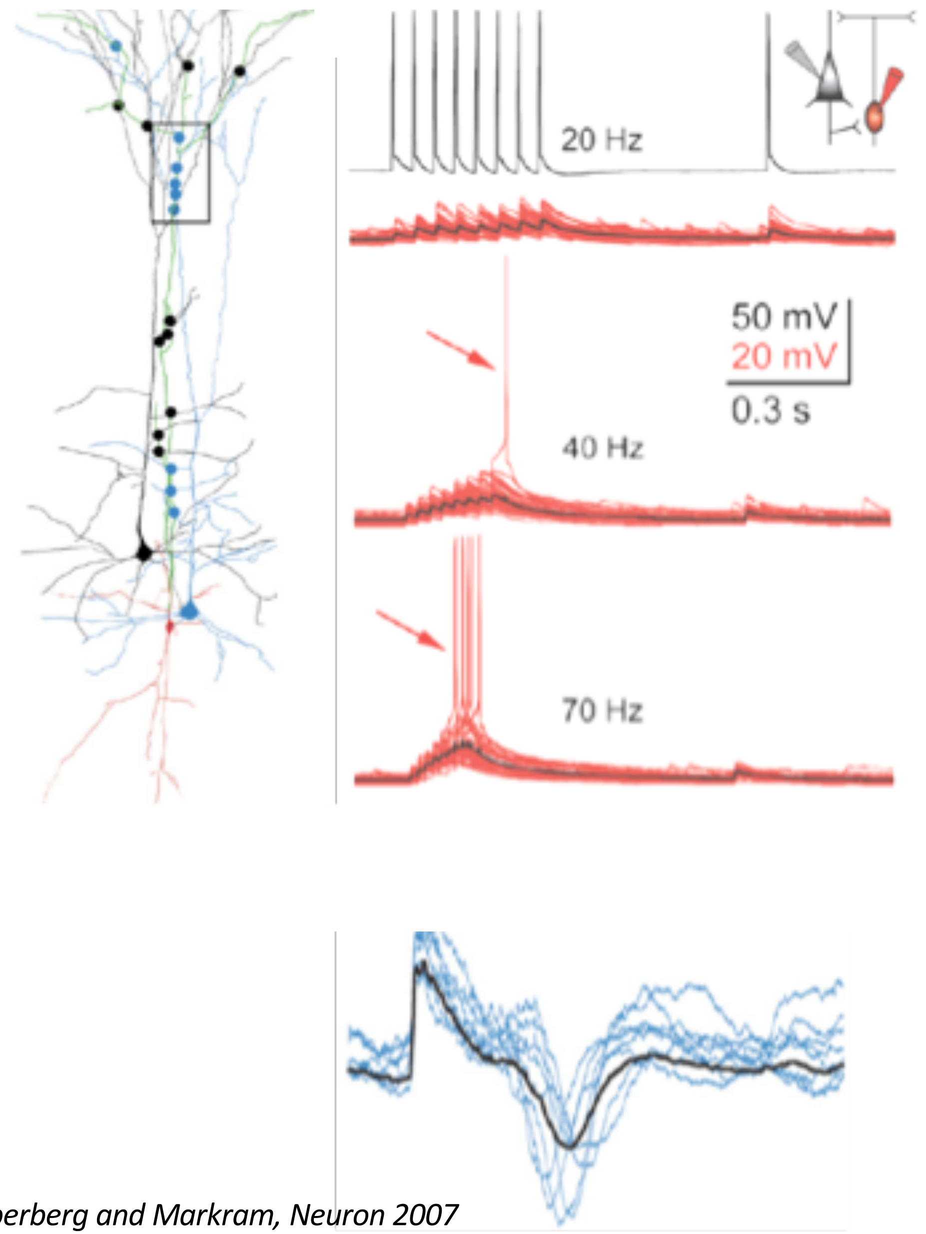
Markram et al., PNAS, 1997

Gupta, Toledo & Markram, Science, 2000

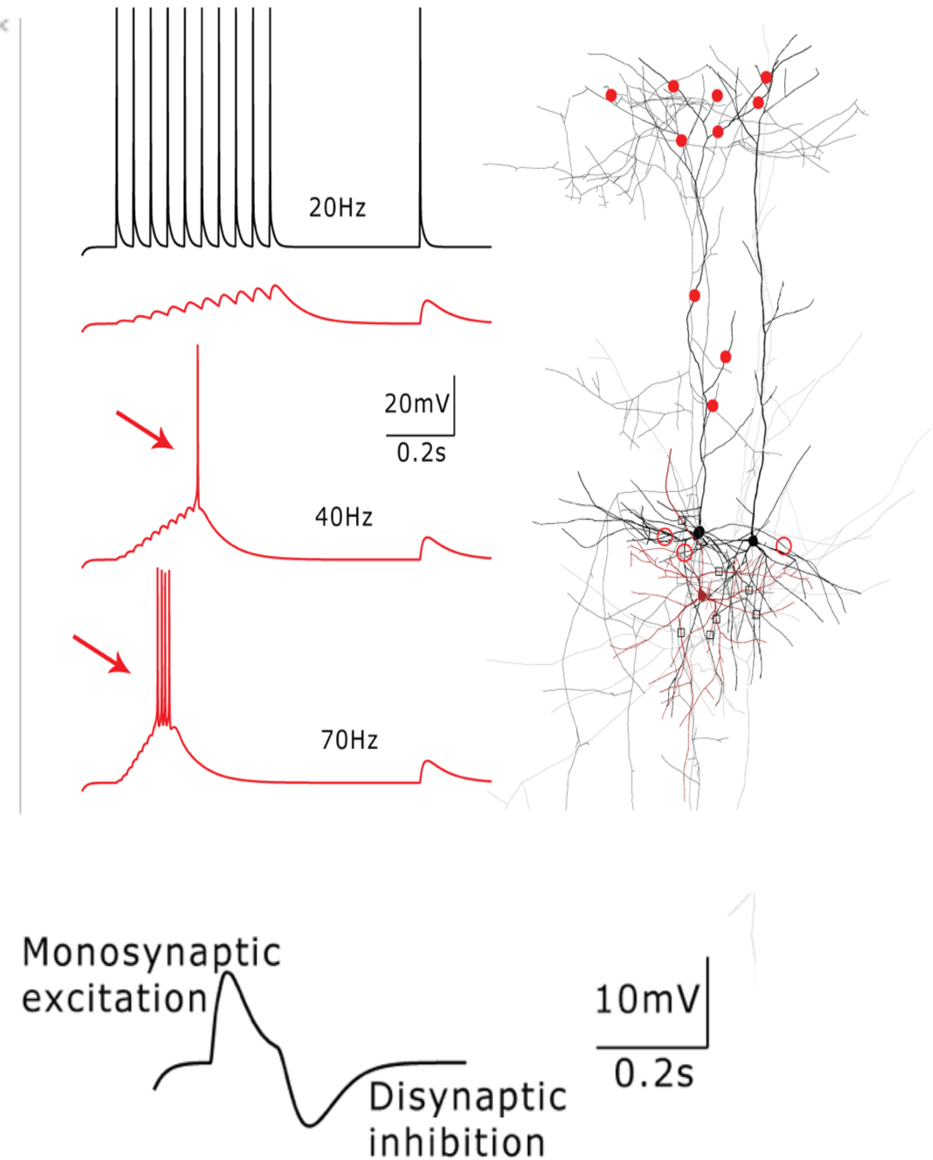
Markram et al., Nature Reviews Neuroscience, 2004

In silico synaptic recordings match in vitro synaptic recordings

In vitro

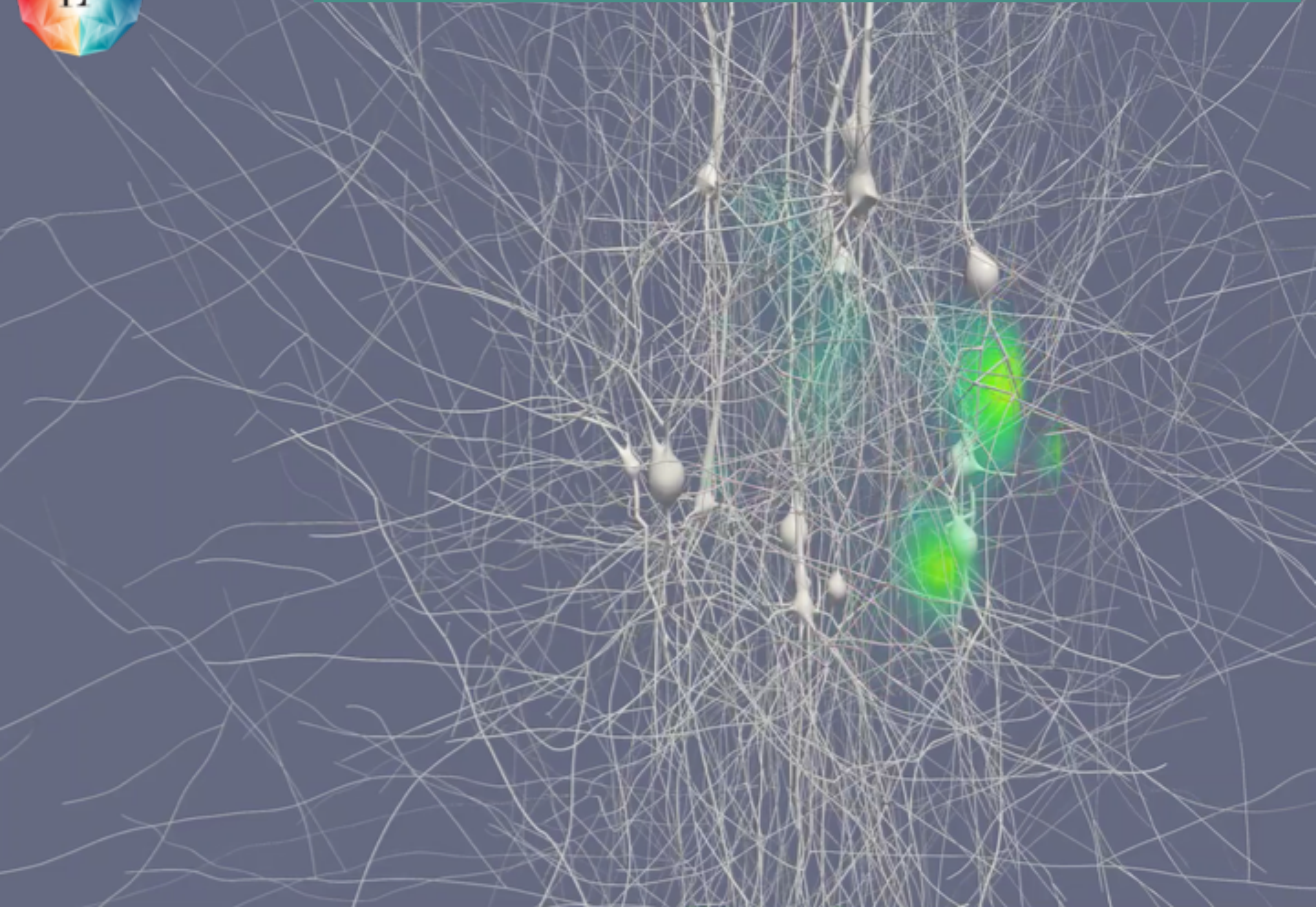


In silico

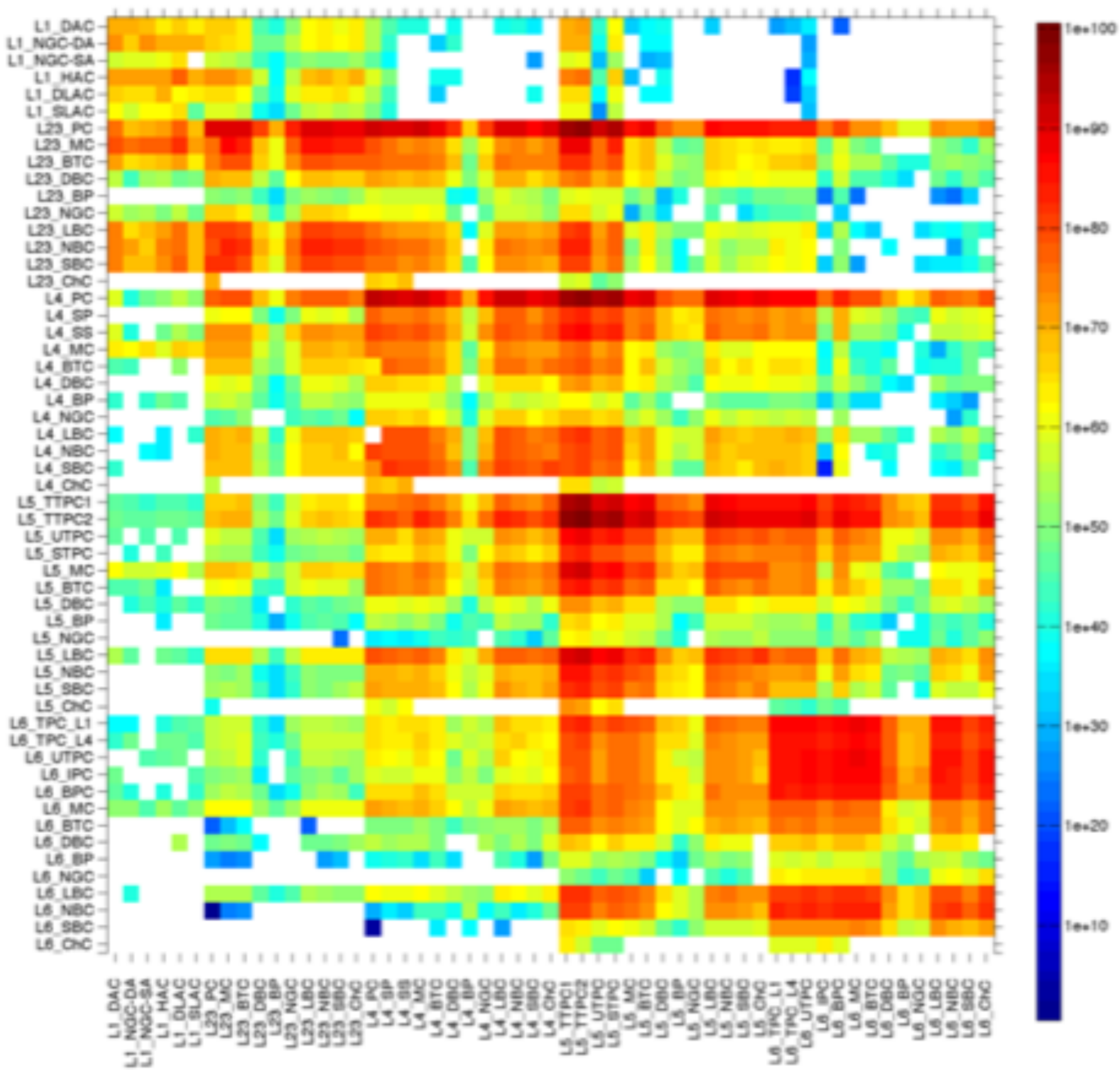


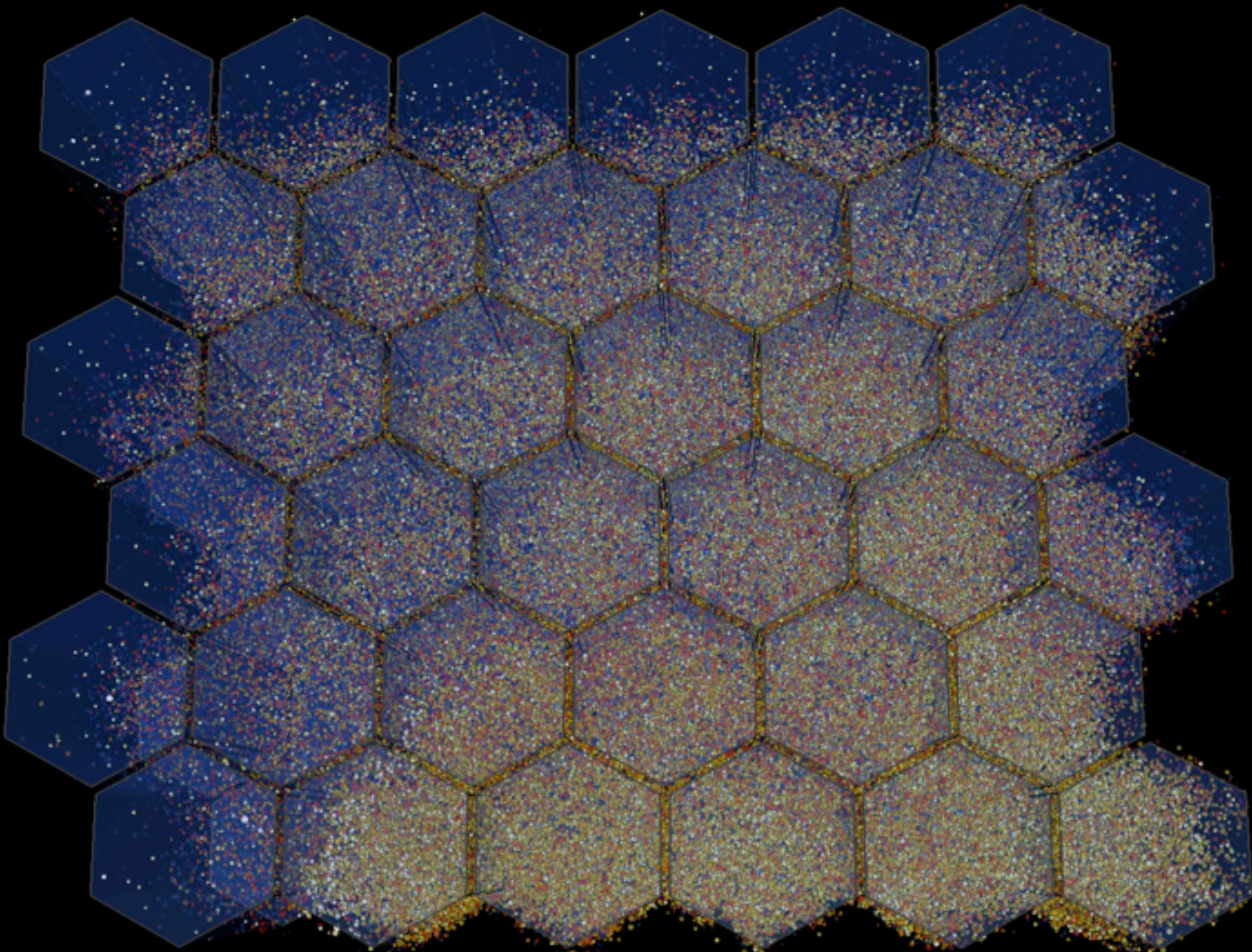
Silberberg and Markram, Neuron 2007

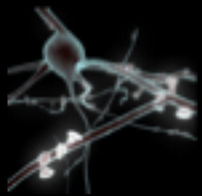
MODELLED LFPs IN A CORTICAL COLUMN



Normalized by number of neurons per mType







NEURONS

$$\frac{C_m dV_m}{dt} = \frac{E_m - V_m}{R_m} + I_{channels\cdots} + I_{synapses} + \frac{2(V_{m_{i+1}} - V_{m_i})}{R_{a_{i+1}} + R_a} + \frac{2(V_{m_{i-1}} - V_{m_i})}{R_{a_{i-1}} + R_a}$$

10,000 neurons

~ 4,000,000

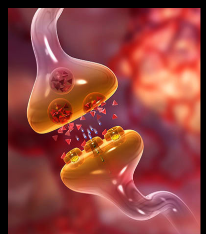
Electrical compartments
(Rall Equations)

ION CHANNELS

$$\frac{dm}{dt} = \alpha_m(V_m)(1-m) - \beta_m(V_m)m$$
$$\frac{dh}{dt} = \alpha_h(V_m)(1-h) - \beta_h(V_m)h$$
$$I_{channel} = m^n h g_{channel}(V_m - E_{channel})$$

80,000,000 Ion Channels

(Hodgkin-Huxley Equations)

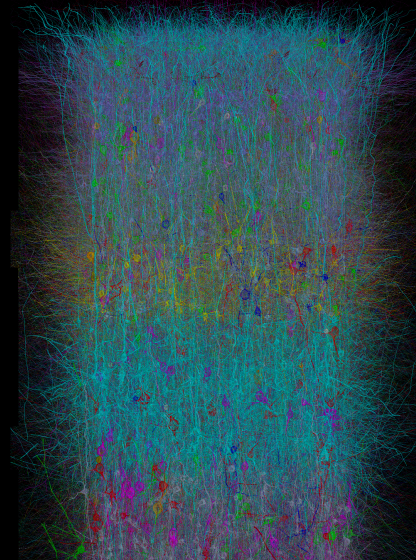


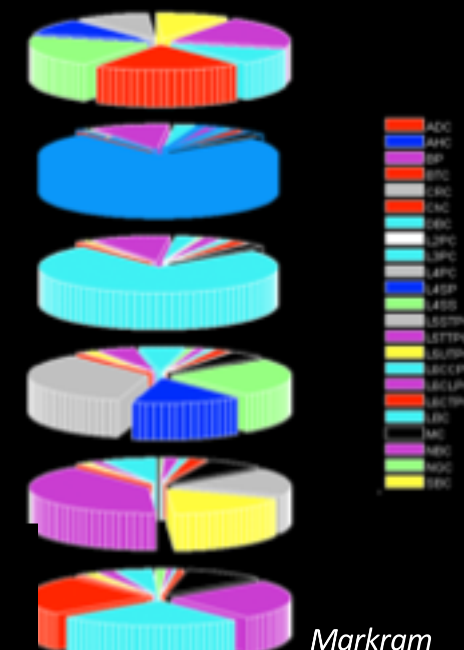
SYNAPSES

$$\frac{dx}{dt} = \frac{z}{\tau_{rec}} - ux\delta(t - t_{sp})$$
$$\frac{dy}{dt} = -\frac{y}{\tau_1} - ux\delta(t - t_{sp})$$
$$\frac{dz}{dt} = \frac{y}{\tau_1} - \frac{z}{\tau_{rec}}$$
$$\frac{du}{dt} = -\frac{u}{\tau_{facil}} + U(1-u)\delta(t - \ldots$$
$$I_{synapse}(t) = \sum_j A_{ij} y_{ij}(t)$$

10,000,000 Synapses

(Tsodyks-Markram Equations)





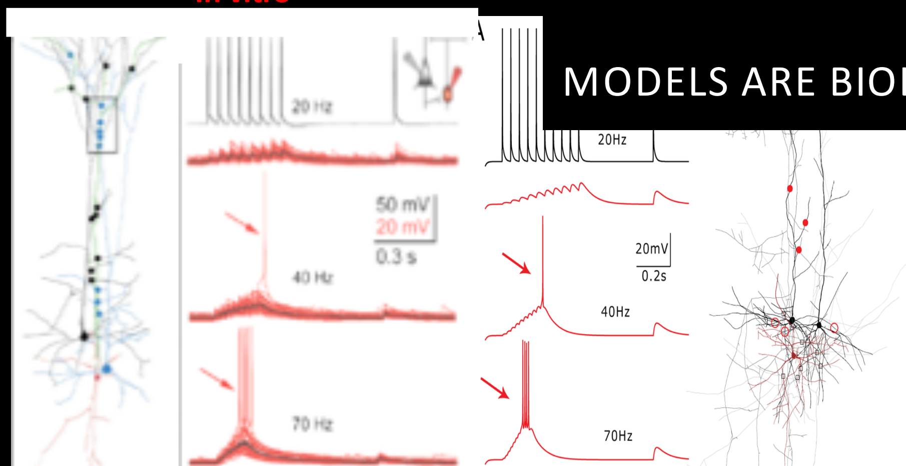
Markram

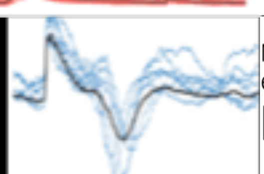
MODELS ARE DATA DRIVEN

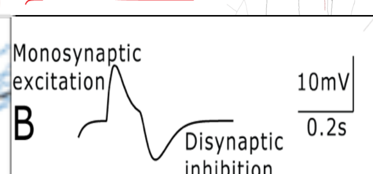
MODELS ARE MATHEMATICALLY EXPRESSED

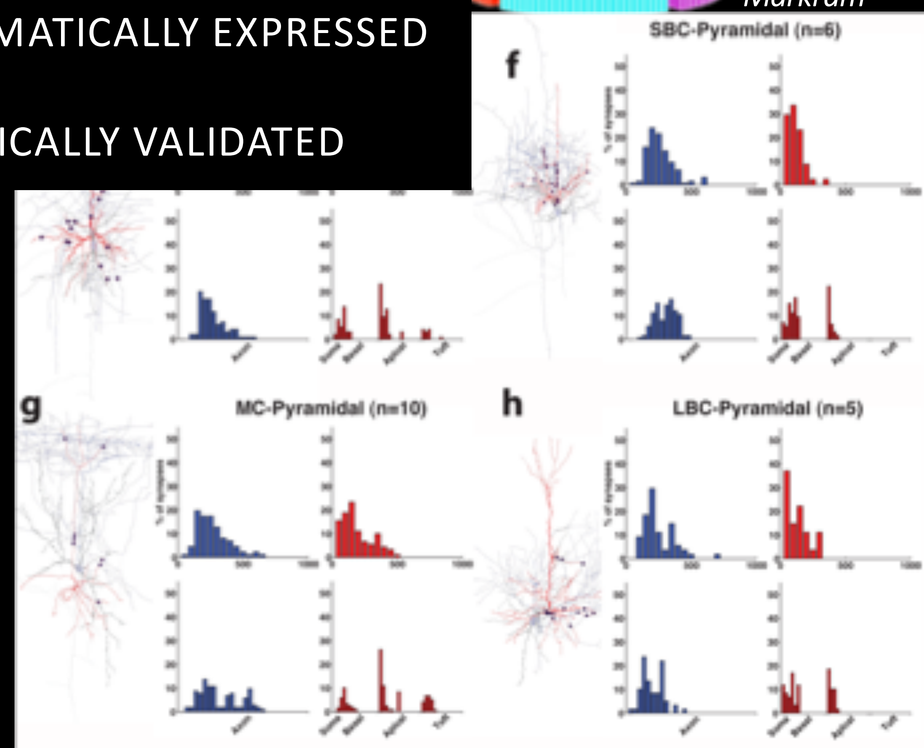
MODELS ARE BIOLOGICALLY VALIDATED

In vitro

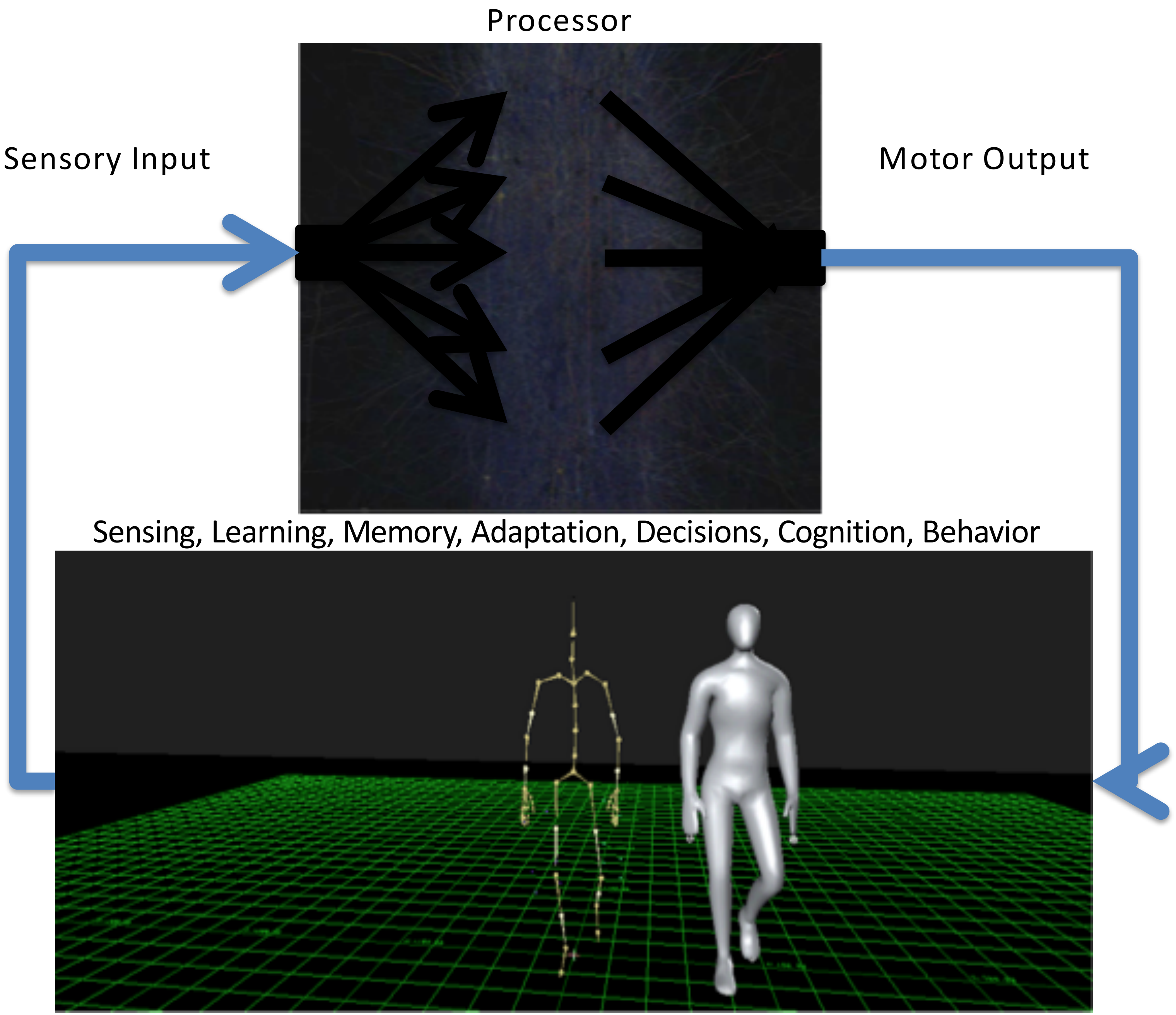




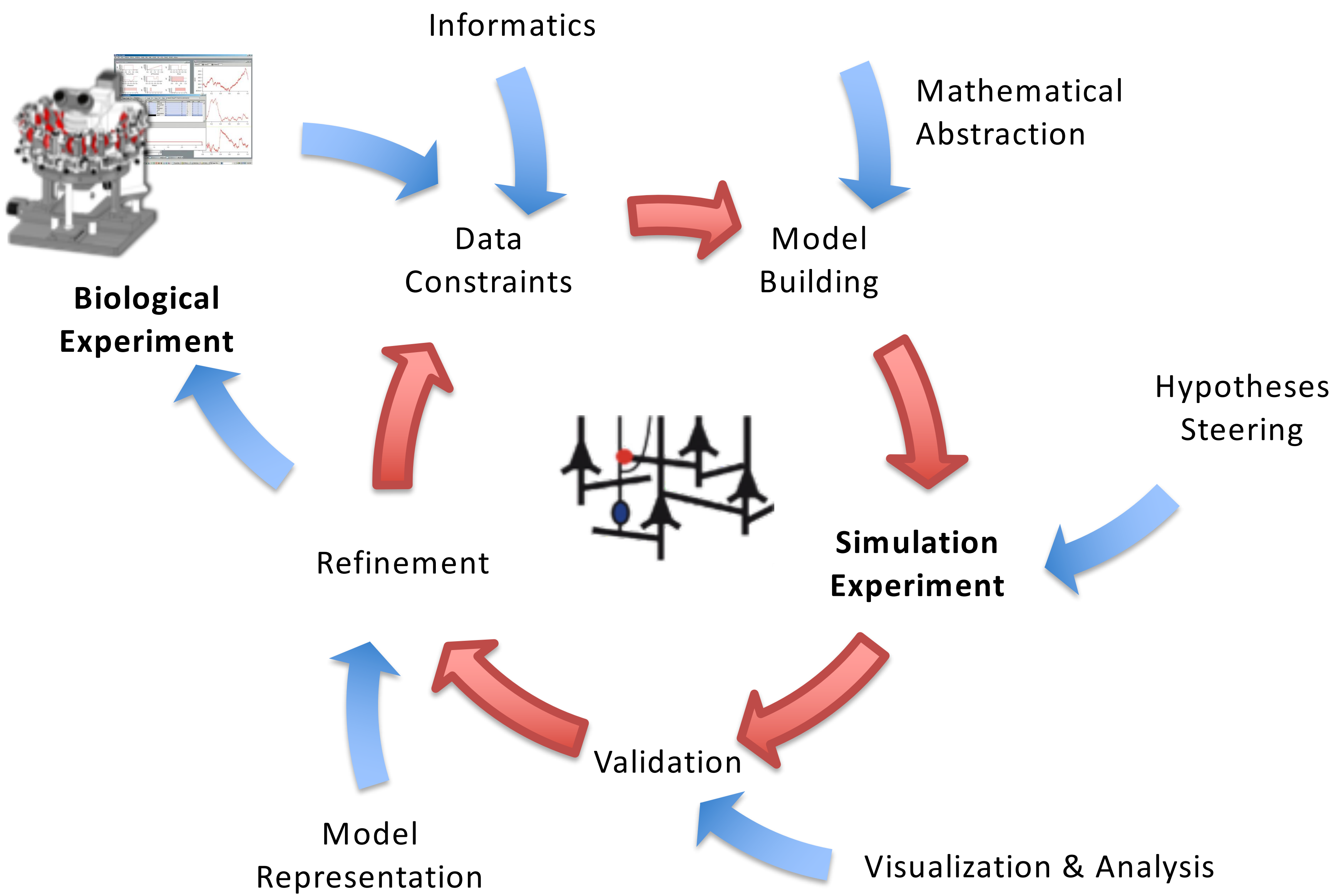




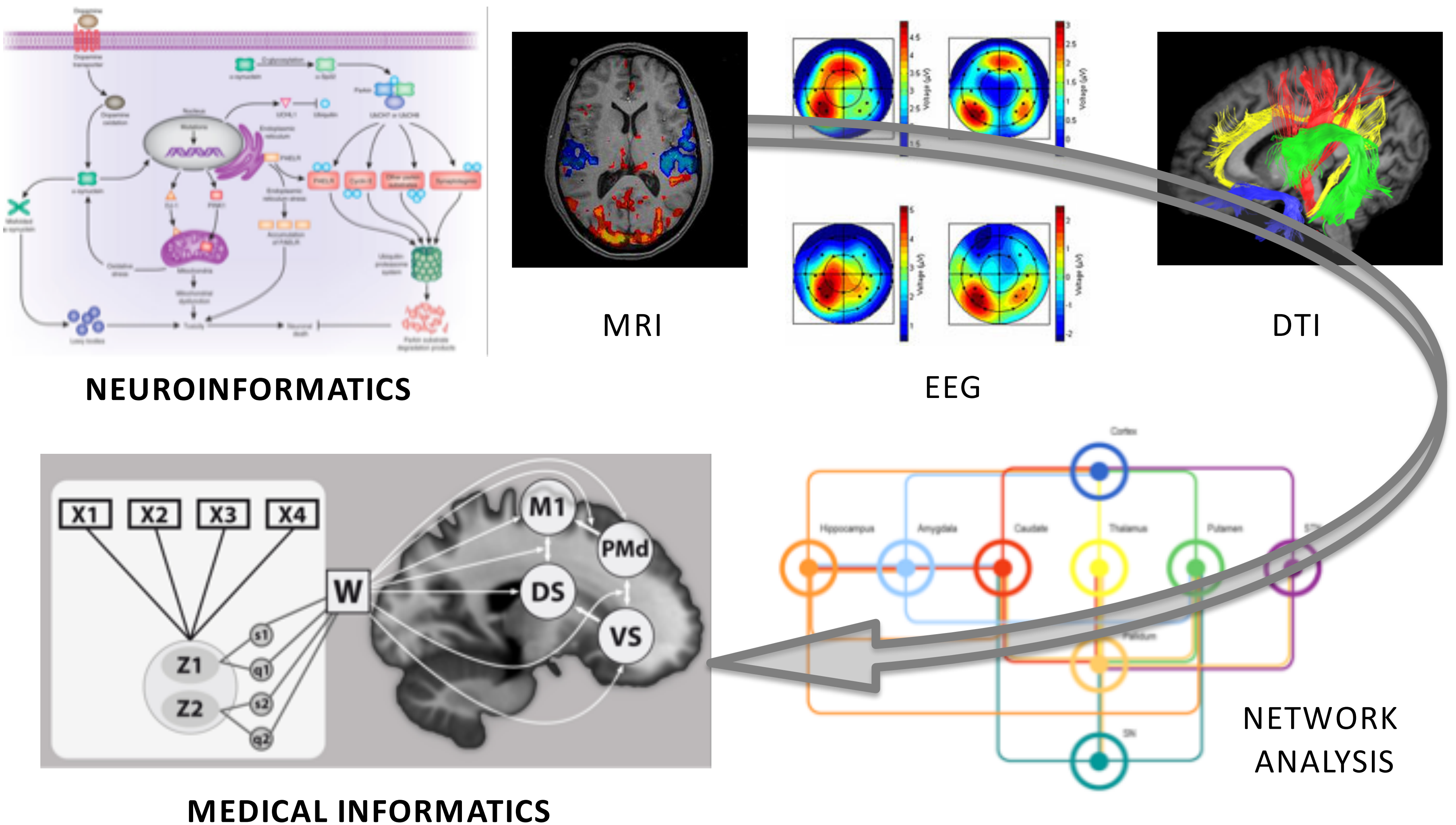
NEURAL COMPUTATION : CHAIN OF EVENTS LEADING TO COGNITION

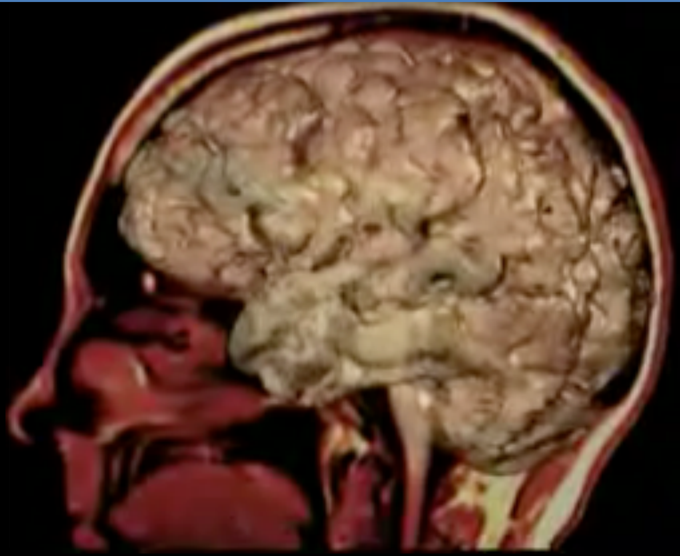
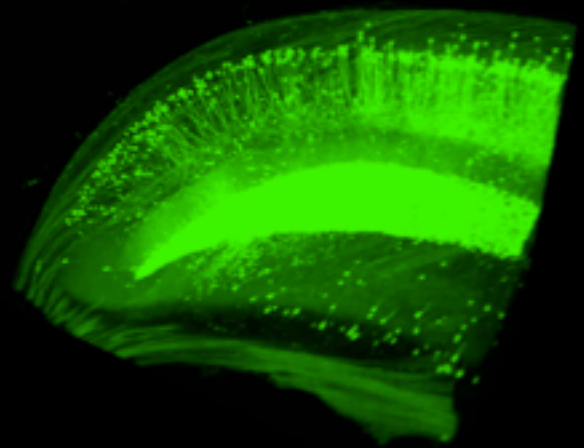


Building *Unifying Models*: a roadmap for *in silico* neuroscience



Integration of theoretical concepts from animal studies and human images by bridging between different scales of acquired data

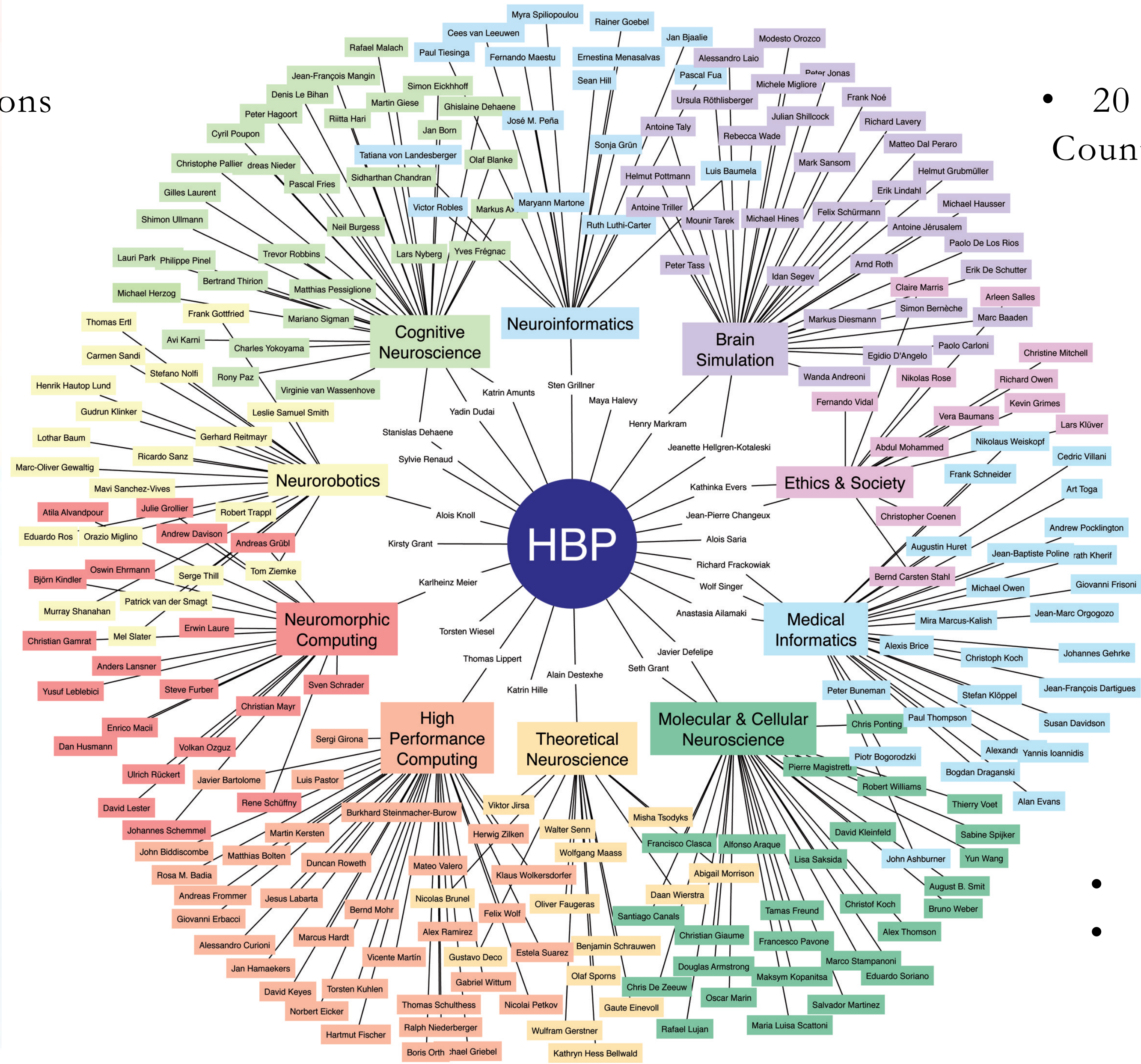



THE CONSORTIUM

- 80 Institutions
- 150 PIs
- 2000 PhDs

- 20 European Countries



- USA
- Israel
- Japan
- China
- Canada

- 50% Core
- 50% Grants