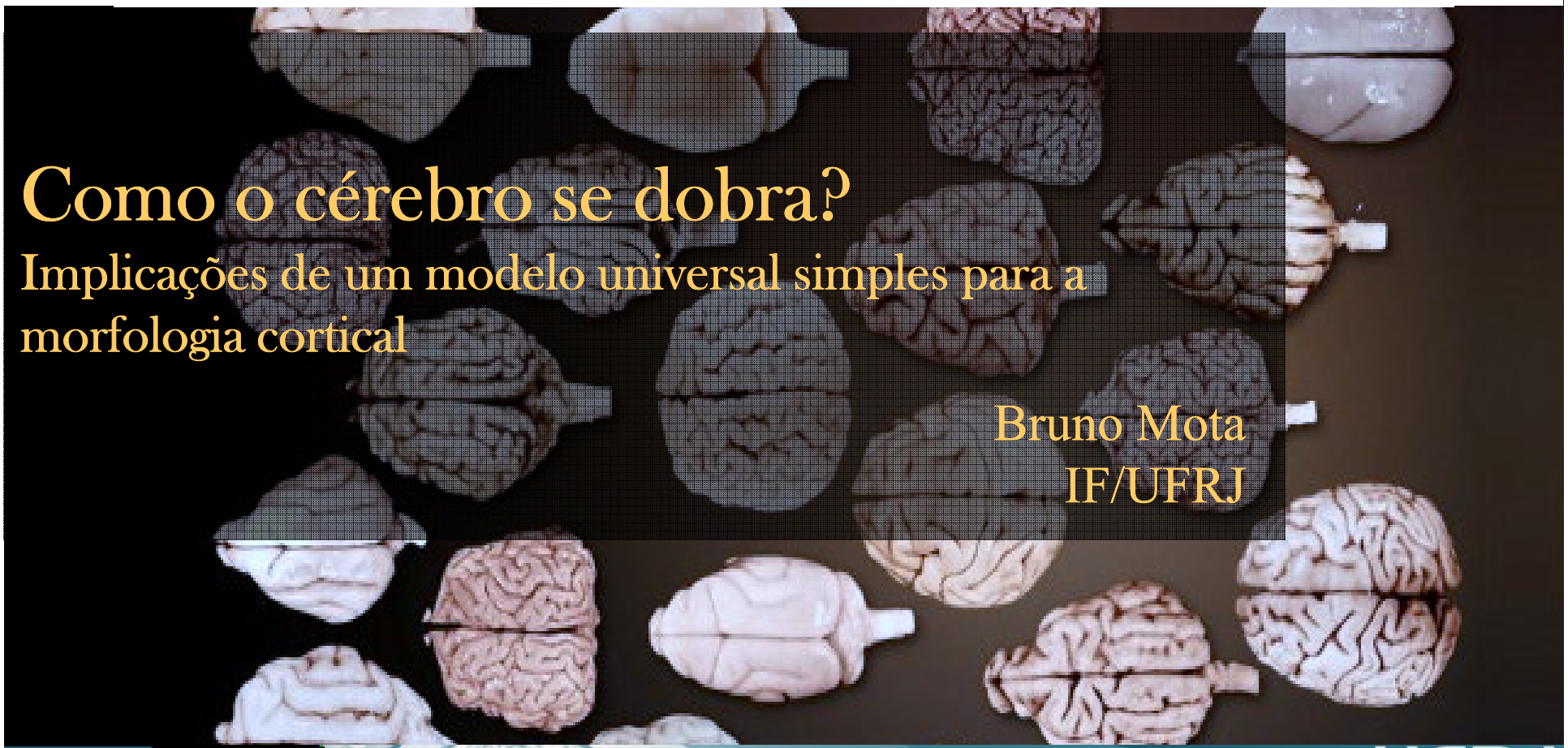
colmea

Colóquio Interinstitucional

Modelos Estocásticos e Aplicações

Quarta-feira, 30 de novembro de 2016



Como o cérebro se dobra?

Implicações de um modelo universal simples para a morfologia cortical

Bruno Mota
IF/UFRJ

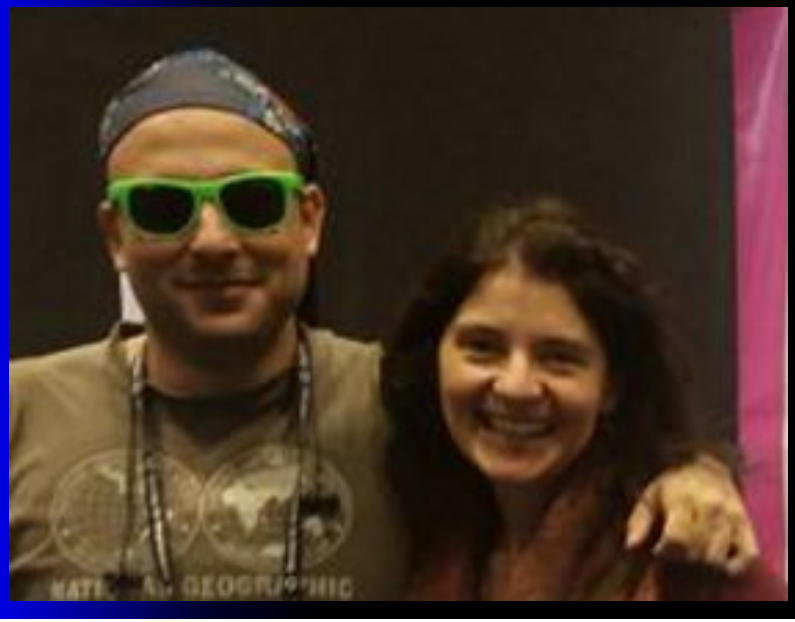
if 50 ANOS

UFRJ

Universidade Federal do Rio de Janeiro

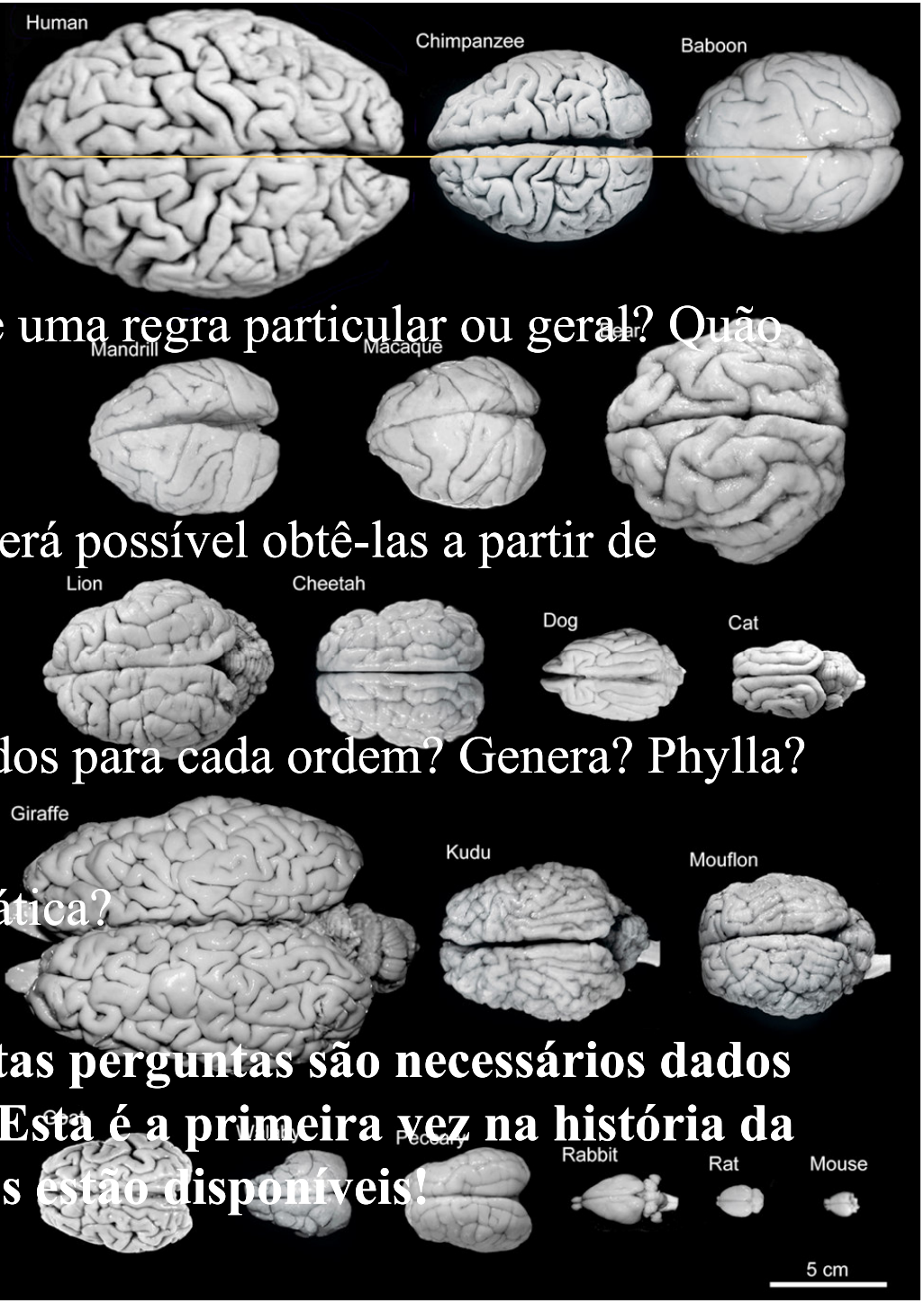
Biologia e física: Um choque de culturas

A aplicação de técnicas experimentais de física na biologia tem uma longa história



O uso dos métodos da física teórica para produzir modelos para biologia, por outro lado, é menos comum

Biologia teórica?

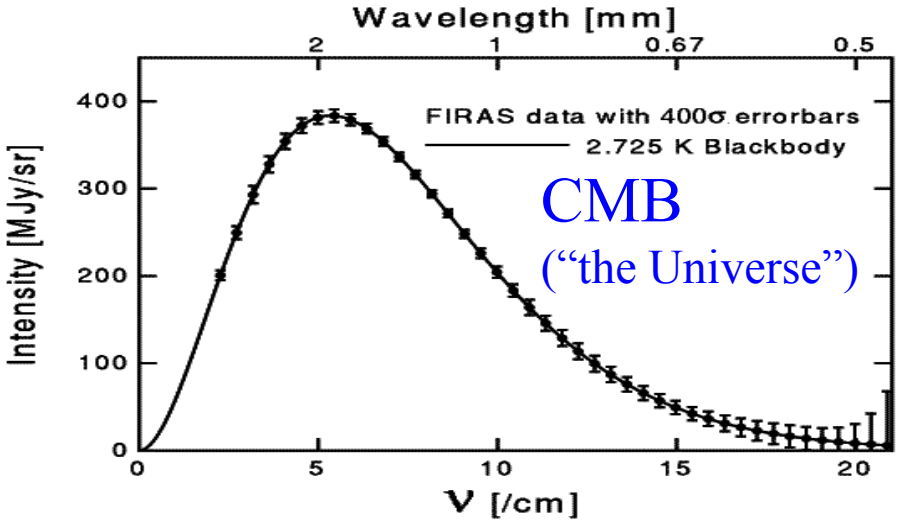


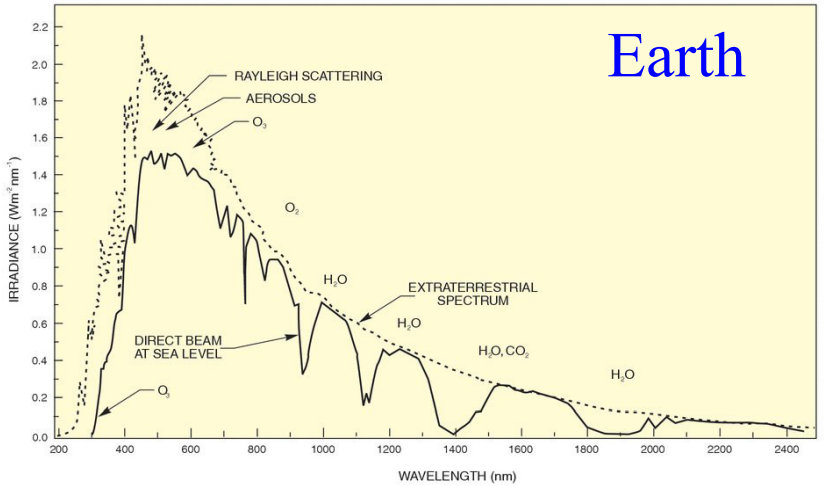
- O cérebro de cada espécie segue uma regra particular ou geral? Quão especiais são os humanos?
- Se tais regras gerais existirem, será possível obtê-las a partir de primeiros princípios?
- Tais princípios são gerais? Válidos para cada ordem? Genera? Phylla?
- Qual deve ser sua forma matemática?
- **Na prática, para responder estas perguntas são necessários dados precisos e em grande volume. Esta é a primeira vez na história da neurociência em que tais dados estão disponíveis!**

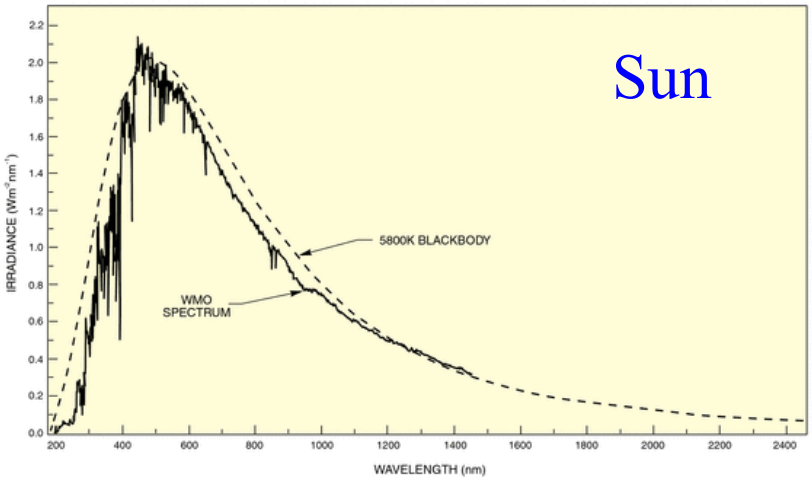
Universalidade pode ser consequência de um princípio fundamental – E.g. Radiação de corpo negro

$$B_\lambda(T) = \frac{2hc^2/\lambda^5}{e^{hc/\lambda kT} - 1}$$

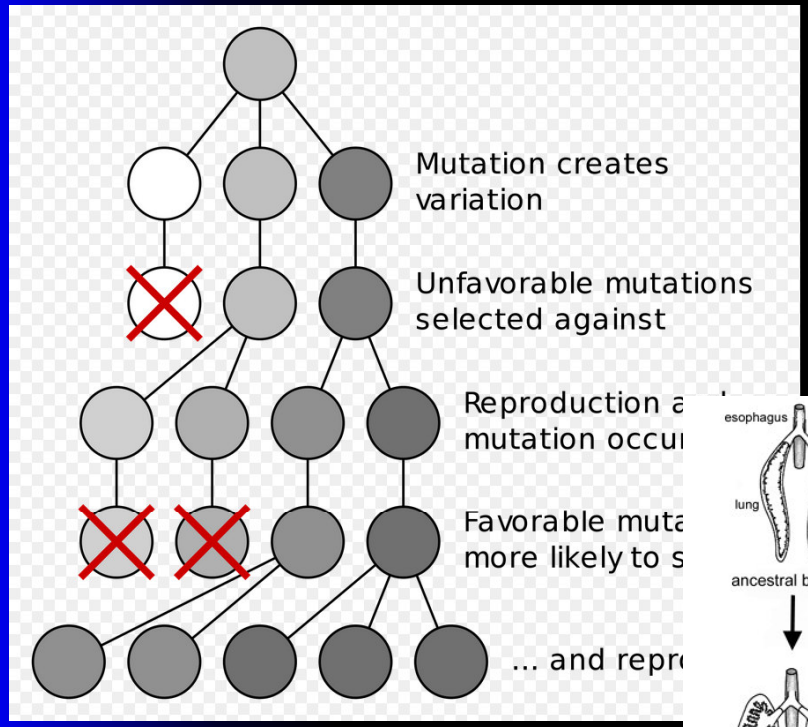
- Só um grau de liberdade(T)
- Aproximadamente verdadeiro para quase toda a matéria
- Mas as divergências importam!
- Ajuste grosso vs ajuste fino

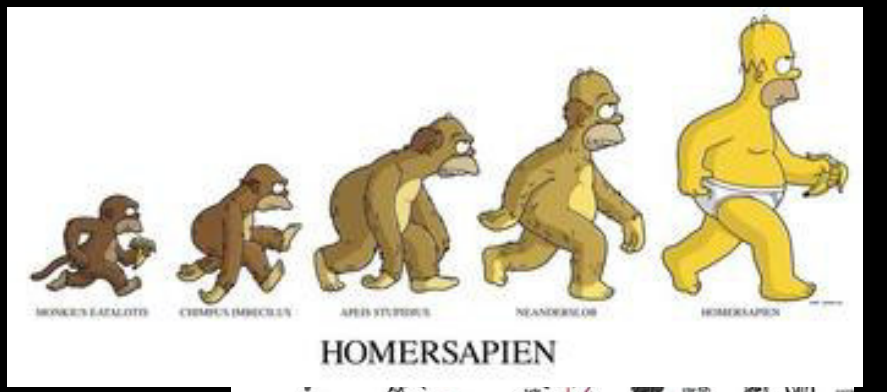


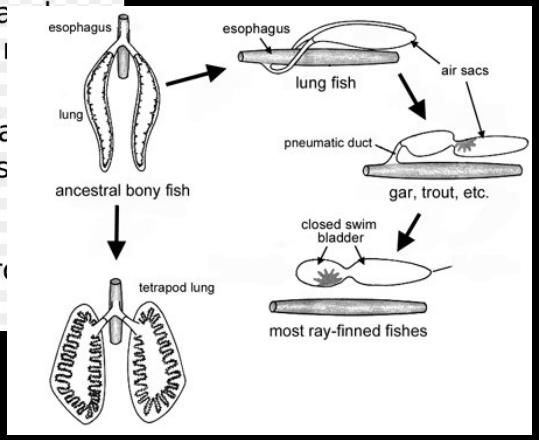


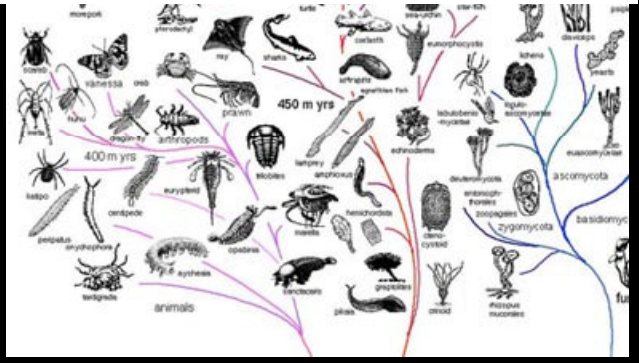


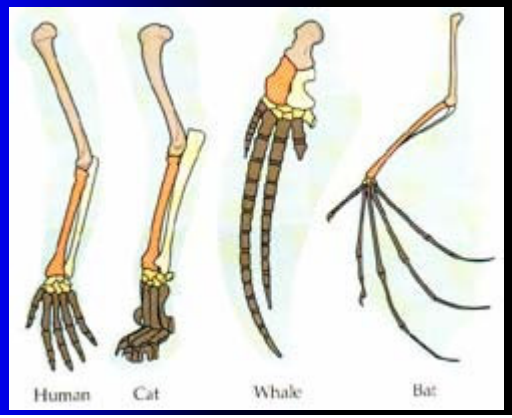
A teoria fundamental da biologia: Evolução através da seleção natural





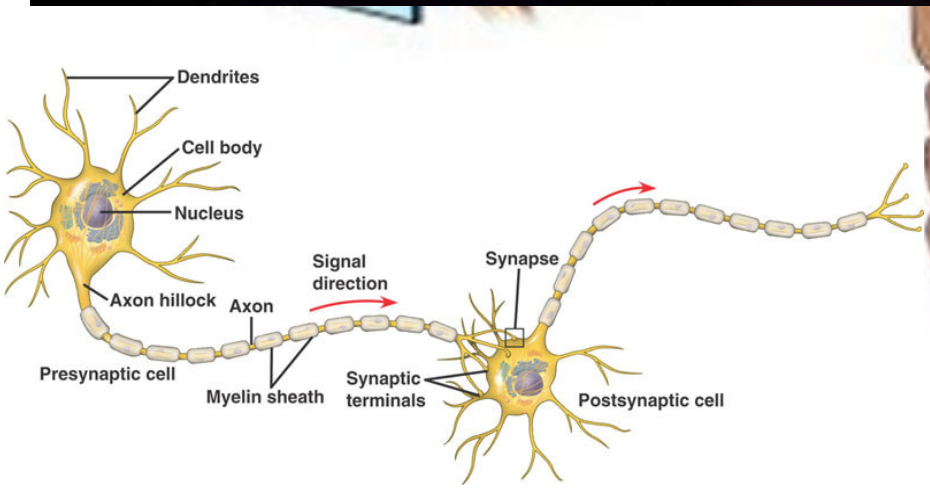






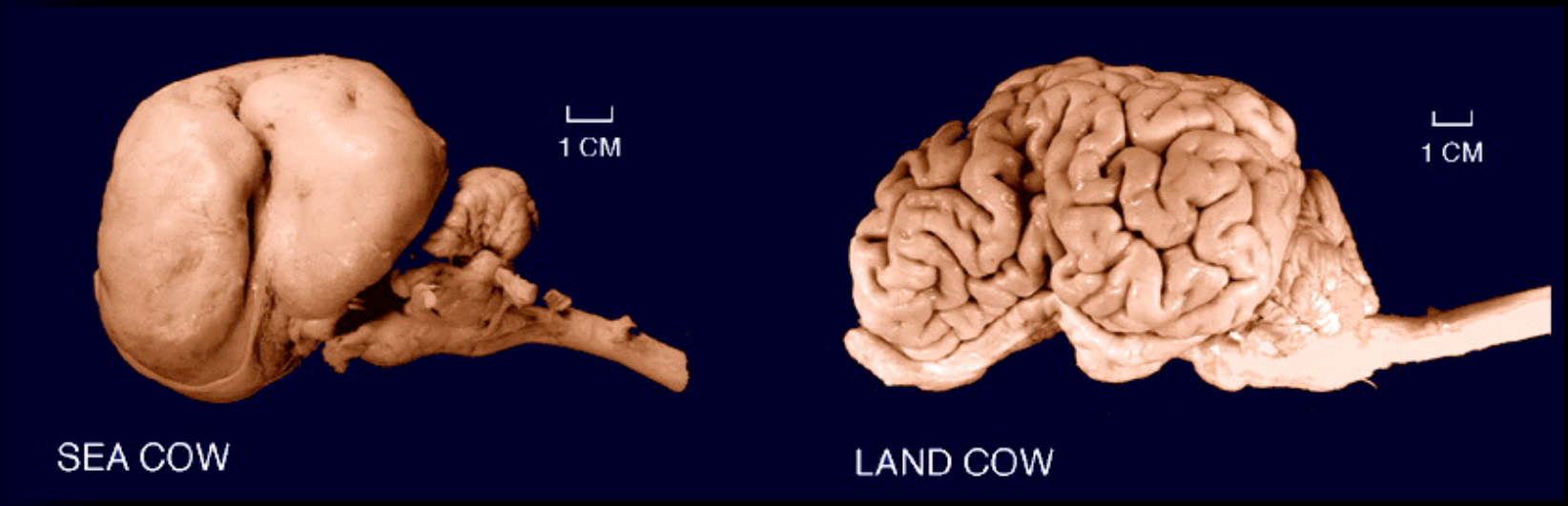
- Evolução é um mecanismo de otimização vinculada
- Não há uma direção – adaptação às circunstancias específicas
- Adaptação a partir de estruturas pré-existentes –
  Não existe 'de volta à prancheta'
- A evolução é conservadora – Reduce, reuse, recycle
- Ancestral comum – Homologia entre estruturas

What about the cortex?



O cortex se dobra...

- Se girificação é uma adaptação, ela ocorreu diversas vezes
- Cortices maiores são em geral mais girificados
- Mas nem sempre!



Como o córtex se dobra? I

- Ele empena para cima!

PNAS PNAS PNAS

CrossMark
click for updates

Gyrification from constrained cortical expansion

Tuomas Tallinen[a], Jun Young Chung[b], John S. Biggins[c], and L. Mahadevan[d,e,f,1]

[a]Department of Physics and Nanoscience Center, University of Jyväskylä, FI-40014 Jyväskylä, Finland; [b]School of Engineering and Applied Sciences, Harvard University, Cambridge, MA 02138; [c]Cavendish Laboratory, Cambridge University, Cambridge CB3 0HE, United Kingdom; [d]Wyss Institute for Biologically Inspired Engineering, [e]Kavli Institute for Bionano Science and Technology, and [f]School of Engineering and Applied Sciences, Department of Organismic and Evolutionary Biology, and Department of Physics, Harvard University, Cambridge, MA 02138

Edited* by John W. Hutchinson, Harvard University, Cambridge, MA, and approved July 15, 2014 (received for review April 1, 2014)

The exterior of the mammalian brain—the cerebral cortex—has a conserved layered structure whose thickness varies little across species. However, selection pressures over evolutionary time scales have led to cortices that have a large surface area to volume ratio in some organisms, with the result that the brain is strongly convoluted into sulci and gyri. Here we show that the gyrification can arise as a nonlinear consequence of a simple mechanical instability driven by tangential expansion of the gray matter constrained by the white matter. A physical mimic of the process using a layered swelling gel captures the essence of the mechanism, and numerical simulations of the brain treated as a soft solid lead to the formation of cusped sulci and smooth gyri similar to those in the brain. The resulting gyrification patterns are a function of relative cortical expansion and relative thickness (compared with brain size), and are consistent with observations of a wide range of brains, ranging from smooth to highly convoluted. Furthermore, this dependence on two simple geometric parameters that characterize the brain also allows us to qualitatively explain how variations in these parameters lead to anatomical anomalies in such situations as polymicrogyria, pachygyria, and lissencephalia.

brain morphogenesis | elastic instability

The mammalian brain is functionally and anatomically complex. Over the years, accumulating evidence (1, 2) shows that there are strong anatomical correlates of its information-

from an unregulated and unpatterned growth of the cortex relative to sublayers.

Nevertheless, there is as yet no explicit biologically and physically plausible model that can convincingly reproduce individual sulci and gyri, let alone the complex patterns of sulci and gyri found in the brain. Early attempts to mechanically model brain folding (13) were rooted in the physics of wrinkling and assumed a thin stiff layer of gray matter that grows relative to a thick soft substrate of white matter. This model falls short in two ways. First, the gray matter is neither thin nor stiff relative to the white matter (17, 18). Second, this model predicts smooth sinusoidal wrinkling patterns, sketched in Fig. 1*A*, whereas even lightly folded brains have smooth gyri but cusped sulci. More complicated mechanical models including, e.g., elasto-plasticity and stress-related growth (14, 19, 20), lead to varying morphologies, but all produced simple smooth convolutions rather than cusped sulci.

A fundamentally different mechanical instability that occurs on the surface of a uniformly compressed soft solid (21, 22) has recently been exposed and clarified, theoretically, computationally, and experimentally (23–26). This sulcification instability arises under sufficient compression leading to the folding of the soft surface to form cusped sulci via a strongly subcritical transition. In Fig. 1*B*, we show a geometry dual to that associated with wrinkling: A soft layer of gray matter grows on a stiff white-matter substrate. Unlike wrinkling, this instability can produce the cusped centers of sulci, but the flat bottom of the gray matter

APPLIED PHYSICAL SCIENCES
BIOPHYSICS AND COMPUTATIONAL BIOLOGY

Como o córtex se dobra? I

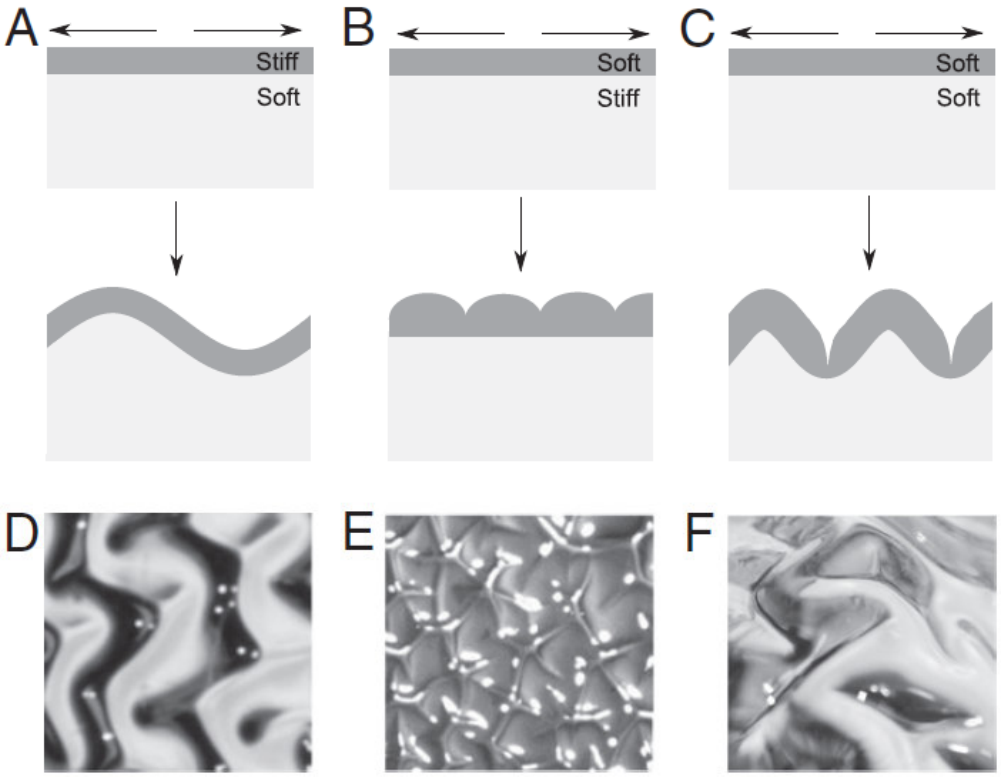


Fig. 1. Wrinkling and sulcification in a layered material subject to differential growth. (*A*) If the growing gray matter is much stiffer than the white matter it will wrinkle in a smooth sinusoidal way. (*B*) If the gray matter is much softer than the white matter its surface will invaginate to form cusped folds. (*C*) If the two layers have similar moduli the gray matter will both wrinkle and cusp giving gyri and sulci. Physical realizations of *A*, *B*, and *C*, based on differential swelling of a bilayer gel (*Materials and Methods*), confirm this picture and are shown in *D*, *E*, and *F*, respectively.

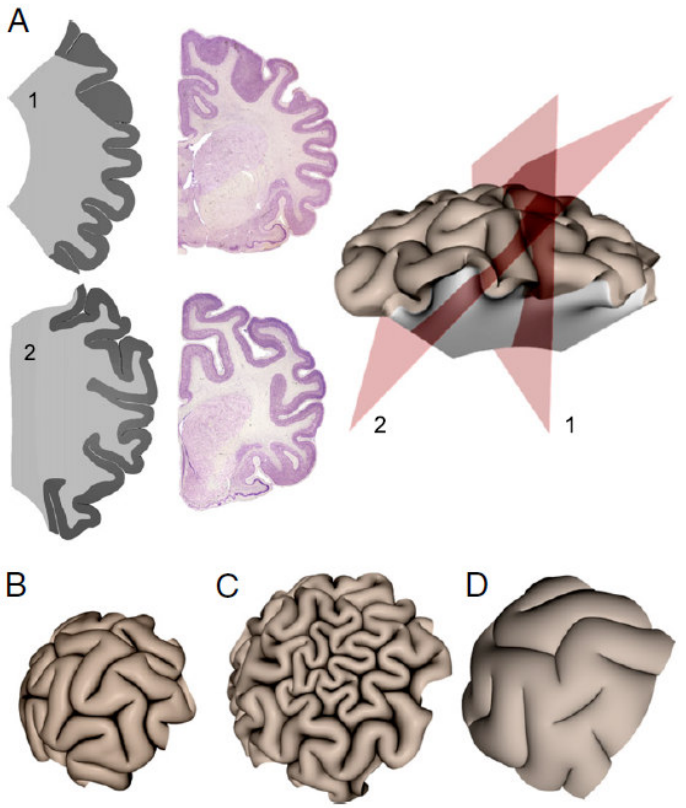


Fig. 4. (*A*) Sections of a simulated brain (section planes indicated at right) are compared with coronal sections of a raccoon brain (from www.brain-museum.org). Cuts through the center of the brain (*Upper*) and the off the center (*Lower*) show that we can capture the hierarchical folds but emphasize how misleading sections can be in characterizing the sulcal architecture. (*B*) Confining our simulations with a uniform pressure of 0.7μ to mimic the meninges and skull leads to a familiar flattened sulcal morphology. (*C*) Changing the gray matter thickness in a small patch of the growing cortex leads to morphologies similar to polymicrogyria in our simulations. Here $g^2 = 5$ and $R/T = 20$ except in the densely folded region where $R/T = 40$. (*D*) A simulated brain of same physical size as that in *C* but with a thickened cortex ($R/T = 12$) and reduced tangential expansion ($g^2 = 2$) displays wide gyri and shallow sulci reminiscent of pachygyric brains.

Como o córtex se dobra? II

- Ele empena para os lados!

Cerebral Cortex August 2014;24:2219–2228
doi:10.1093/cercor/bht082
Advance Access publication March 29, 2013

Differential Tangential Expansion as a Mechanism for Cortical Gyrification

Lisa Ronan[1], Natalie Voets[2], Catarina Rua[1], Aaron Alexander-Bloch[1,5], Morgan Hough[2], Clare Mackay[2], Tim J. Crow[3], Anthony James[4], Jay N. Giedd[5] and Paul C. Fletcher[1]

[1]Brain Mapping Unit, Department of Psychiatry, University of Cambridge, Cambridge CB2 3EB, UK, [2]FMRIB Centre, Nuffield Department of Clinical Neurosciences, University of Oxford, OX3 9DU, UK, [3]SANE POWIC, Department of Psychiatry, Warneford Hospital, University of Oxford, OX3 7JX, [4]Highfield Adolescent Unit, Warneford Hospital, Oxford OX3 7JX, UK and [5]Child Psychiatry Branch, NIH, Bethesda MD, 20892, USA

Address correspondence to Dr Lisa Ronan, Brain Mapping Unit, University of Cambridge, Sir William Hardy Building, Downing Site, Downing Street, Cambridge CB2 3EB, UK. Email: lr344@cam.ac.uk

Gyrification, the developmental buckling of the cortex, is not a random process—the forces that mediate expansion do so in such a way as to generate consistent patterns of folds across individuals and even species. Although the origin of these forces is unknown, some theories have suggested that they may be related to external cortical factors such as axonal tension. Here, we investigate an alternative hypothesis, namely, whether the differential tangential expansion of the cortex alone can account for the degree and pattern-specificity of gyrification. Using intrinsic curvature as a measure of differential expansion, we initially explored whether this parameter and the local gyrification index (used to quantify the degree of gyrification) varied in a regional-specific pattern across the cortical surface in a manner that was replicable across independent datasets of neurotypicals. Having confirmed this consistency, we further demonstrated that within each dataset, the degree of intrinsic curvature of the cortex was predictive of the degree of cortical folding at a global and regional level. We conclude that differential expansion is a plausible primary mechanism for gyrification, and propose that this perspective offers a compelling mechanistic account of the co-localization of cytoarchitecture and cortical folds.

Keywords: cortical development, differential expansion, gyrification, intrinsic curvature

Introduction

Gyrification, the characteristic folding of the cortical mantle that emerges during development, mitigates the problems inherent in enclosing a large surface area in a small volume. It is thought to be a mechanical process whereby as yet

connected regions drift (Van Essen 1997; Mota and Herculano-Houzel 2012). However, there is evidence against this hypothesis. First, axons do not follow the pattern specified by the model—specifically they run parallel to the sulcal walls rather than perpendicular to them (Xu et al. 2010). Second, it has been shown that while axons pull on the brain, they are not under sufficient tension to affect folding patterns of individual gyri, as the primary forces occur in the deep subcortical white matter (Xu et al. 2010). Moreover, cortico-cortical projections as postulated by the model post-date the emergence of the primary sulci, ruling them out as a mechanical factor in gyrogenesis (Goldman-Rakic 1987).

What other processes perhaps internal to the cortex might drive folding? A number of theories have been proposed. These are largely variations on the theme that the tangential expansion of the cortex itself drives folding. One such theory is that the expansion of the cortex is non-uniform in the radial direction, meaning that upper cortical layers expand more than lower layers (Richman et al. 1975). This excess growth in turn is postulated to engender the buckling of the cortex, with varying patterns of differential growth producing the characteristic patterns of gyri and sulci. However, it has been pointed out (Van Essen 1997; Toro and Burnod 2005) that the same pattern of differential growth could equally be a consequence, rather than a cause, of folding. A subsequent modified version of this idea (Toro and Burnod 2005; Xu et al. 2010) suggests that cortical folding arises more simply from tangential surface expansion. According to this view, tangential expansion of the cortex would lead to increases in tangential pressure across the expanding surface with the emergence

How do cortices fold? II

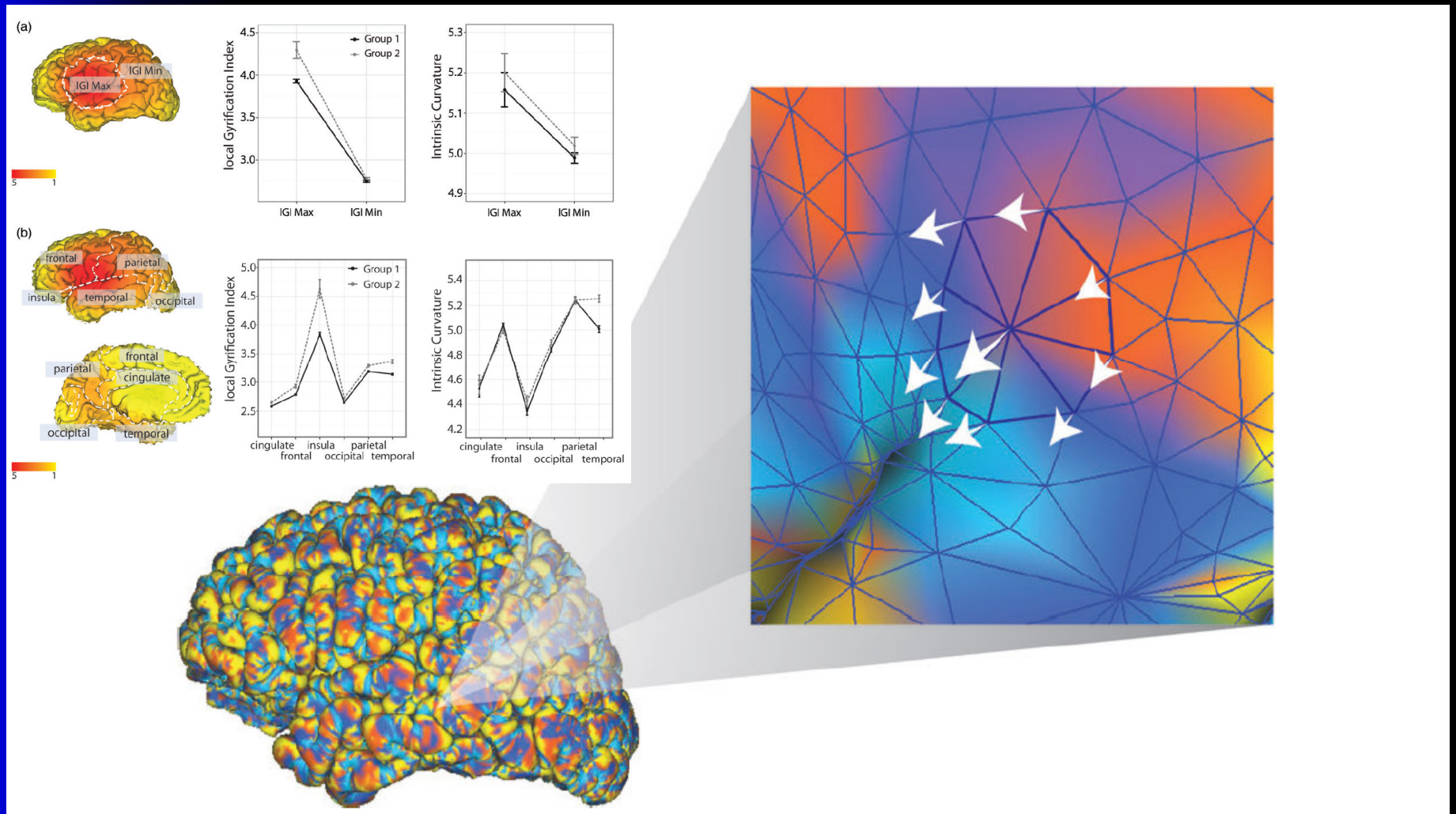


Figure 2. Illustration of Caret-derived intrinsic curvature which is calculated per vertex on the FreeSurfer-derived surface reconstruction. In the vertex illustrated, the associated surface normals are drawn. For the calculation of curvature at this vertex, the surface normal is taken as an average of these surrounding surface normals.

Como o córtex se dobra? III

- Ele estica!

Annals of Biomedical Engineering (© 2015)
DOI: 10.1007/s10439-015-1312-9

BMES BIOMEDICAL ENGINEERING SOCIETY™ www.bmes.org

Emerging Brain Morphologies from Axonal Elongation

MARIA A. HOLLAND,[1] KYLE E. MILLER,[2] and ELLEN KUHL[3]

[1]Department of Mechanical Engineering, Stanford University, Stanford, CA 94305, USA; [2]Department of Zoology, Michigan State University, East Lansing, MI 48824, USA; and [3]Departments of Mechanical Engineering, Bioengineering, and Cardiothoracic Surgery, Stanford University, Stanford, CA 94305, USA

(*Received 7 October 2014; accepted 23 March 2015*)

Associate Editor Gerhard A. Holzapfel oversaw the review of this article.

Abstract—Understanding the characteristic morphology of our brain remains a challenging, yet important task in human evolution, developmental biology, and neurosciences. Mathematical modeling shapes our understanding of cortical folding and provides functional relations between cortical wavelength, thickness, and stiffness. Yet, current mathematical models are phenomenologically isotropic and typically predict non-physiological, periodic folding patterns. Here we establish a mechanistic model for cortical folding, in which macroscopic changes in white matter volume are a natural consequence of microscopic axonal growth. To calibrate our model, we consult axon elongation experiments in chick sensory neurons. We demonstrate that a single parameter, the axonal growth rate, explains a wide variety of *in vitro* conditions including immediate axonal thinning and gradual thickness restoration. We embed our axonal growth model into a continuum model for brain development using axonal orientation distributions motivated by diffusion spectrum imaging. Our simulations suggest that white matter anisotropy—as an emergent property from directional axonal growth—intrinsically induces symmetry breaking, and predicts more physiological, less regular morphologies with regionally varying gyral wavelengths and sulcal depths. Mechanistic modeling of brain development could establish valuable relationships between brain connectivity, brain anatomy, and brain function.

Keywords—Neuromechanics, Brain development, Cortical folding, Mechanotransduction, Growth, Symmetry breaking.

in information processing capacity,[27] are widely appreciated, the mechanism of how it arises is still under investigation.[49] Also unknown is the exact role that cortical folding plays in the function of the brain, although research has indicated that abnormal folding can be associated with mental and psychological problems including autism[34] and schizophrenia.[45] A deeper understanding of the process of cortical folding and its relationship to the workings of the healthy brain could lead to improved diagnostics, treatments, and interventions for folding abnormalities in the diseased brain.

While some folds, known as the primary gyri and sulci, are located fairly consistently across individuals of the same species, secondary and tertiary folds exhibit a more varied pattern.[6] The consistency of primary folding has been attributed to specific heterogeneities including spatial or temporal variations in growth.[58] The variation of secondary and tertiary folding is thought to be an instability phenomenon triggered by some form of stress in the developing brain.[6] During the later stages of development, when primary folds are already in place,[23] the formation and loss of cortico-cortical connections may alter the cortical thickness and reshape existing folds, particularly in certain pathologies including autism[25] and schizophrenia.[45]

Como o córtex se dobra?? IV

- Ele se amassa!

BRAIN STRUCTURE

Cortical folding scales universally with surface area and thickness, not number of neurons

Bruno Mota[1] and Suzana Herculano-Houzel[2,3]*

Larger brains tend to have more folded cortices, but what makes the cortex fold has remained unknown. We show that the degree of cortical folding scales uniformly across lissencephalic and gyrencephalic species, across individuals, and within individual cortices as a function of the product of cortical surface area and the square root of cortical thickness. This relation is derived from the minimization of the effective free energy associated with cortical shape according to a simple physical model, based on known mechanisms of axonal elongation. This model also explains the scaling of the folding index of crumpled paper balls. We discuss the implications of this finding for the evolutionary and developmental origin of folding, including the newfound continuum between lissencephaly and gyrencephaly, and for pathologies such as human lissencephaly.

The expansion of the cerebral cortex, the most obvious feature of mammalian brain evolution, is generally accompanied by increasing degrees of folding of the cortical surface into sulci and gyri (*1*). Cortical folding has been considered a means of allowing numbers of neurons in the cerebral cortex to expand beyond what would be possible in a lissencephalic cortex, presumably as the cortical sheet expands laterally with a constant number of neurons beneath the surface (*2*, *3*). Although some models have shown cortical convolutions

[1]Instituto de Física, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil. [2]Instituto de Ciências Biomédicas, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil. [3]Instituto Nacional de Neurociência Translacional, INCT/MCT, São Paulo, Brazil.
*Corresponding author. E-mail: suzanahh@gmail.com

… como uma bola de papel

A4

A5

A6

A7

A8

A9

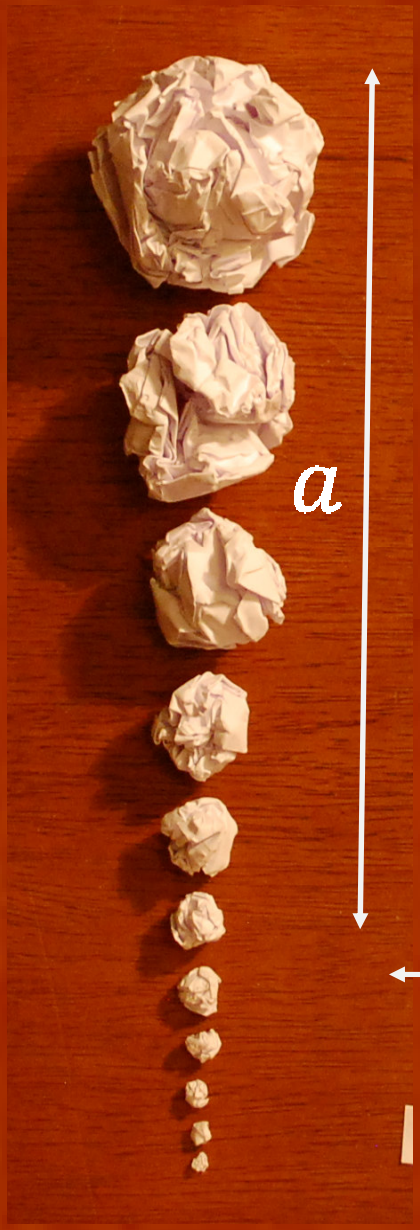
.

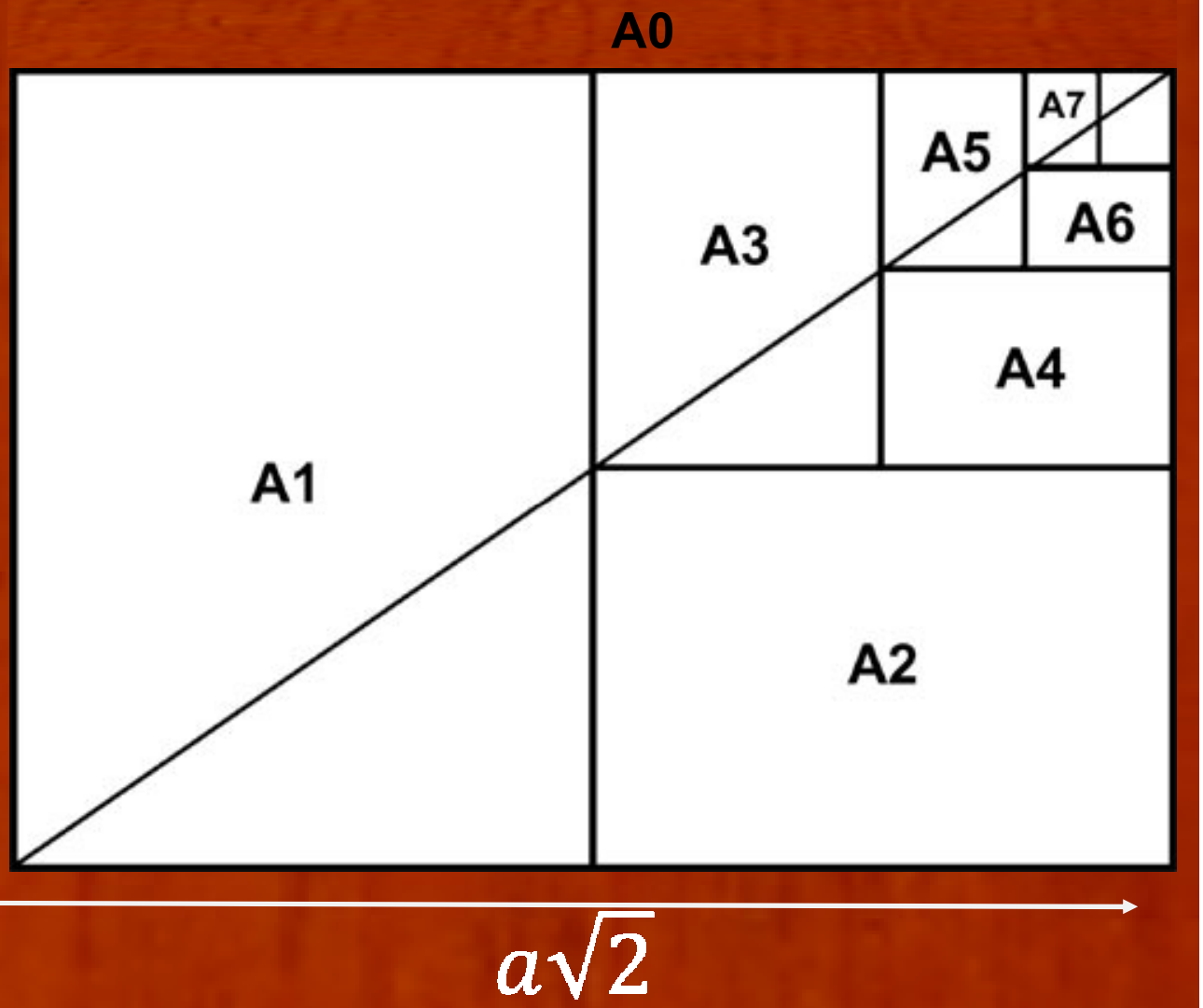
.

.

.

.





Dicotomias falsas

- Baixa resolução vs alta resolução
- Neuroanatomia comparativa vs MRI humano
- Efeitos de superfície vs efeitos de volume
- Ciência dos matérias vs geometria diferencial vs física estatística

Precisamos de previsões quantitativas para testar hipóteses!

Afinal, estas são modelos. Nenhum deve explicar completamente todas as características da morfologia cortical.

Quantificando a girificação

- As variáveis de baixa resoluçãp
  - Area total A_T
  - Area exposta A_E
  - Espessura média T

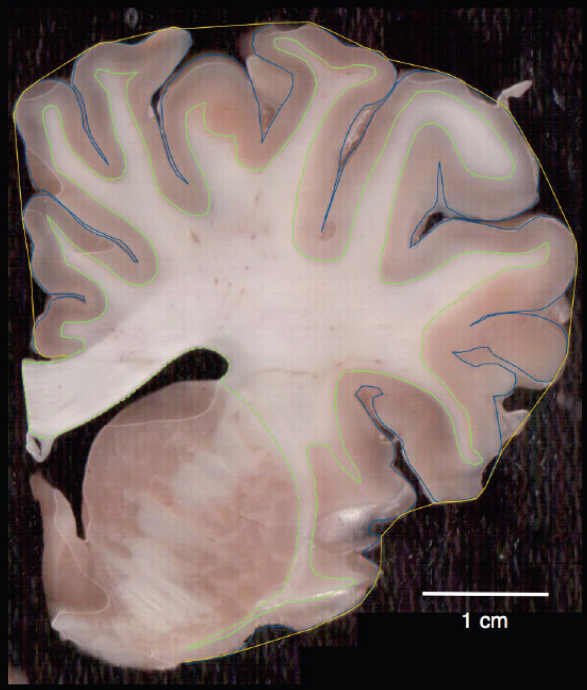
Single hemisphere

A_T , A_E

Folding index = A_T / A_E

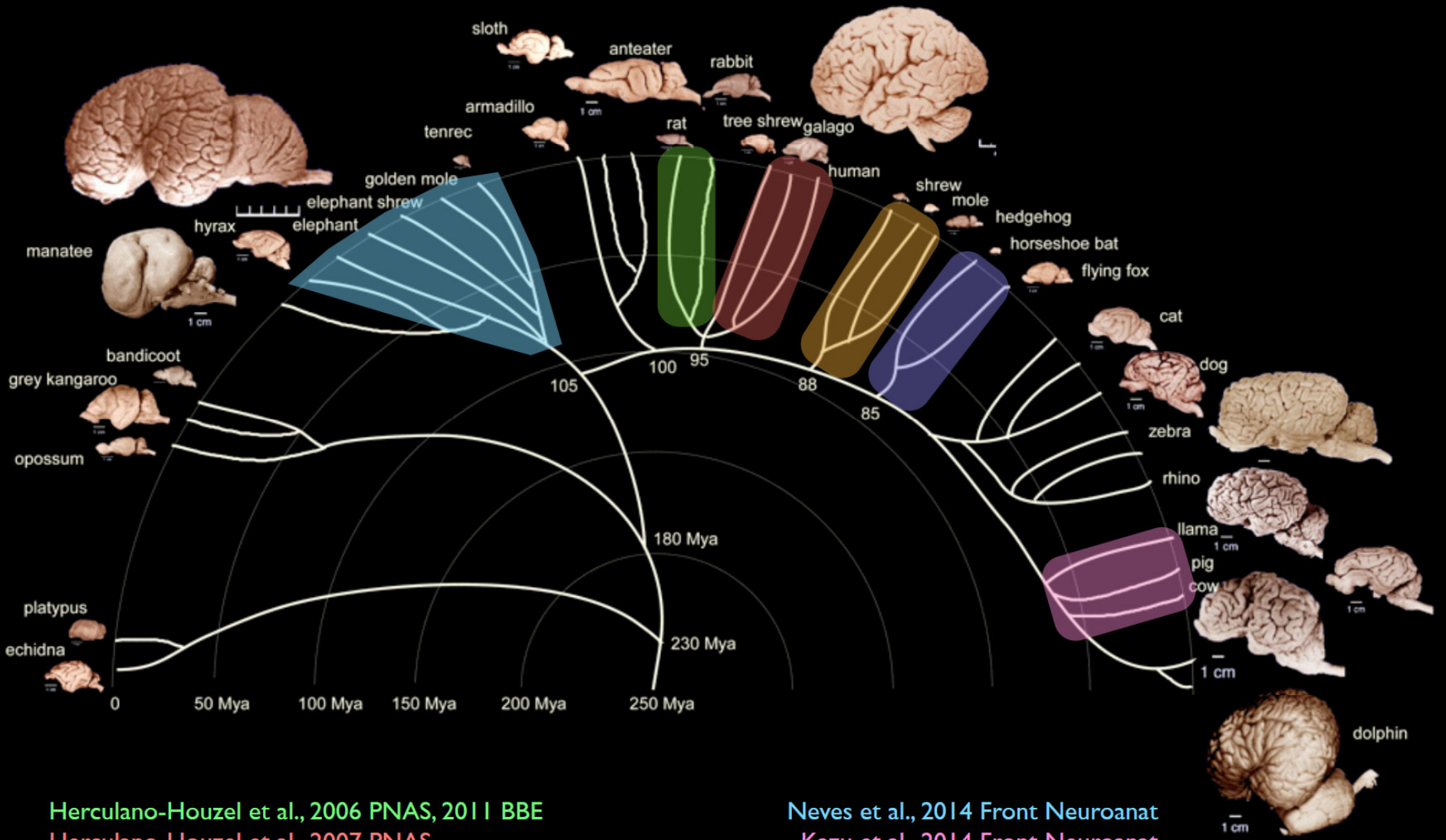
V_G from Cavalieri

$T = V_G / A_T$



Giraffe, Kazu et al.

Cortical diversity in the light of evolution

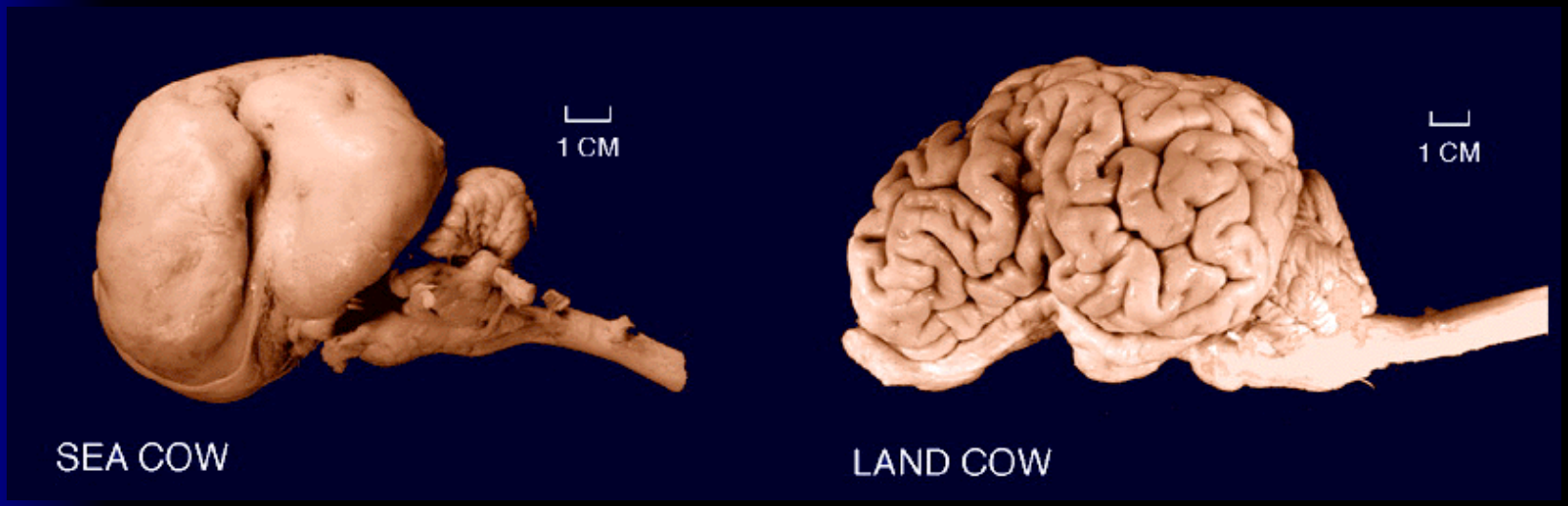


Herculano-Houzel et al., 2006 PNAS, 2011 BBE
Herculano-Houzel et al., 2007 PNAS
Azevedo et al., 2009 JCN
Gabi et al., 2010 BBE
Sarko et al., 2009 FrontNeuroanat

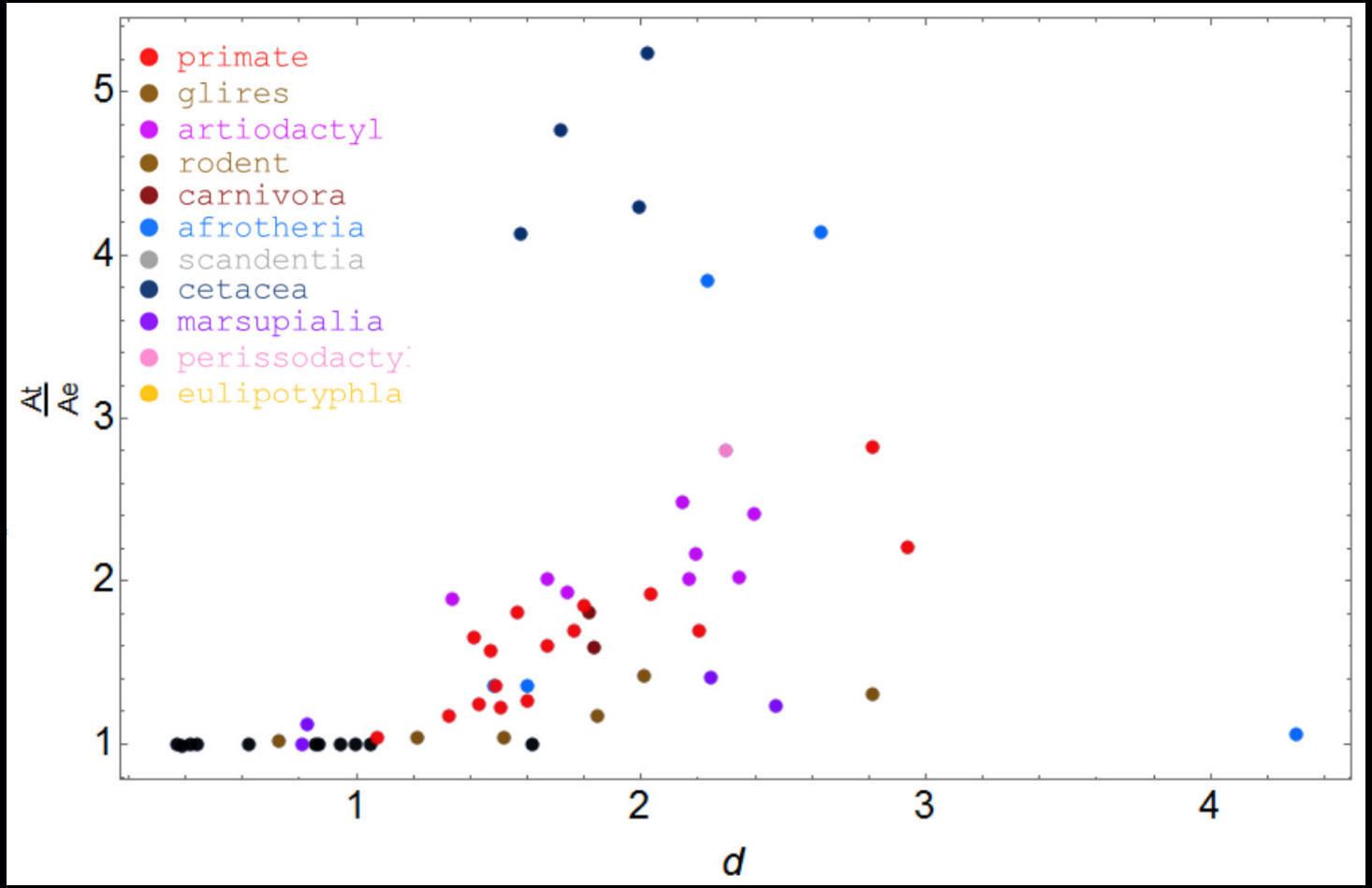
Neves et al., 2014 Front Neuroanat
Kazu et al., 2014 Front Neuroanat
Herculano-Houzel et al., in preparation
in collaboration
with Paul Manger, U. Witwatersrand, South Africa

O Cortex cerebral

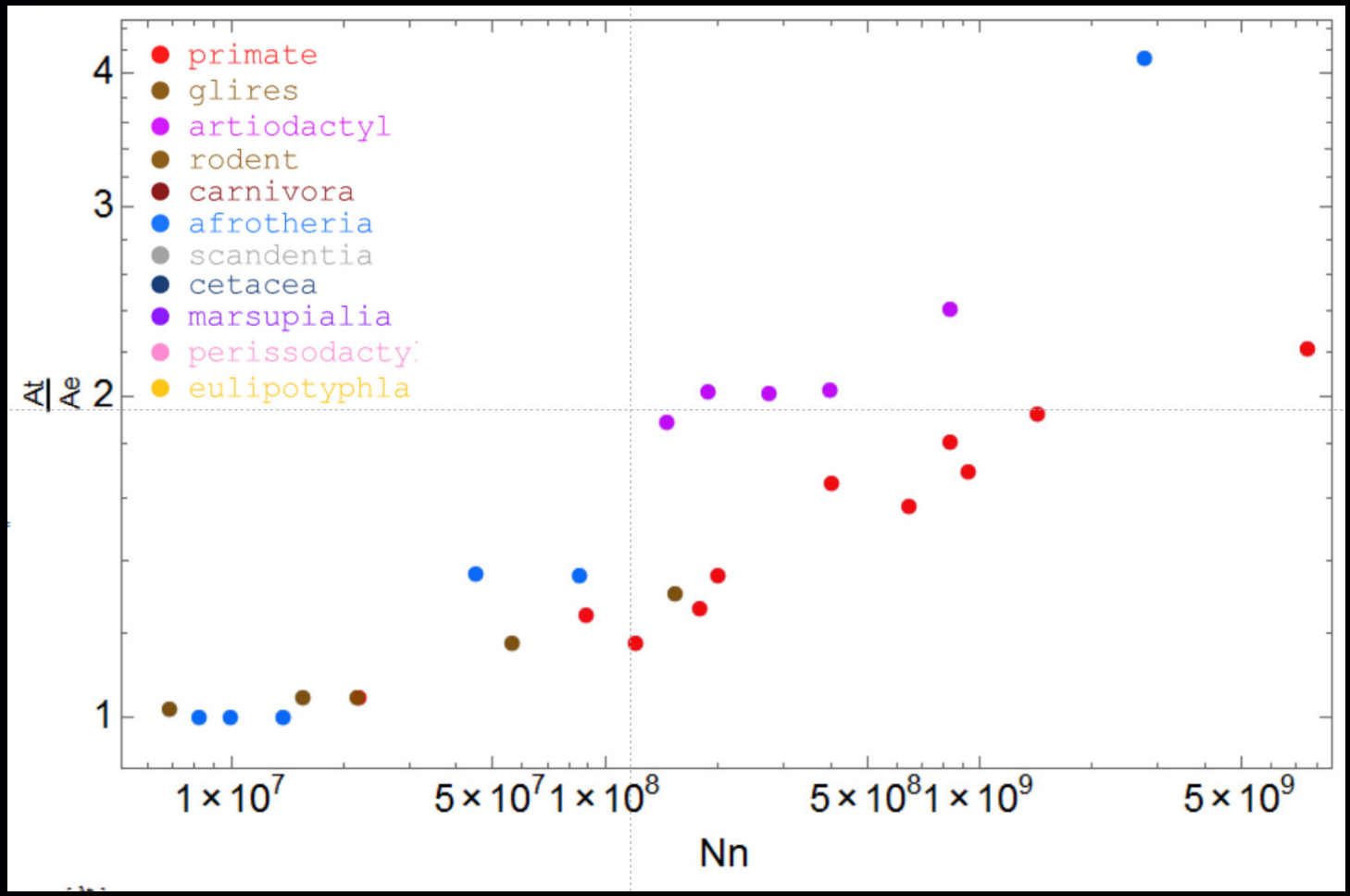
- Se girificação é uma adaptação, ela ocorreu diversas vezes
- Cortices maiores são em geral mais girificados
- Mas nem sempre!



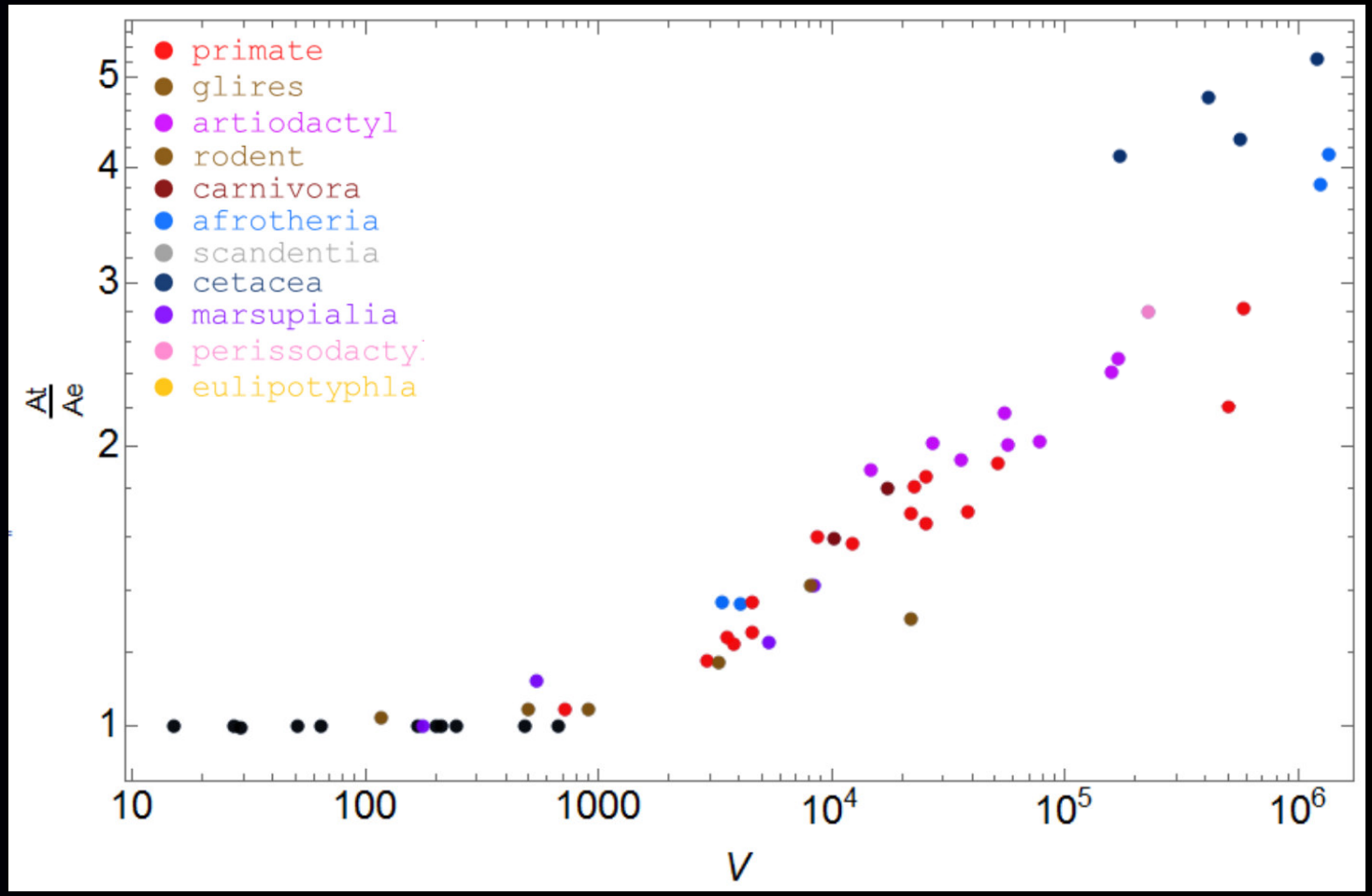
Folding is not determined by cortical thickness…



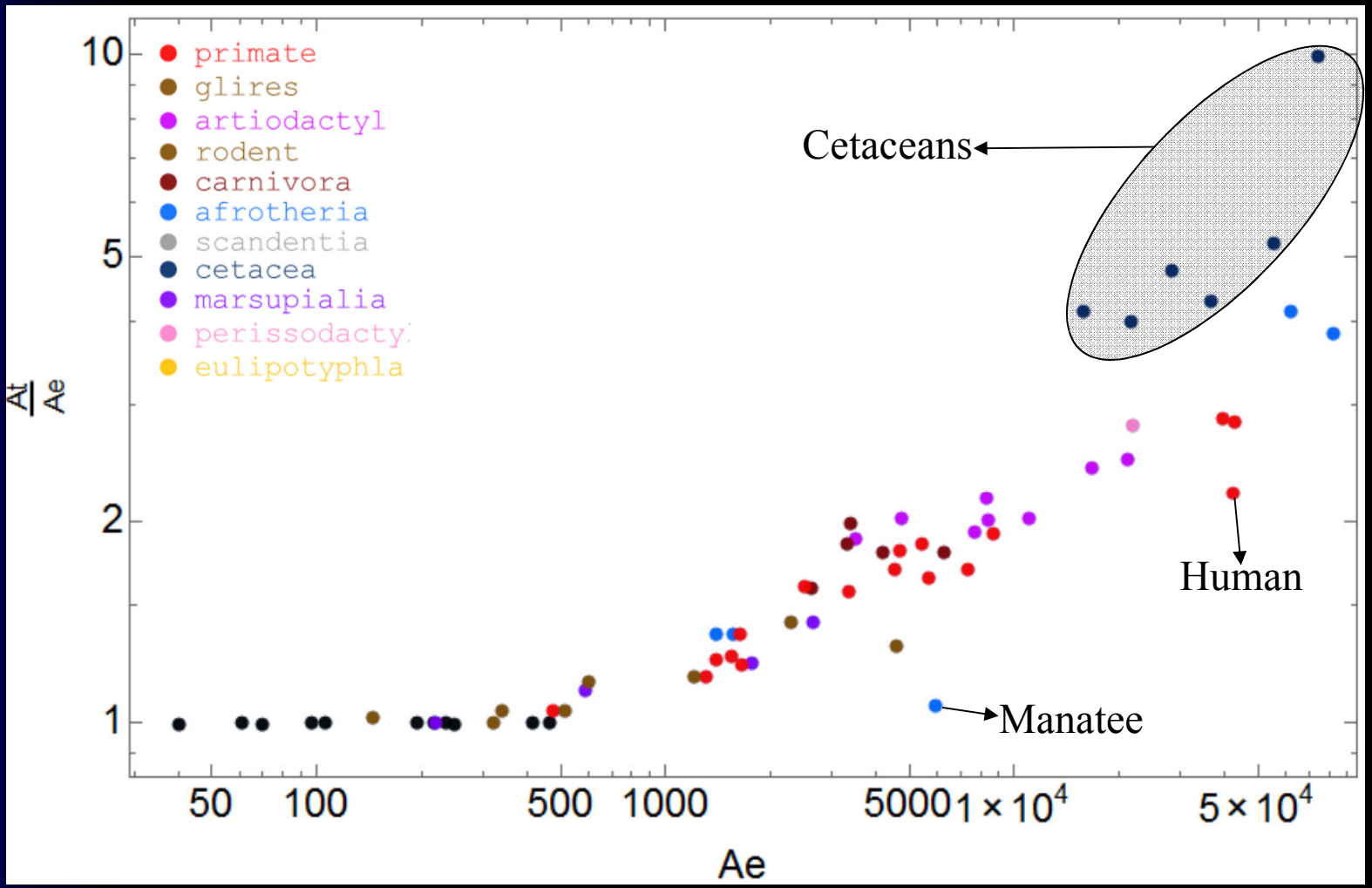
… or number of neurons



Folding is sort of related to volume…

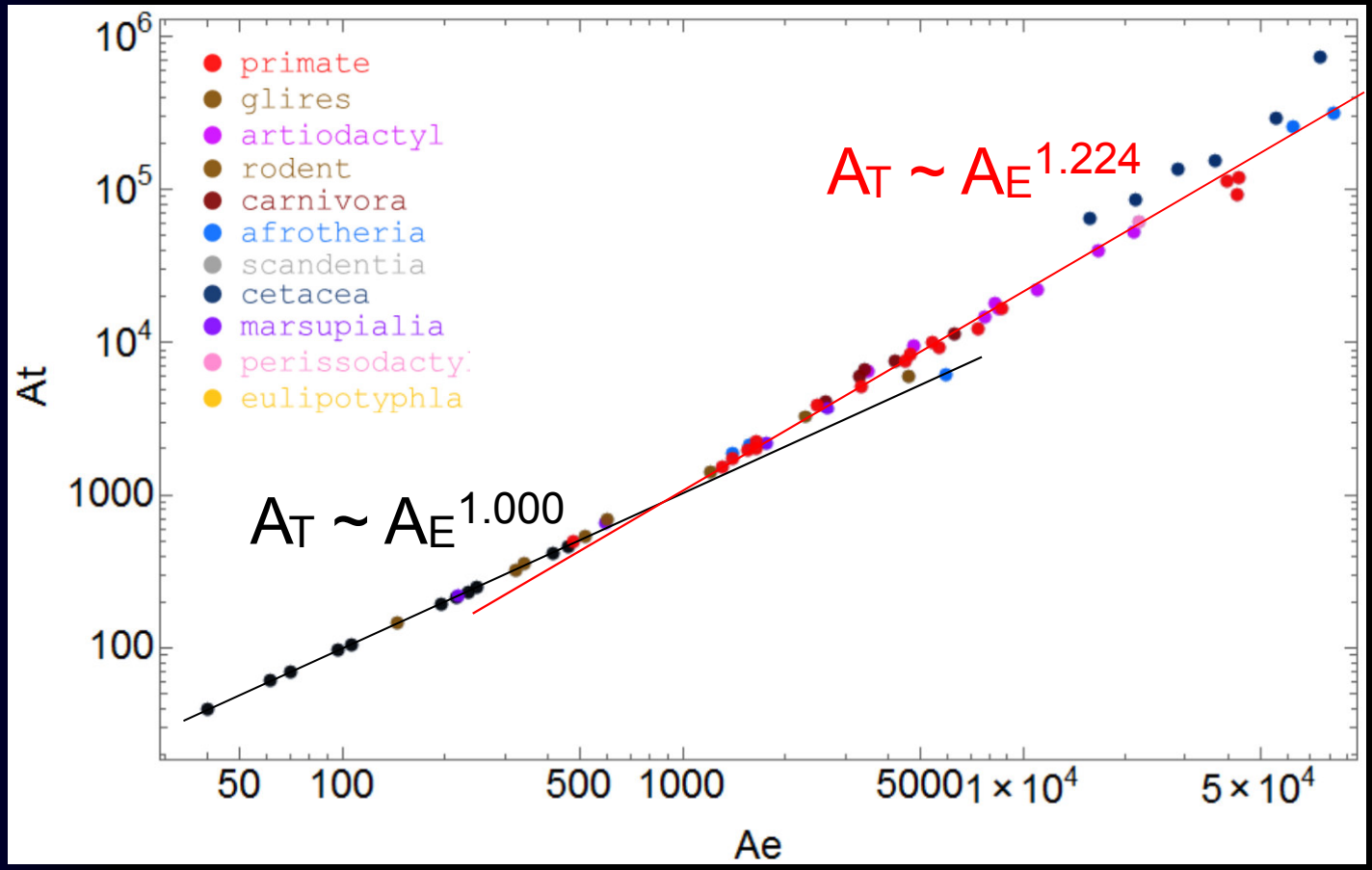


Folding is a better function of cortical surface area



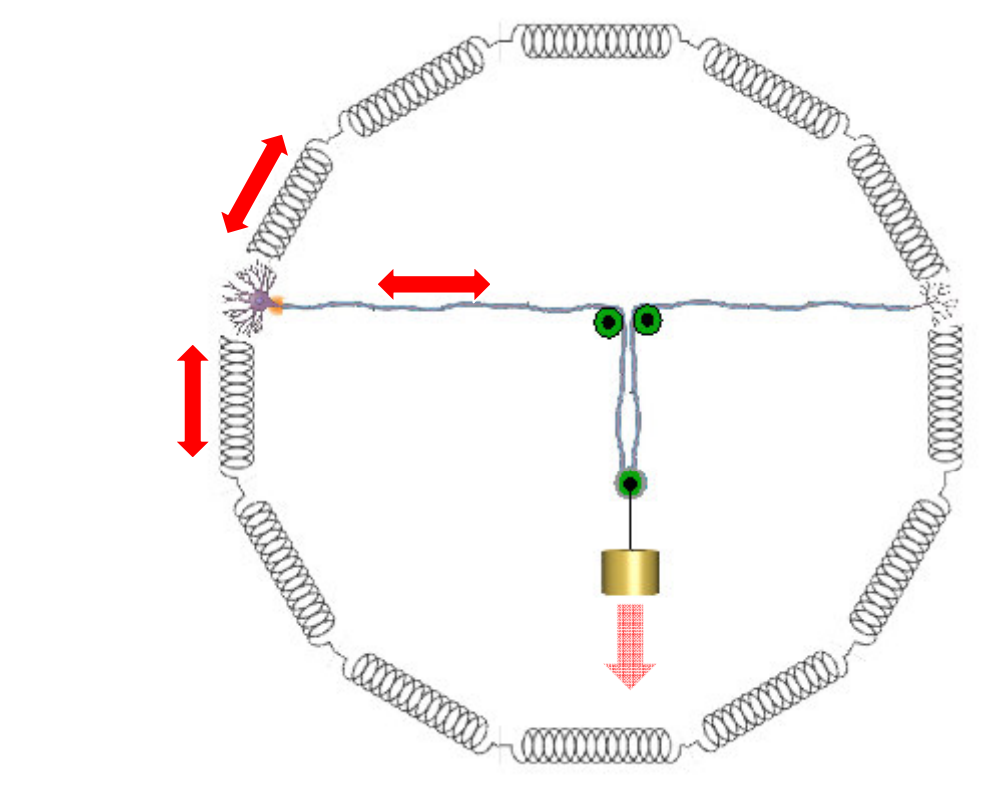
Folding index is a RATIO: look directly at A_T x A_E

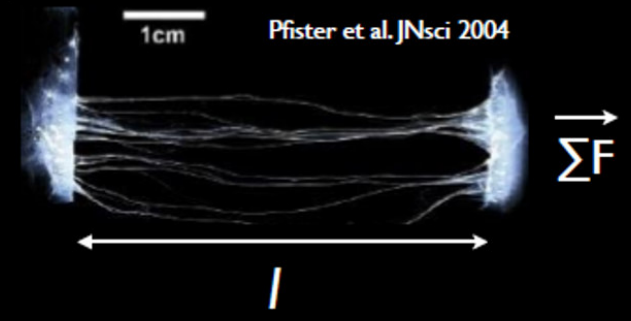
Equivalently, comparing total and exposed areas



Power law suggests cortices are self-similar down to some fundamental scale

The dynamics I: Axonal effective energy minimization





$$\frac{dl}{dt} = (\sum F_{ext} - F_0).b.a$$

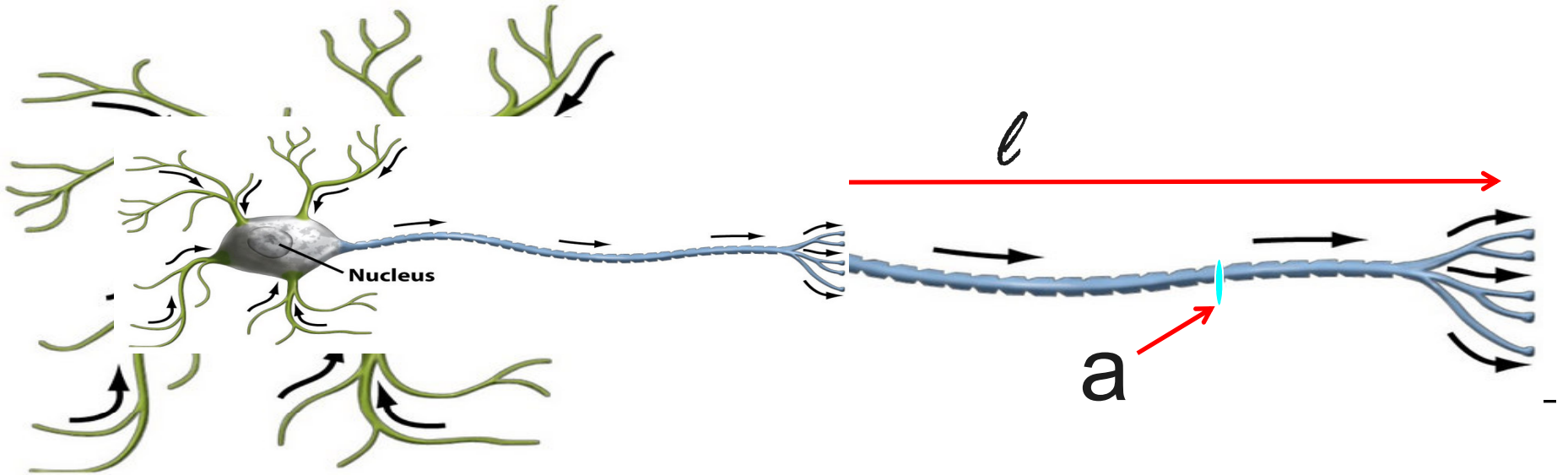
$$E_{axon} = F_0.b.a.l$$

p v

$$E_V = p\sum v = p.V_w$$

$$E_V = (p + p_{csf})\frac{2}{9\sqrt{3\pi}}\left(\frac{2}{9\sqrt{3\pi}}A_E^{3/2} - TA_T\right) - \sigma A_T$$

The dynamics II: Wiring length minimization?

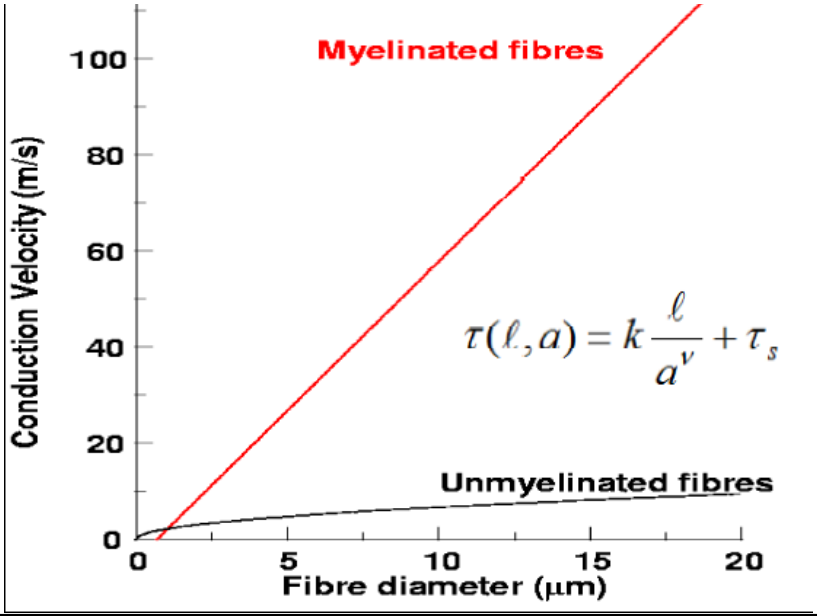


$v_{axon} = a\,\ell$

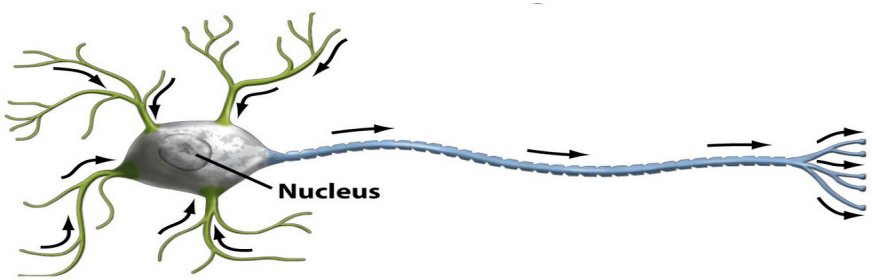
$v_{axon} = v'_{axon}$

$\nu_{myelinated} = 1/2$

$\nu_{unmyelinated} = 1/4$



The dynamics II: Wiring length minimization?



$$T_{\text{big axon}} = T_{\text{small axon}}$$

So, why doesn't the WM shrink to a point?

Self-avoidance! The surface can´t intersect itself

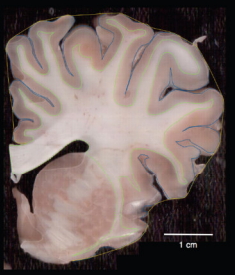
Single hemisphere

A_T , A_E

Folding index = A_T / A_E

V_G from Cavalieri

$T = V_G / A_T$



Giraffe, Kazu et al.

$$E_S[\vec{s},n] = \int d^2\vec{x}_1 d^2\vec{x}_2 \delta^2\left(\vec{s}(\vec{x}_1) - \vec{s}(\vec{x}_2)\right)\Lambda_T\left(n(\vec{x}_1) - n(\vec{x}_2)\right)$$

$$\Lambda_T(u) = T - 2|u| \quad \text{if} \quad -T/2<u<T/2, \quad 0 \quad \text{otherwise}$$

$$F_S \alpha\, T\frac{A_T^2}{A_E} \quad \text{(Flory)}$$

The free energy

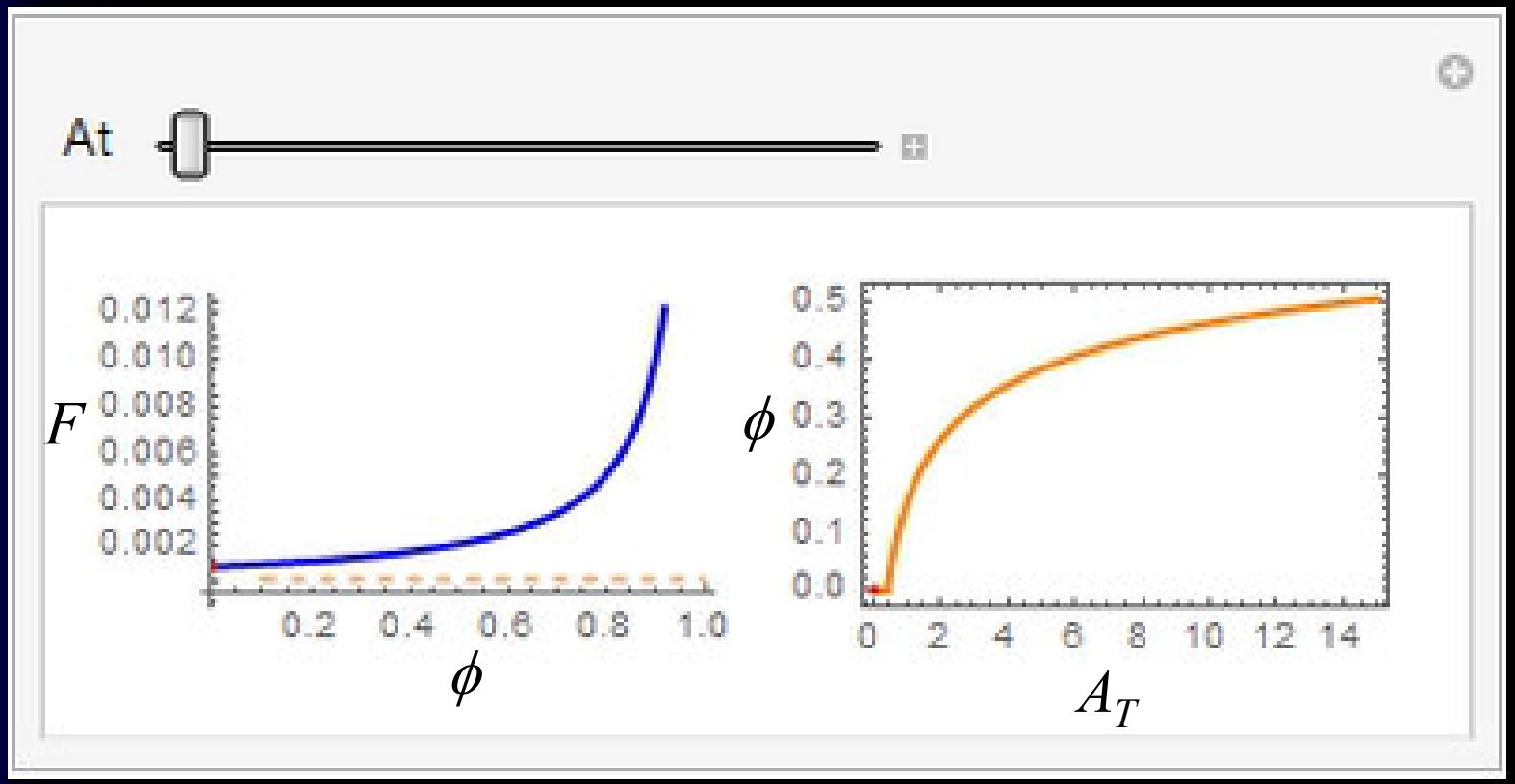
$$F = \alpha T \frac{A_T^2}{A_E} - \sigma A_T + (p + p_{csf}) \left(\frac{2}{9\sqrt{3\pi}} A_E^{3/2} - T A_T \right)$$

$$\frac{\partial F}{\partial A_E} = 0$$

$$T^{1/2} A_T = k A_E^{\frac{5}{4}}$$

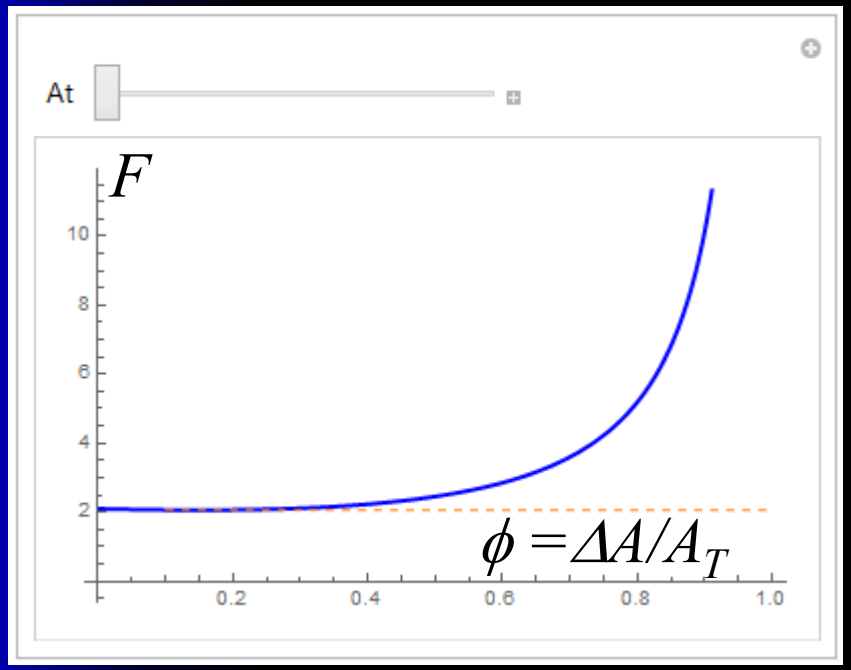
The free energy

$$F = \alpha T \frac{A_T^2}{A_E} - \sigma A_T + (p + p_{csf}) \left(\frac{2}{9\sqrt{3\pi}} A_E^{3/2} - T A_T \right)$$

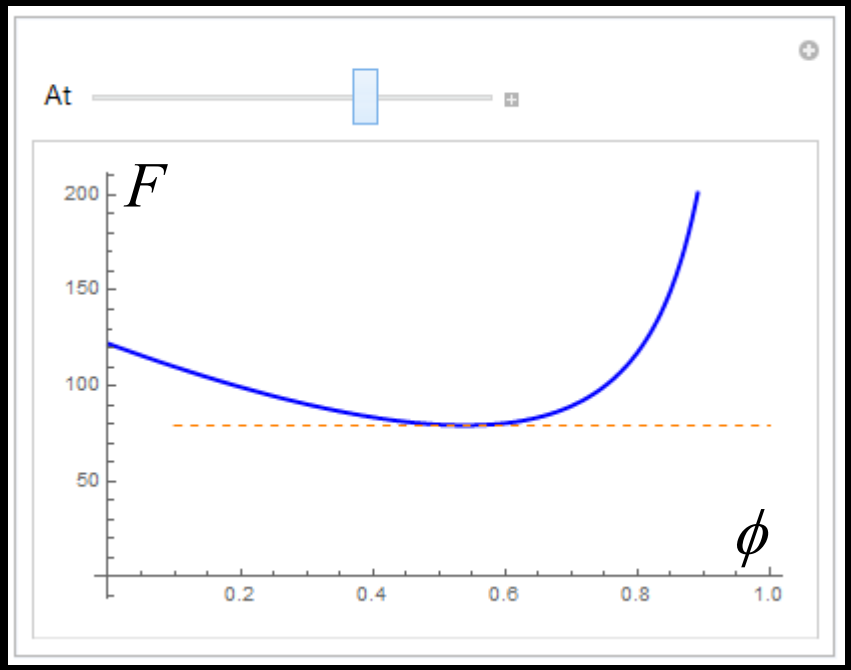


The free energy

$$F = \alpha T \frac{A_T^2}{A_E} - \sigma A_T + (p + p_{csf}) \left(\frac{2}{9\sqrt{3\pi}} A_E^{3/2} - T A_T \right)$$



Lisencephalic (smooth) cortex



Gyroencephalic (folded) cortex

A general rule for cortical folding...

$$\frac{A_T}{T^2} = k\left(\frac{A_E}{T^2}\right)^{\frac{5}{4}} \quad \Longleftrightarrow \quad T^{1/2}A_T = kA_E^{\frac{5}{4}}$$

Onset of folding

$$A_T \equiv A_E$$

$$A_T = k^{-4}\,T^2$$

From Gauss-Bonnet:

$$\overline{K_G} = \frac{4\pi}{A_-}$$

Onset of folding:

$$T^2\overline{K_G} = 4\pi\,\mathrm{k}^4$$

A general rule for cortical folding...

$$\frac{A_T}{T^2} = k\left(\frac{A_E}{T^2}\right)^{\frac{5}{4}}$$

Onset of folding

$$A_T \equiv A_E$$

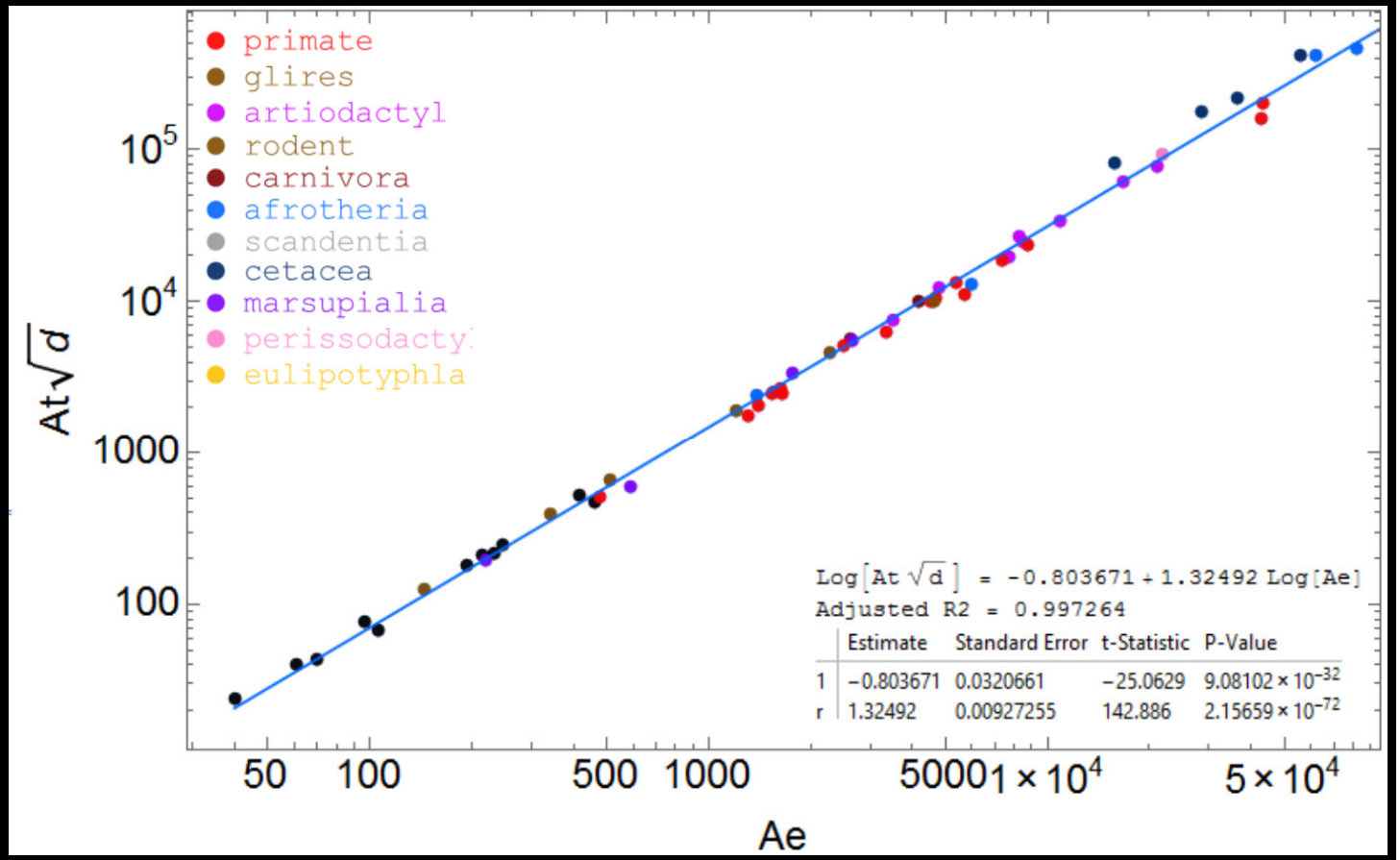
$$A_T = k^{-4}\, T^2$$

From Gauss-Bonnet:

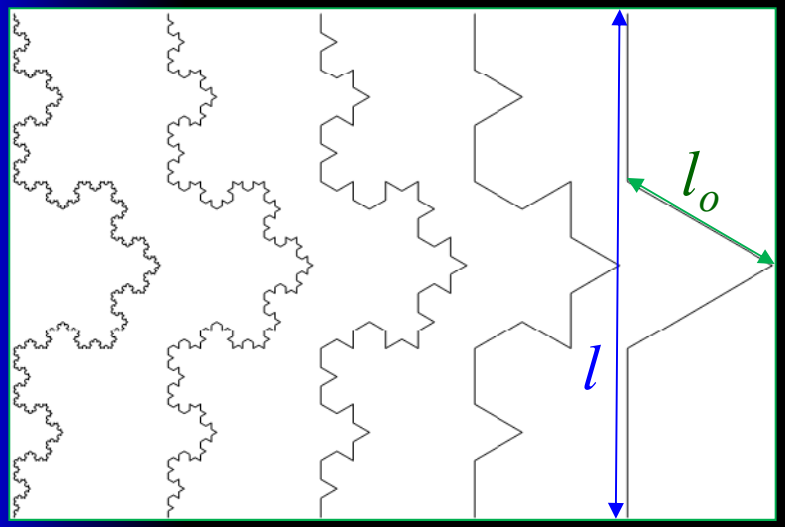
$$\overline{K_G} = \frac{4\pi}{A_-}$$

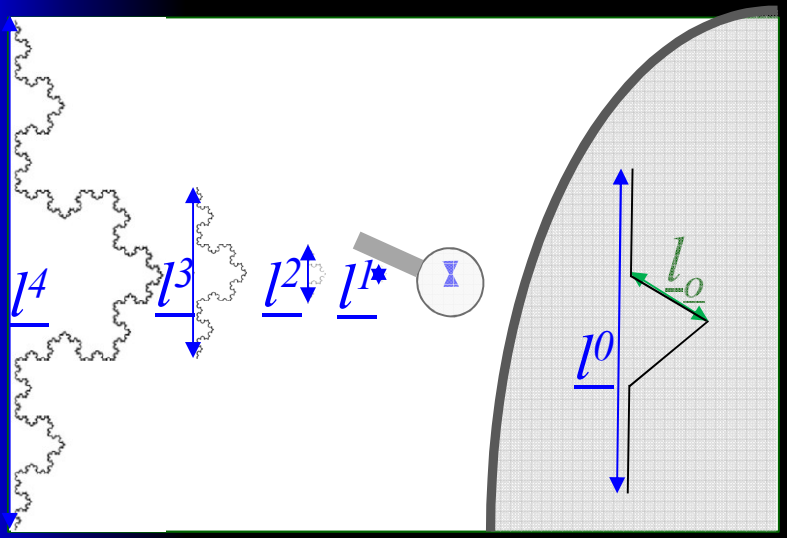
Onset of folding:

$$T^2\overline{K_G} = 4\pi\, k^4$$



A curva de Koch





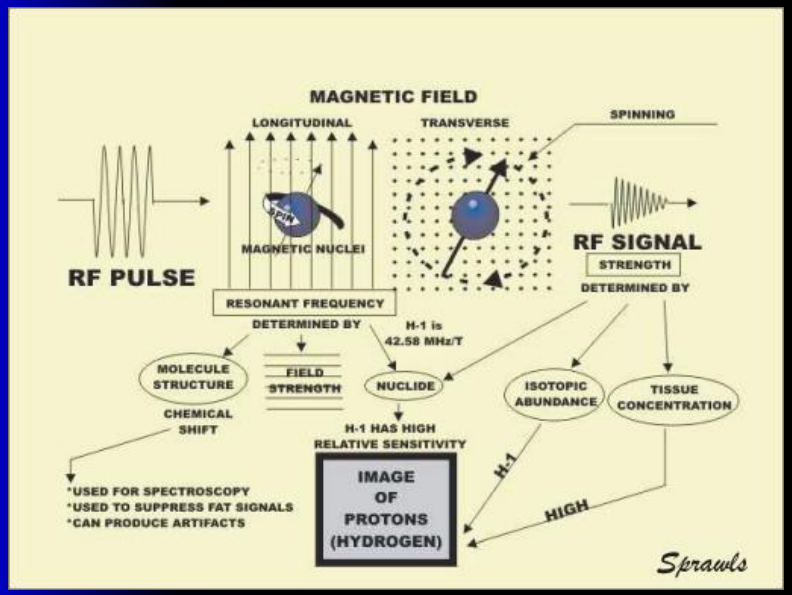
$$n = \left(\frac{l}{l_o}\right)^d$$

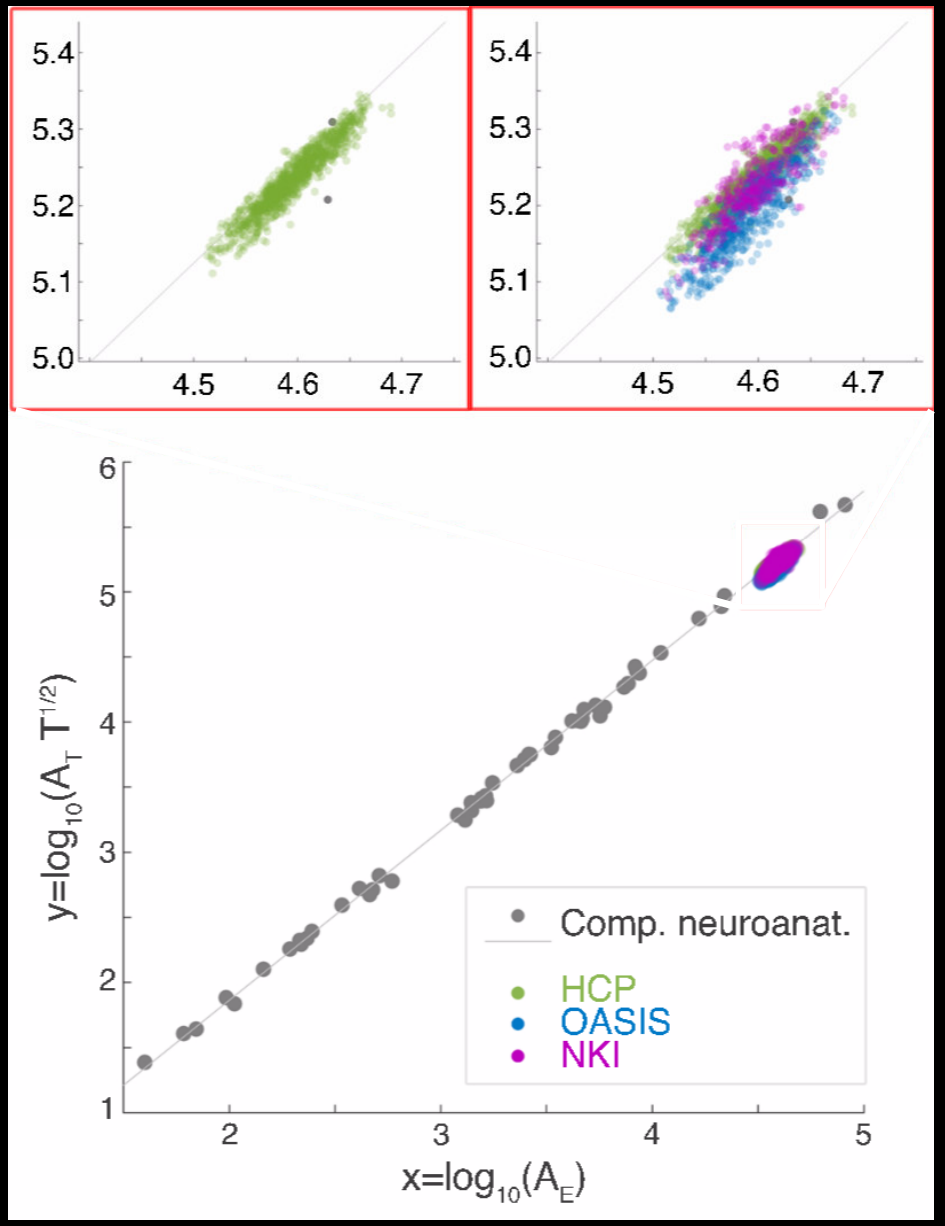
$$l_{intrinsic} = nl_0 = \frac{l^d_{extrinsic}}{l_0^{d-1}}$$

$$\frac{l_i}{l_o} = \left(\frac{l_e}{l_o}\right)^d$$

$$\frac{A_T}{T^2} = k\left(\frac{A_E}{T^2}\right)^{\frac{5}{4}}$$

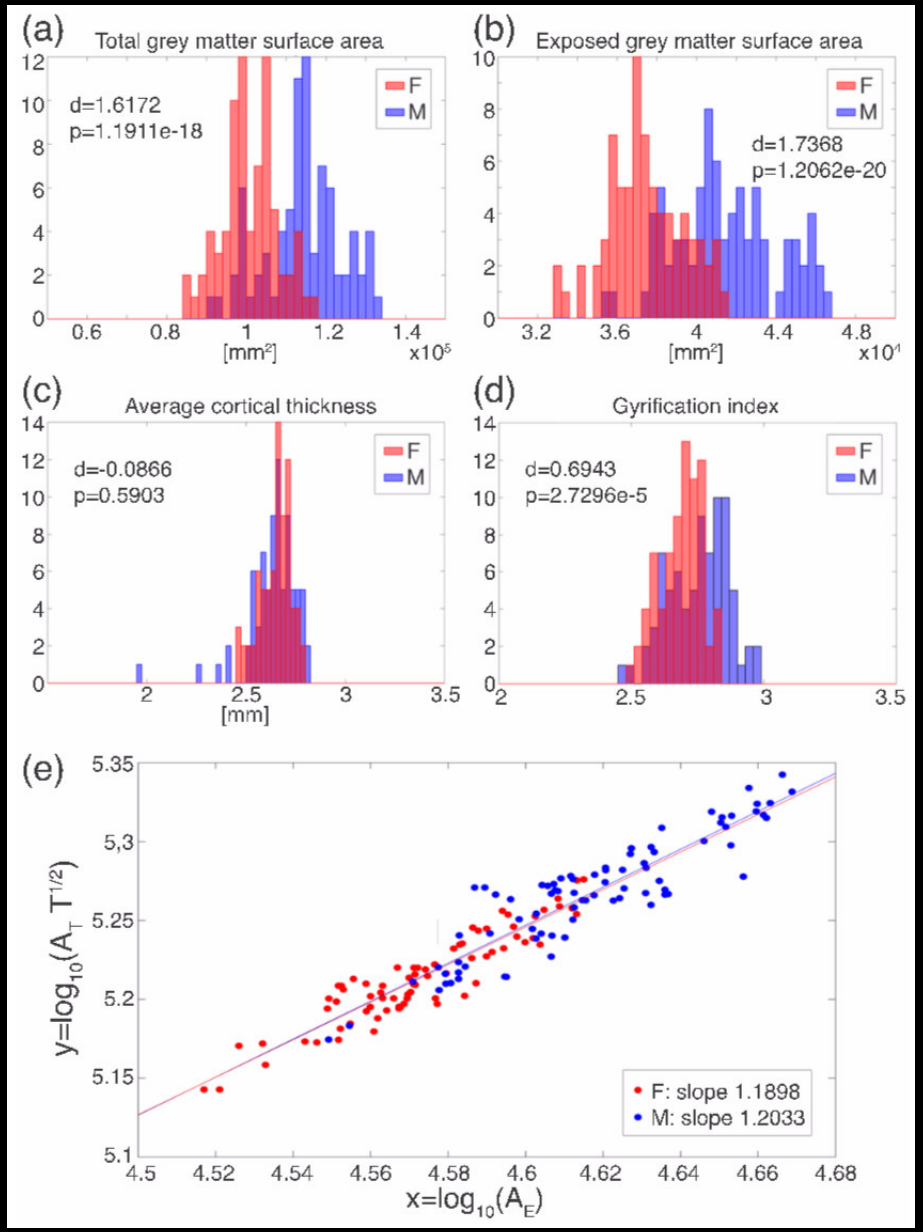
The human cortex: MRI scans and surface reconstruction





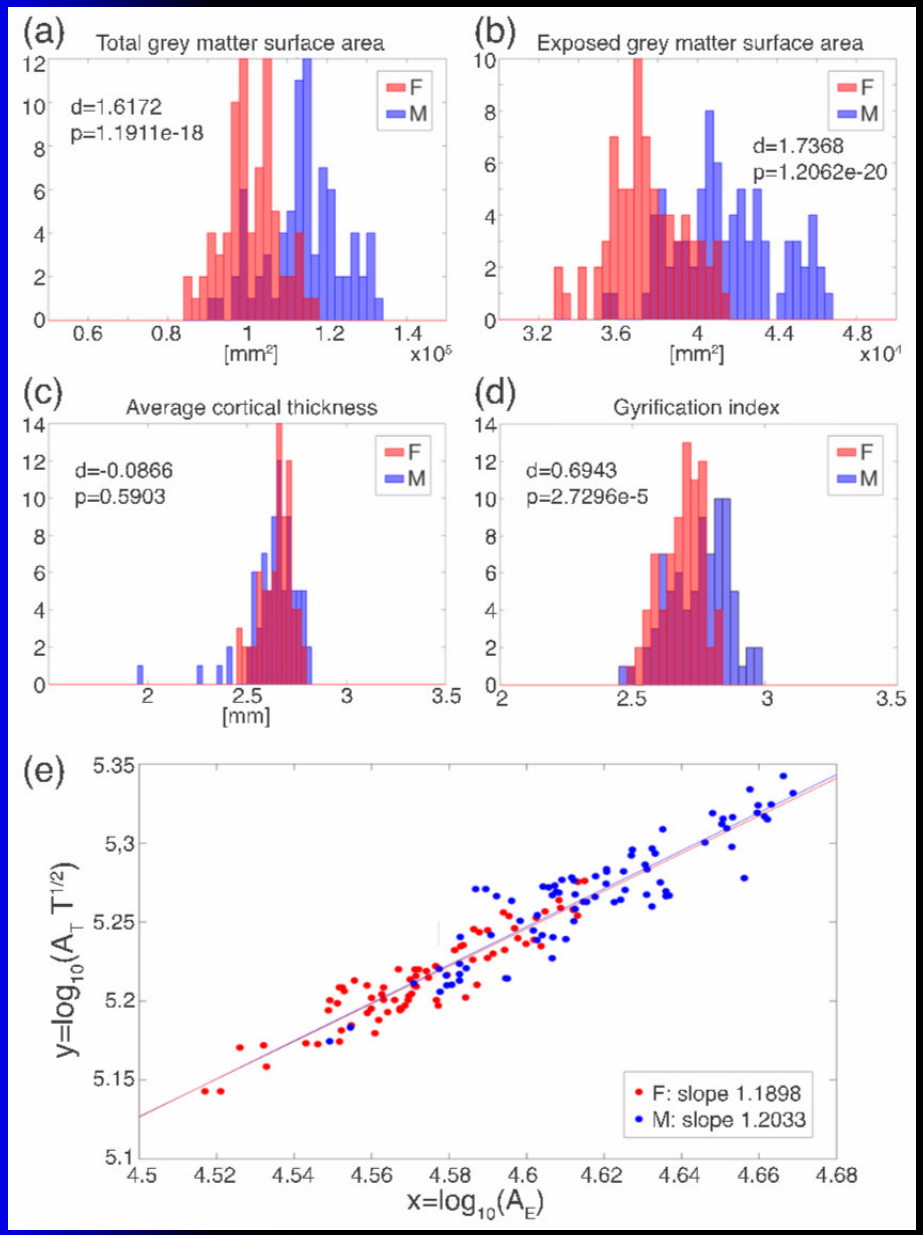
Wang, Y., Necus, J., Marcus, K, Mota, B. PNAS 2016

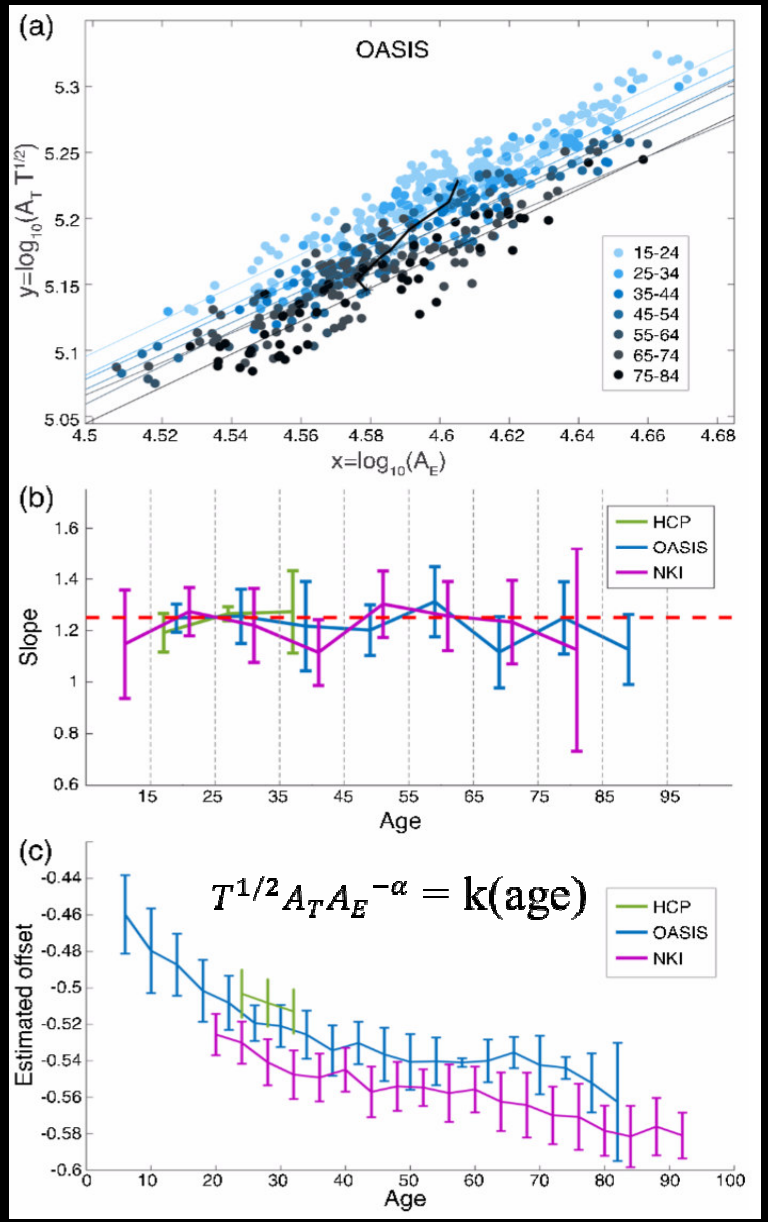
Same rule for men and women



Wang, Y., Necus, J., Marcus, K, Mota, B. PNAS 2016

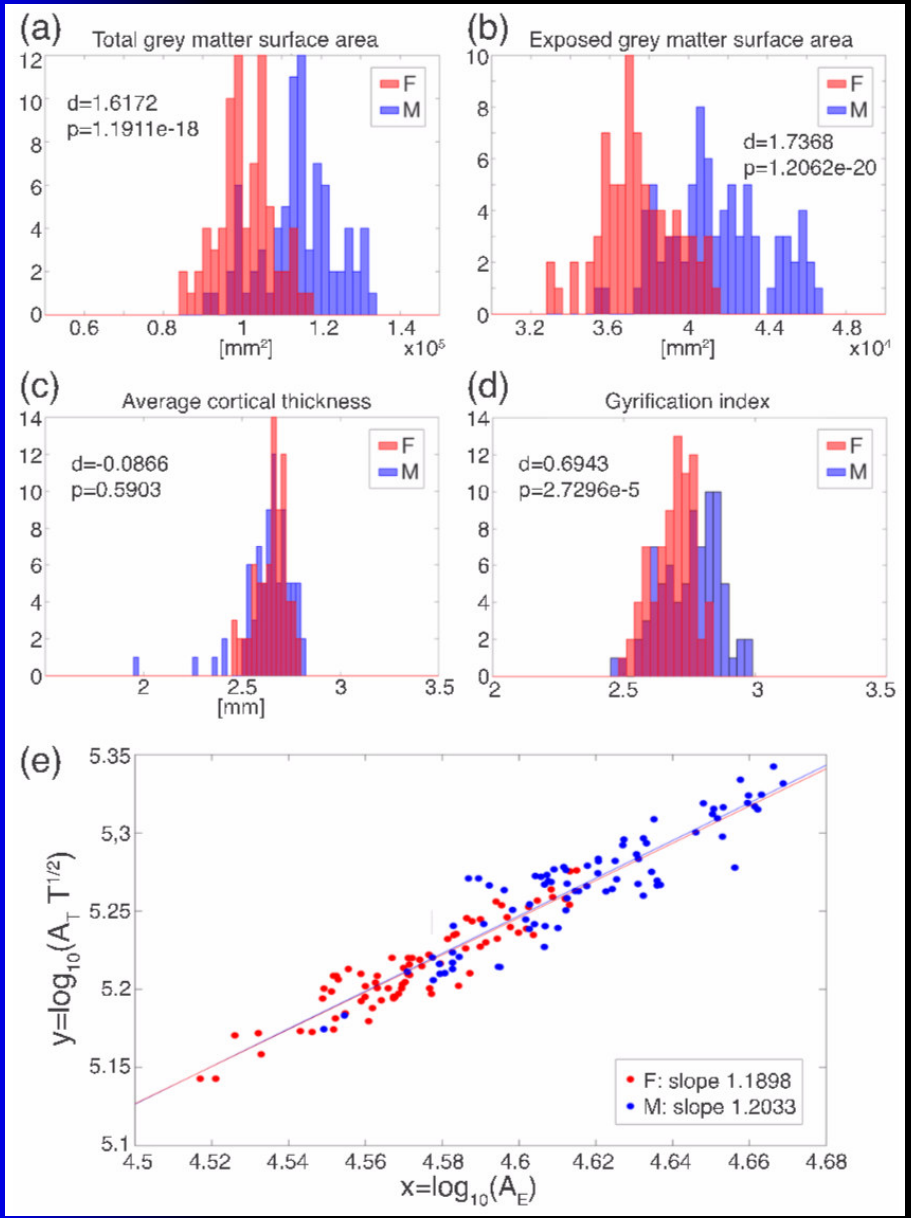
The offset changes with age, but not the slope

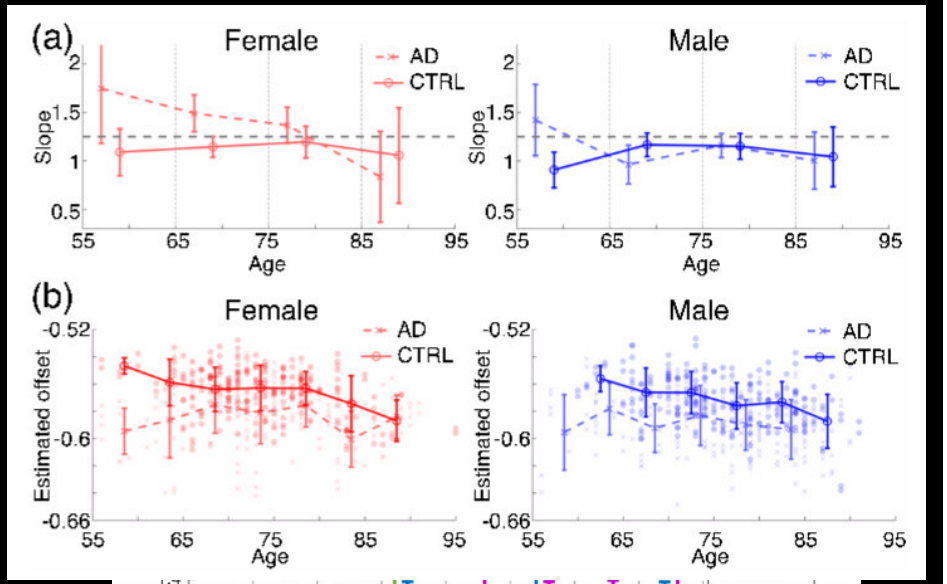


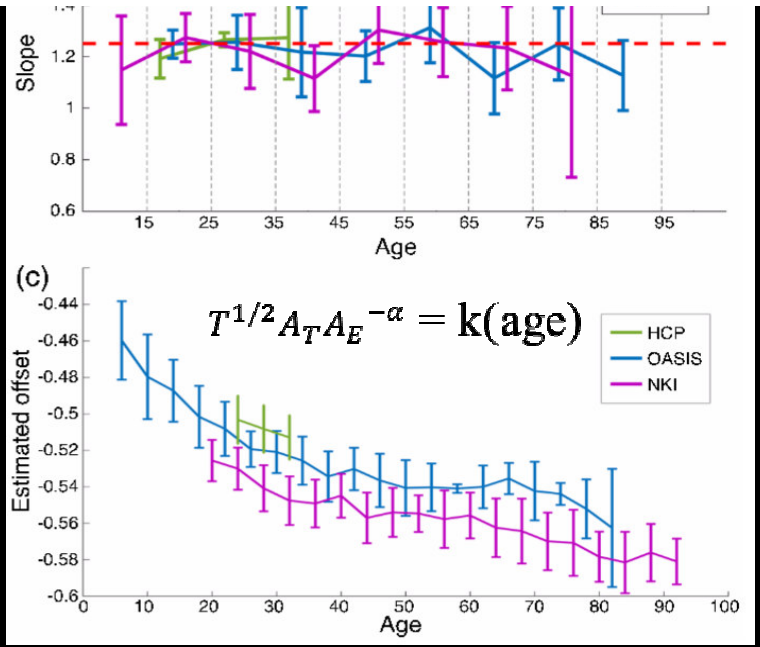


Wang, Y., Necus, J., Marcus, K, Mota, B. PNAS 2016

Alzheimer's is morphologically equivalent to premature aging







Wang, Y., Necus, J., Marcus, K, Mota, B. PNAS 2016

Criteria for realistic cortical folding theory needs?

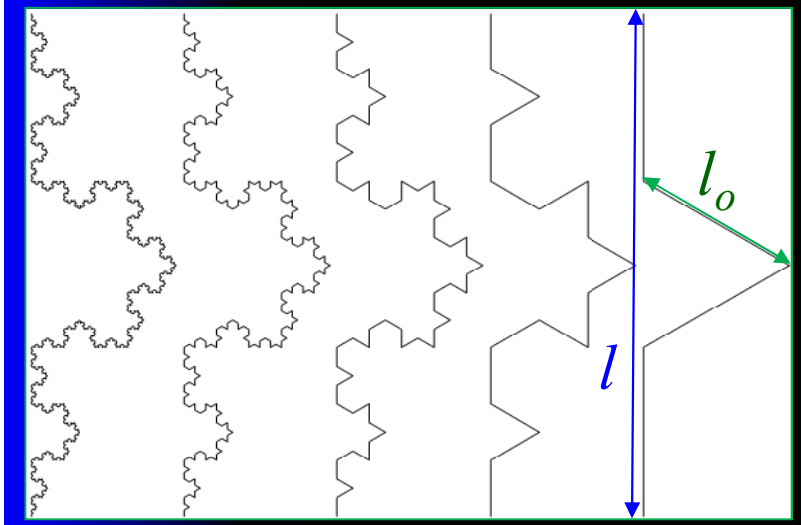
- T is (almost) the only length scale
- Account for surface and bulk dynamics
- Lisencephaly and gyrencephaly generated by the same dynamics
- $A_T T^{1/2} = k\, A_E^{5/4}$ scaling
- Deal with self-avoidance explicitally
- Folding not dependent on number or size of neurons

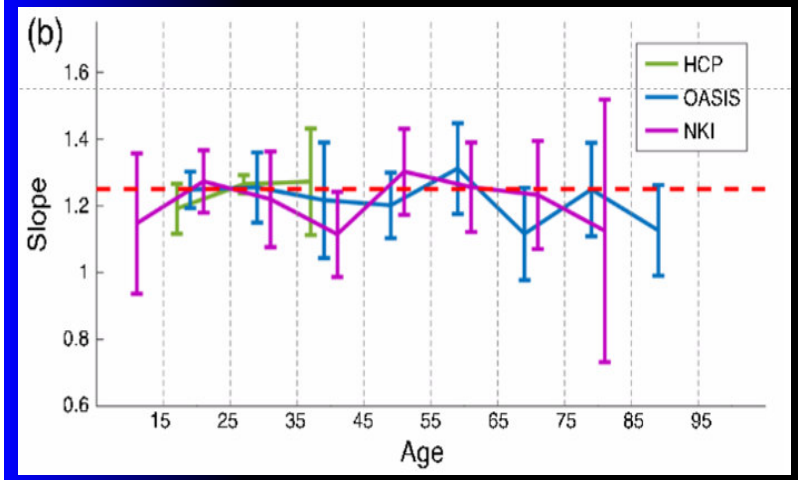
What drives, what is driven cortical folding is
also a false dichotomy!

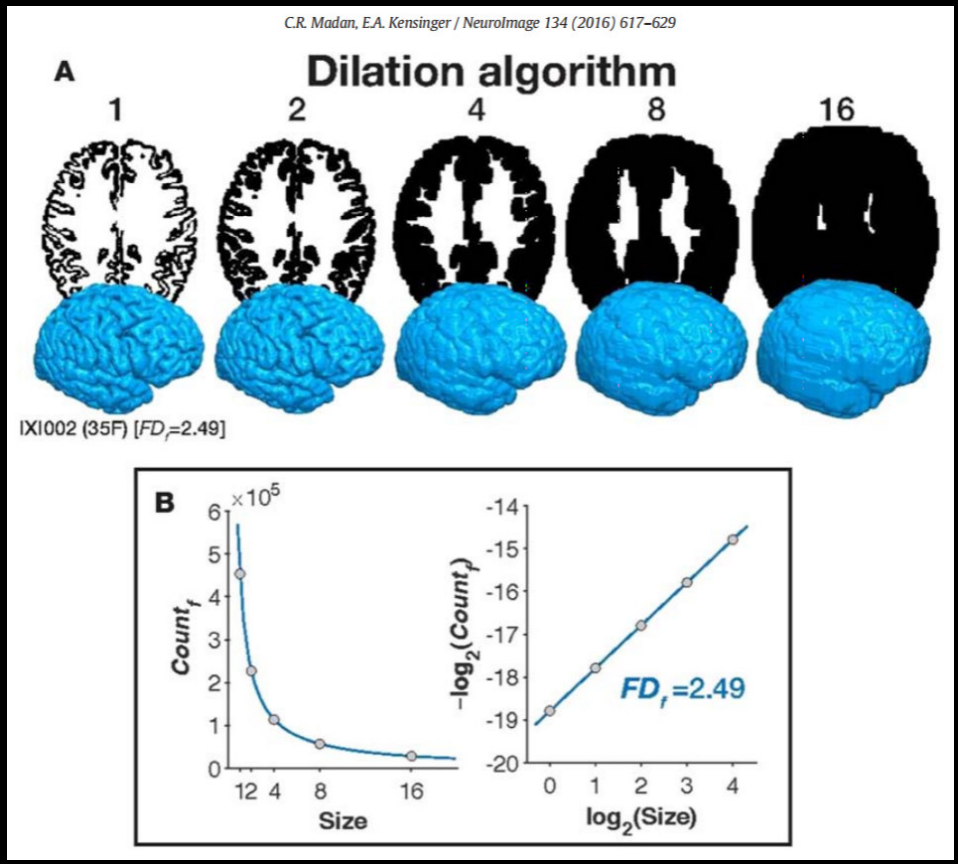
Lembrando: A curva de Koch

$$\frac{l_i}{l_o} = \left(\frac{l_e}{l_o}\right)^d \qquad \frac{A_T}{T^2} = k\left(\frac{A_E}{T^2}\right)^{d/2}$$

$$d = \frac{5}{2}$$







… just like paper balls

A4

A5

A6

A7

A8

A9

.

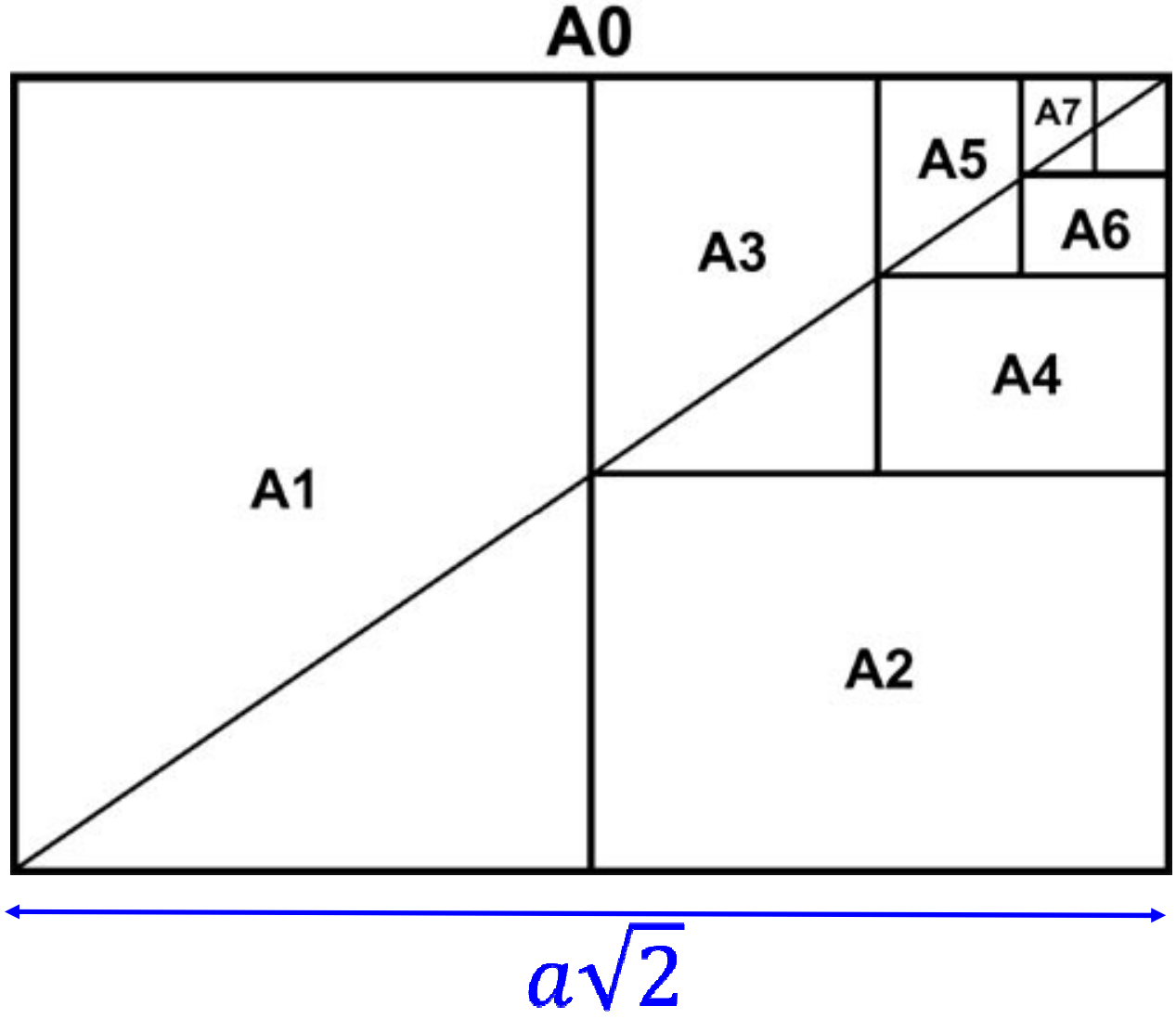
.

.

.

.

a



$a\sqrt{2}$

Another type of self-avoiding surface…

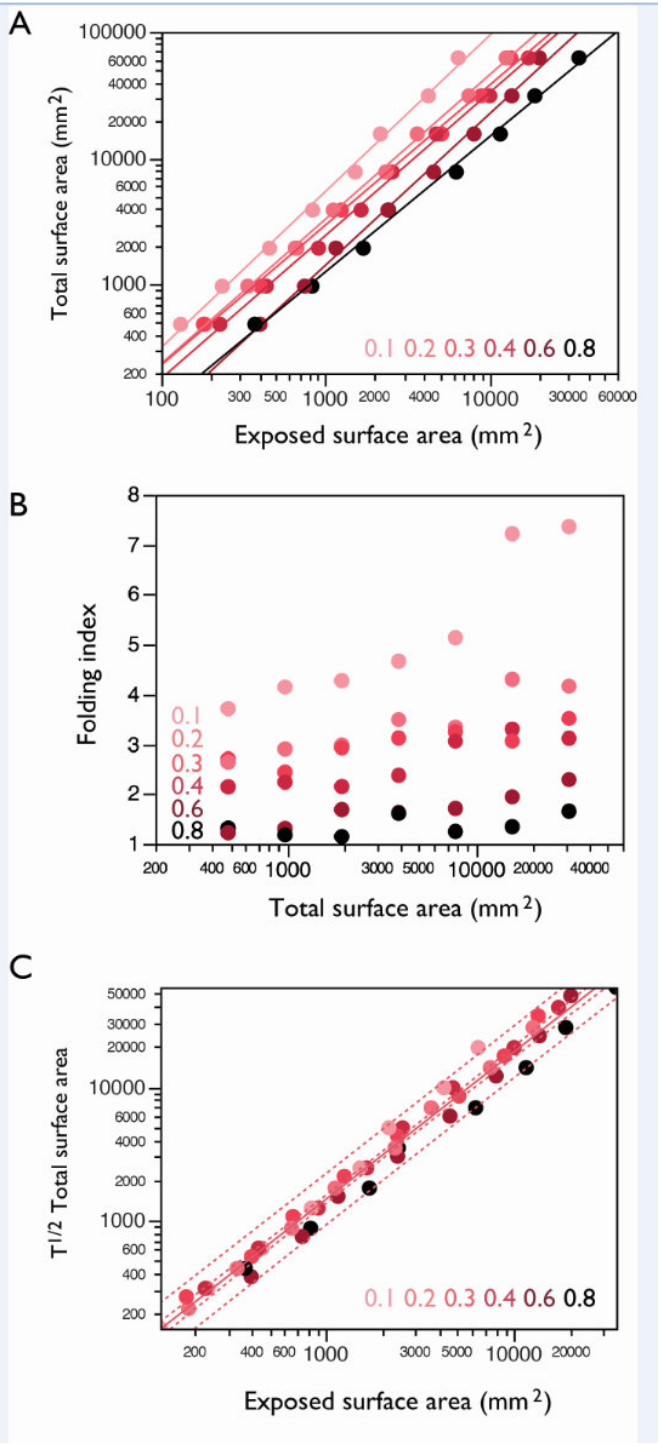
Luiza Houzel

…where sheet thickness is the fundamental length scale

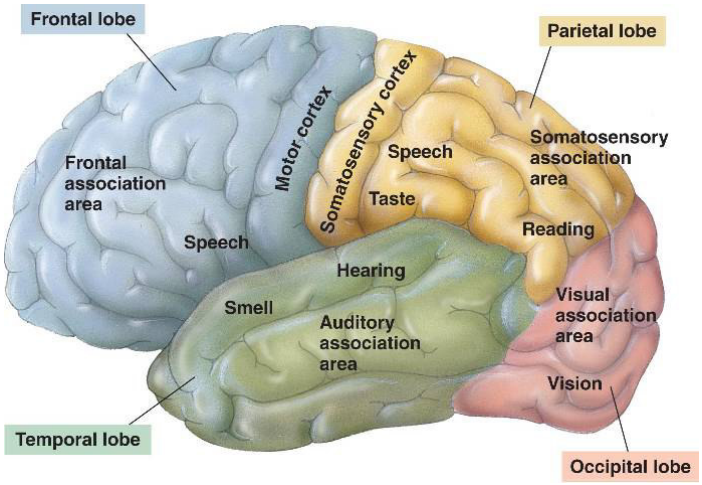
$$A_T \propto A_E^{\alpha}$$

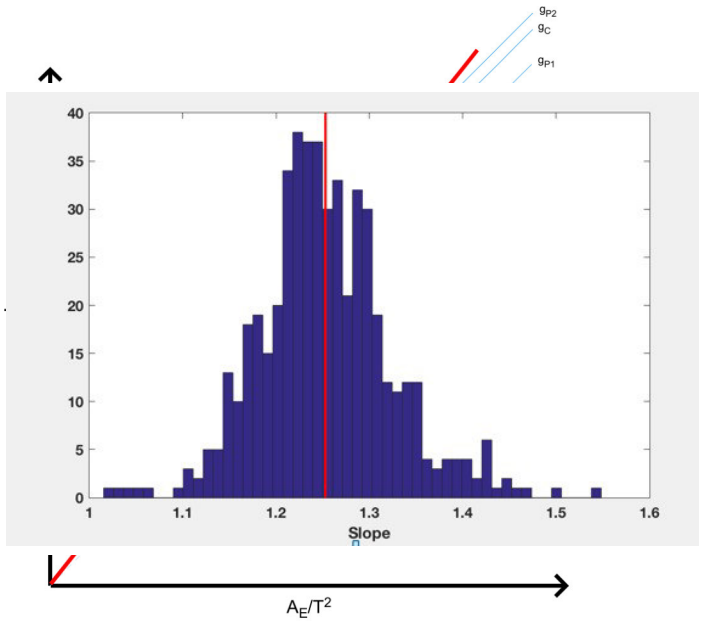
2α is the fractal dimension.

$$\frac{A_T}{T^2} = k\left(\frac{A_E}{T^2}\right)^{\frac{5}{4}}$$



Perspectives II: Localizing the universal rule





- Segmenting the cortex into lobes
- Lobes (or patches) cannot be directly comparable in k_1
- Total gaussian curvature in surface is topological invariant (Gauss-Bonnet)

$$K^e(P) = \int_{P_e} k\tilde{d}a + \oint_{\partial P_e} k_g.d\ell$$

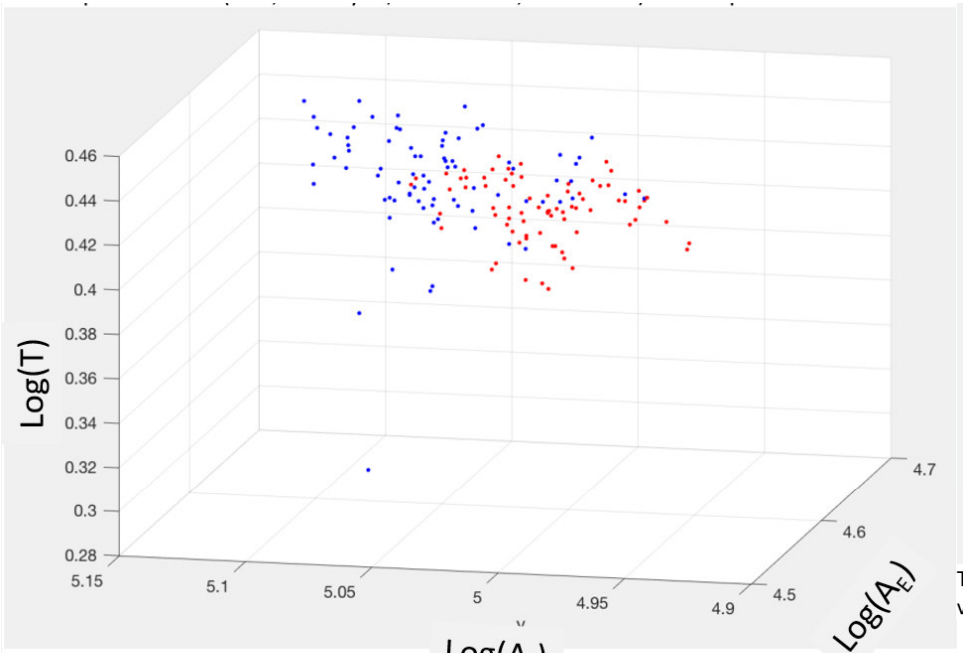
- Use it to reconstruct virtual cortex from each patch

$$A'_e(P) = \frac{K^e(L)}{K^e(P_L)} A_e(P) \left(\frac{A_e(L) + A_e(M)}{A_e(L)} \right)$$

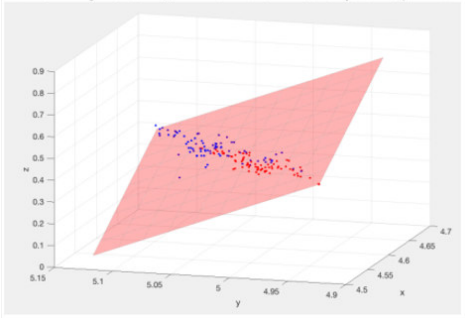
$$A'_t(P) = \frac{K^e(H)}{K^e(P)} A_e(P) \left(\frac{g(P_L)A_e(L) + g(P_M)A_e(M)}{A_e(L)} \right)$$

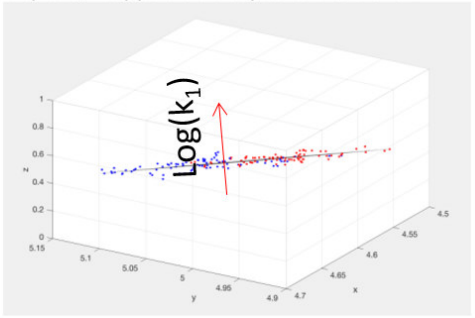
- Universal rule applies for lobes in the same córtex!
- This may become a prognosis method for medial temporal lobe epilepsy

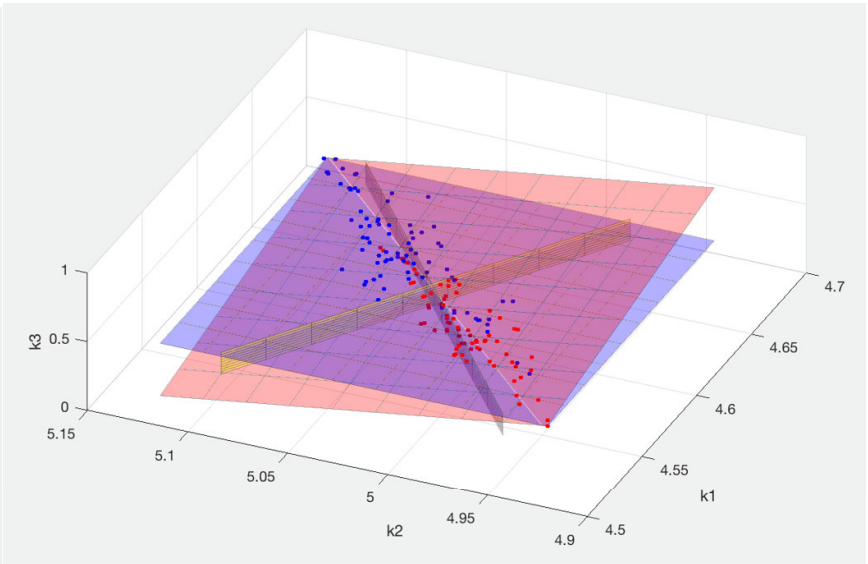
Perspectives I: A new, more natural, set of variables



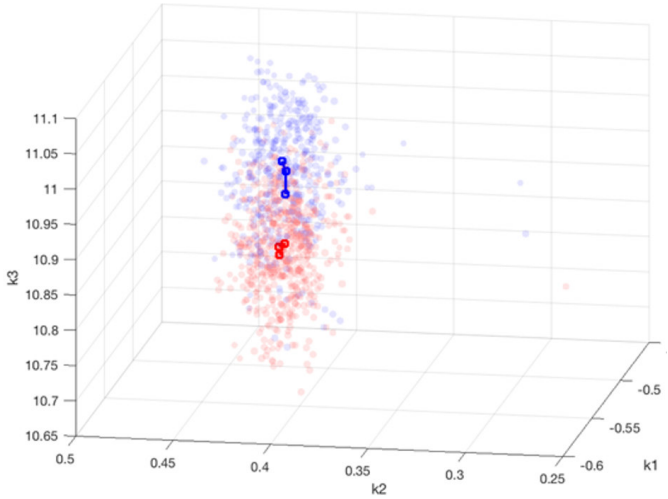
We can see that the data has an intrinsic [illegible] which supports the idea that the three quantities are related by some physical law/principle, as previously proposed [Mota & Herculano-Houzel 2015]. Indeed, when we plot the proposed scaling law (**k1=-1.25*x+y+0.5*z**, which defines a plane) in this space, it appears to capture the trend:





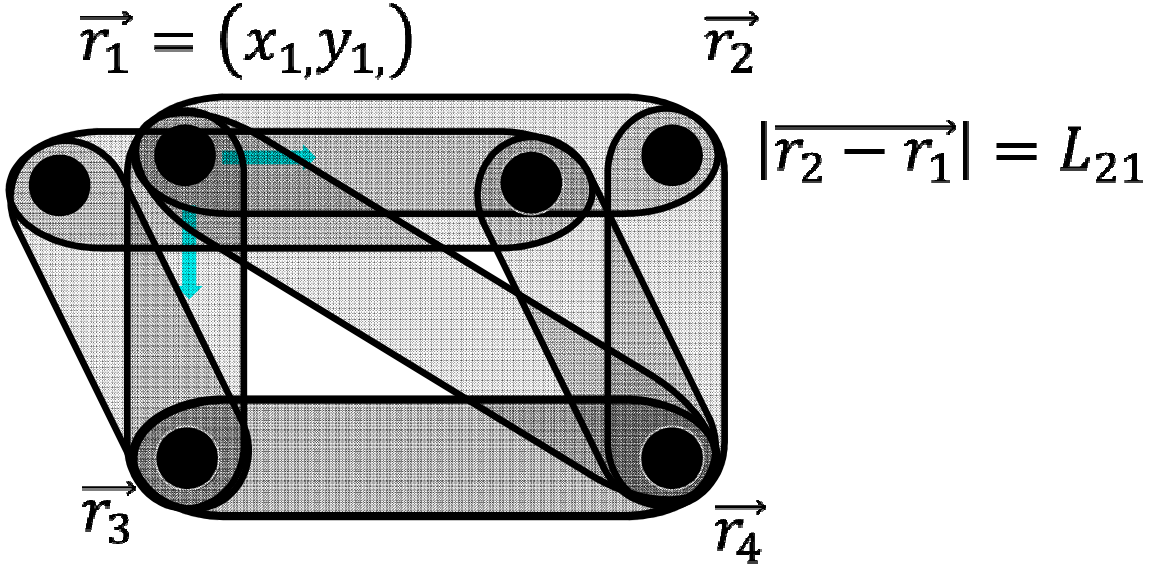


The plane corresponding plane to the gyrification index is the grey plane. As immediately visible, the gyrification index plane is not a natural plane that describes the trend in the data.



How many degrees of freedom are needed to build a shelf?

- The position of each nail: +2 dof
- Each strut constraints the distance between two nails: -1 dof
- Wobbliness does not depend on fine-grained degrees of freedom (color of the strut, color, shape)
- Choice of dof is not unique

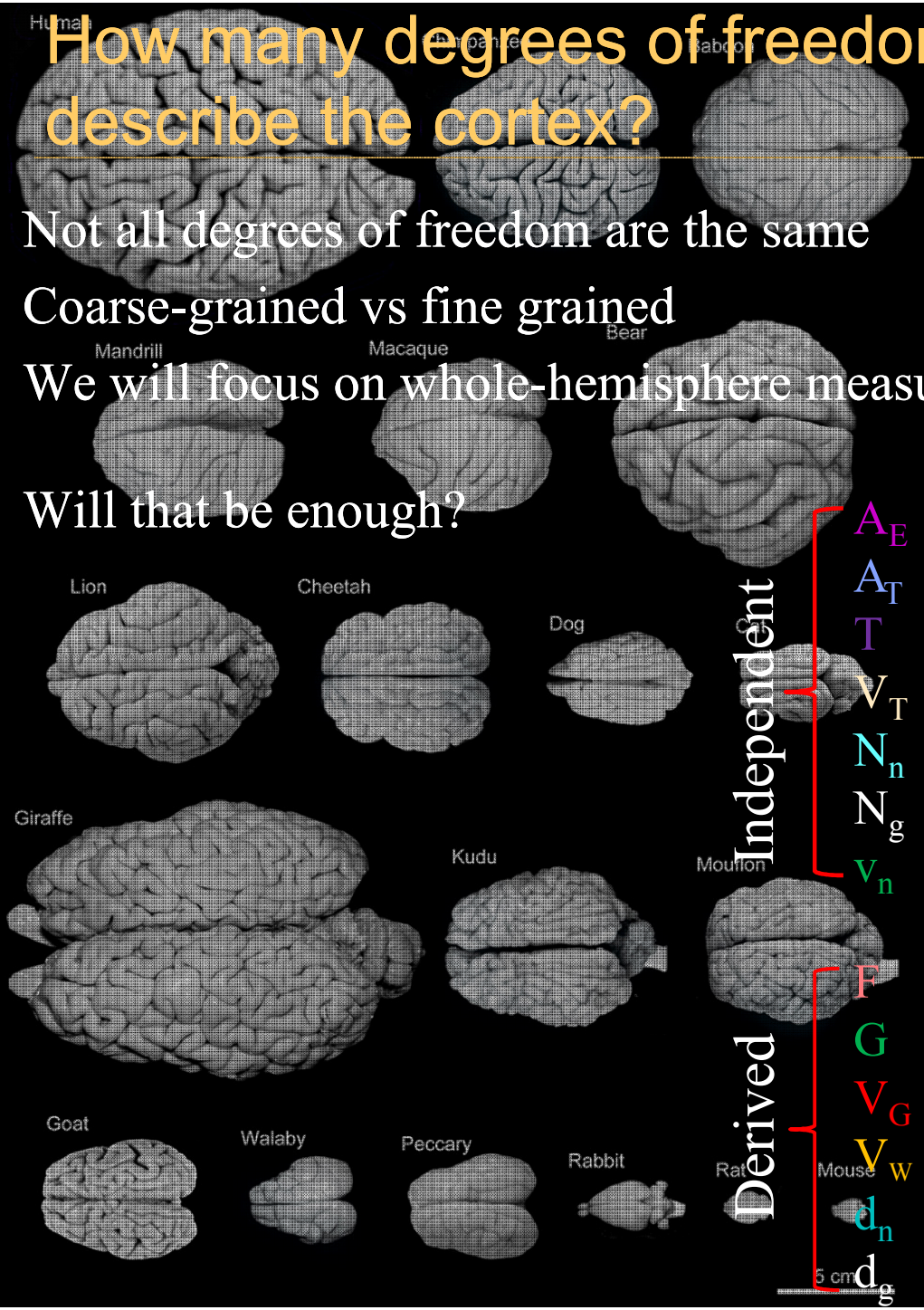


- Non wobbly with 4 nails and 5 struts
  (+2 × 4 - 5 ×1 - 1 × global rotation - 2 × global translation = 0)

How many degrees of freedom are needed to describe the cortex?

- Not all degrees of freedom are the same
- Coarse-grained vs fine grained
- We will focus on whole-hemisphere measures

Will that be enough?



Independent

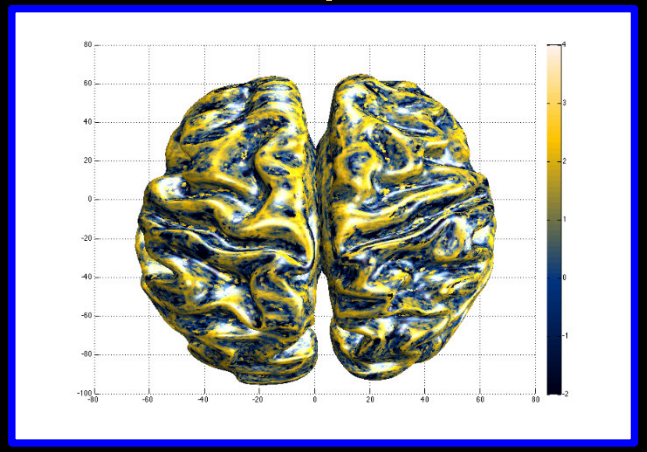
A_E	- Exposed area
A_T	- Total area
T	- Average thickness
V_T	- Total volume
N_n	- Number of neurons
N_g	- Number of non-neurons
v_n	- Neuron avg. volume

Derived

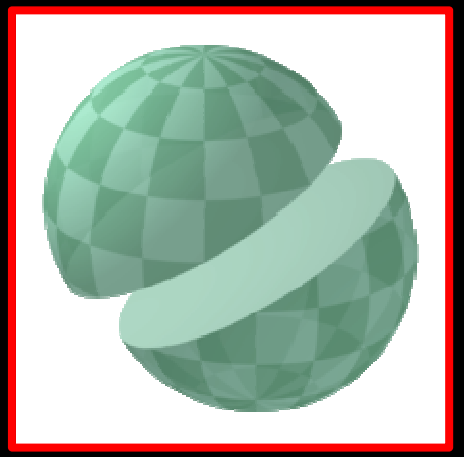
$F = A_E / A_T$	- Folding index
$G = V_G / V_T$	- Volume index
$V_G = T A_T$	- Grey matter volume
$V_W = V_T - V_G$	- White matter volume
$d_n = N_n / V_G$	- Neuron density
$d_g = N_g / V_G$	- non-neuron density

Looking for constraints 1:

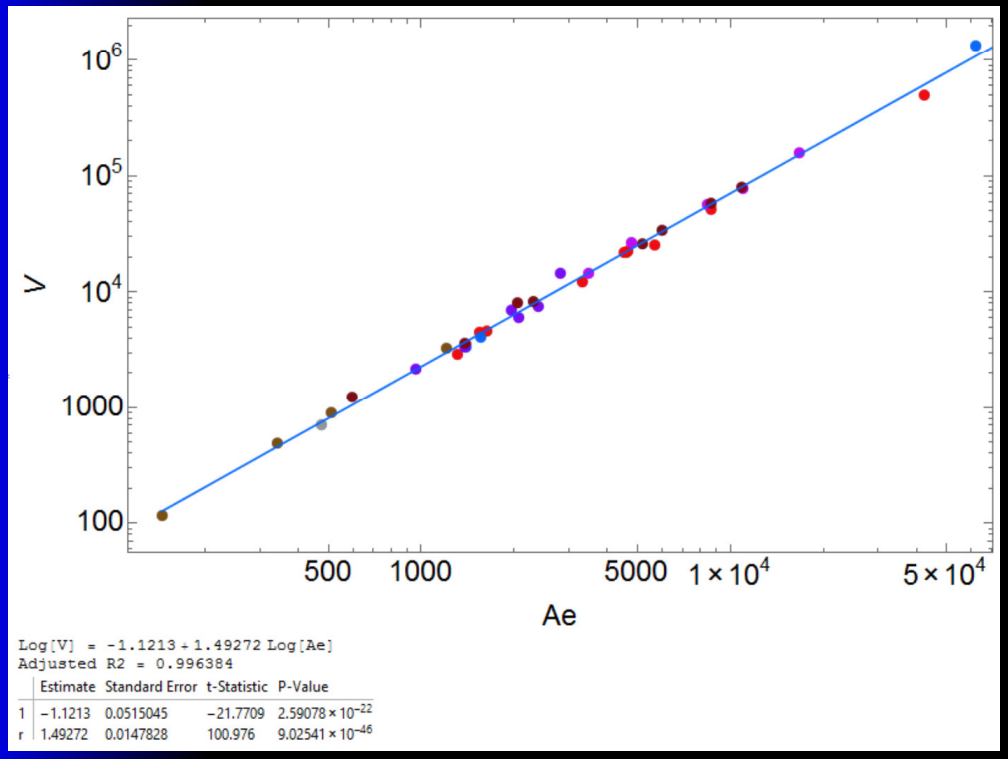
Hemispheres are hemi-spheric!



=



?

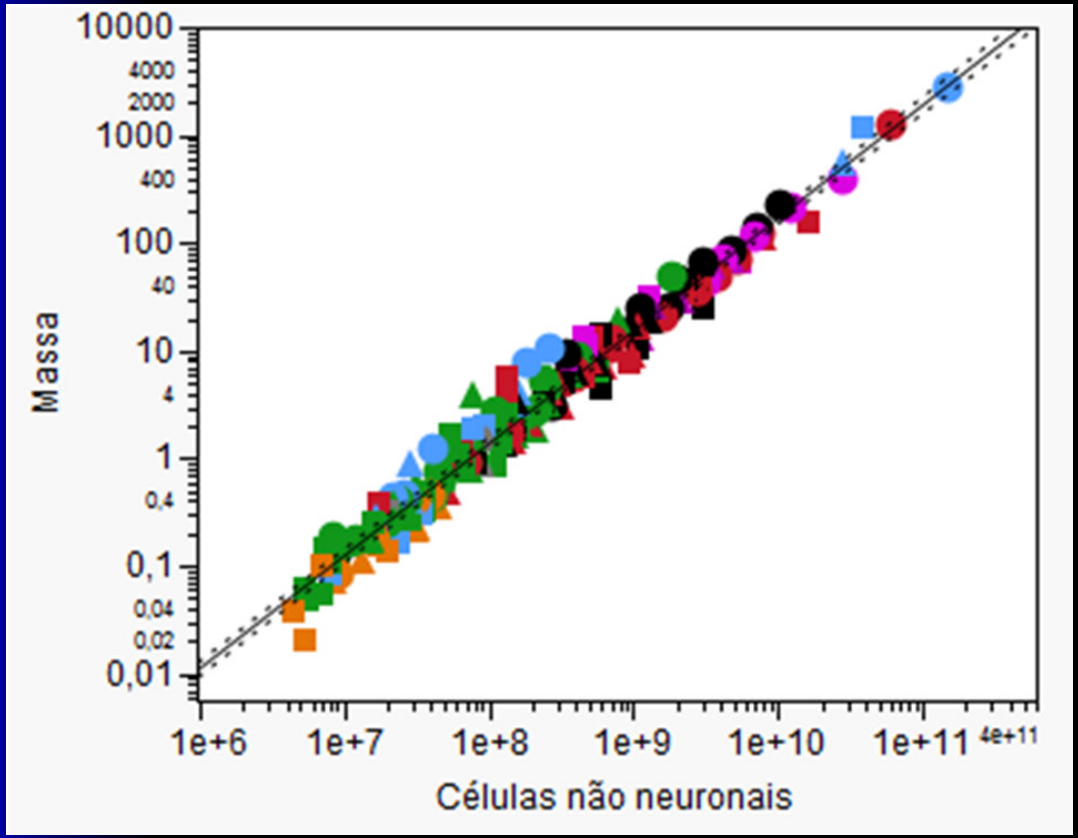


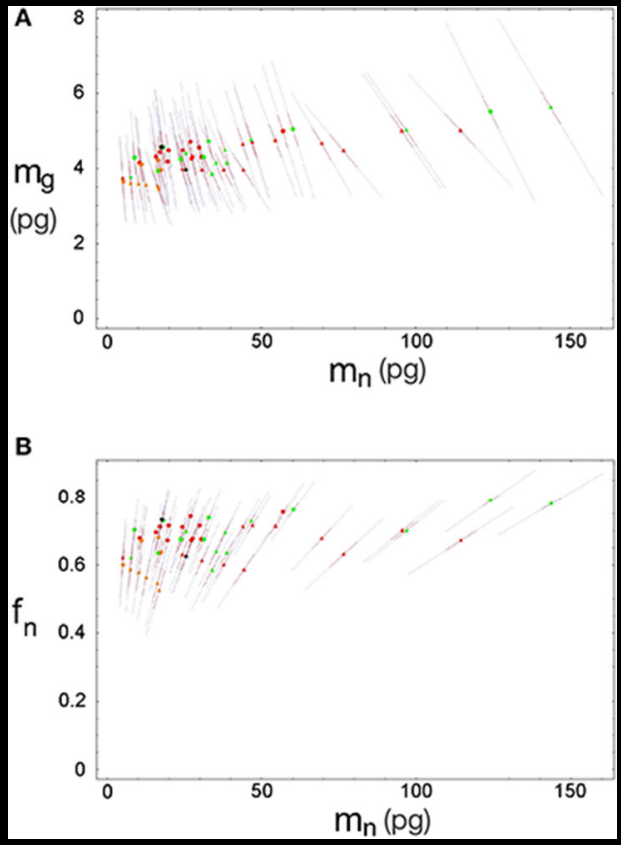
Log[V] = -1.1213 + 1.49272 Log[Ae]
Adjusted R2 = 0.996384

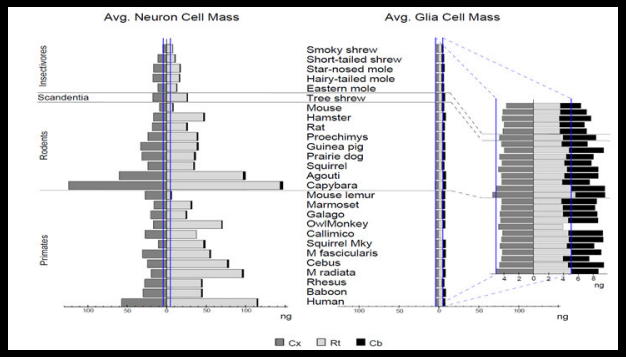
	Estimate	Standard Error	t-Statistic	P-Value
1	−1.1213	0.0515045	−21.7709	2.59078×10^{-22}
r	1.49272	0.0147828	100.976	9.02541×10^{-46}

$$V_T = \frac{2}{9\sqrt{3\pi}} {A_E}^{3/2}$$

Looking for constraints 2:
Glial invariance







$d_g \cong$ constant

$d_n \propto 1/ v_n$

It takes 3 variables to describe a cortex

v_N N_N A_T T A_E V_W

Six fundamental, independent variables

d V_G V_T F G

Five derived variables

$v_N \sim 1/d$

$V_T = \{2/[9(3\pi)]^{1/2}\}.A_E^{3/2}$

$A_T.T^{1/2} = \kappa.A_E^{\alpha}$

Three non-trivial constraints

Six independent variables - three constraints = 3 degrees of freedom

Putting all together

The 37 combinations of 11 variables that can be used to solve the system of equations fall into 8 classes of equivalence:

$A_T\ T\ N_N$
$d\ A_T\ V_G$
$d\ A_T\ N_N$
$d\ T\ N_N$
$d\ A_T\ T$
$d\ T\ V_G$
$V_G\ A_T\ N_N$

$d\ A_T\ V_T$
$N_N\ T\ A_E$
$N_N\ F\ V_G$
$N_N\ F\ d$
$d\ F\ V_G$

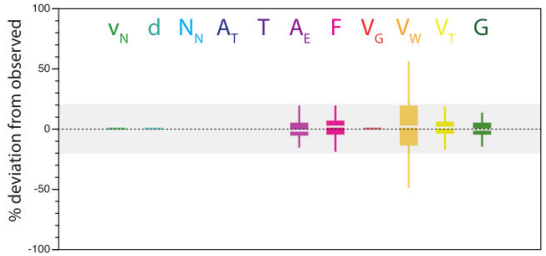
$d\ A_E\ V_G$
$N_N\ A_E\ V_G$
$d\ A_E\ N_N$
$d\ A_T\ A_E$
$d\ A_T\ F$
$d\ A_E\ F$

$N_N\ A_T\ F$
$N_N\ A_E\ F$
$N_N\ A_E\ A_T$
$d\ T\ F$
$N_N\ T\ F$

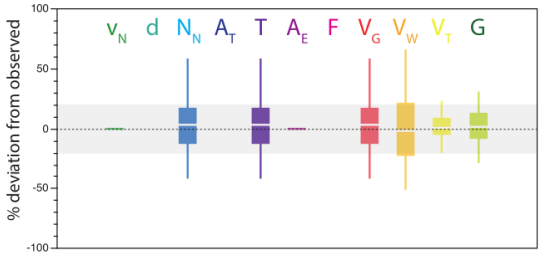
($d = 1/v_N$)

$A_T\ T\ N_N$

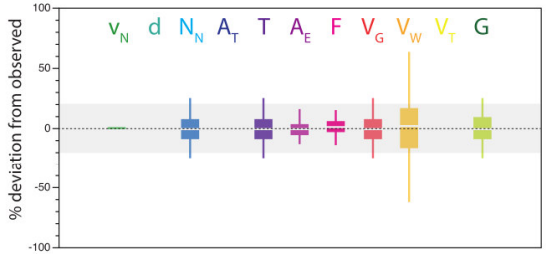
(best predictors)



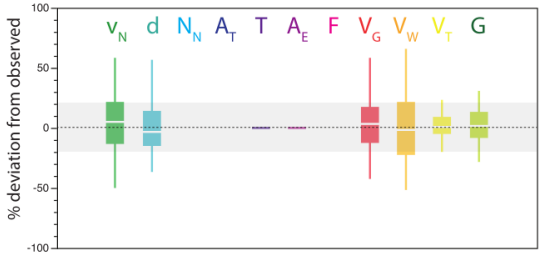
$d\ A_T\ F$



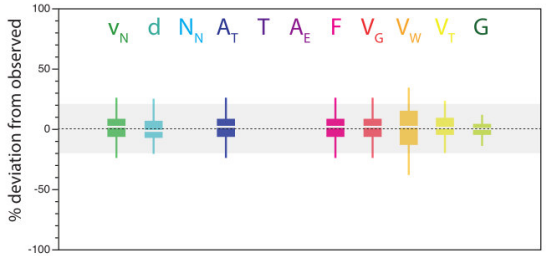
$d\ A_T\ V_T$



$N_N\ A_T\ F$

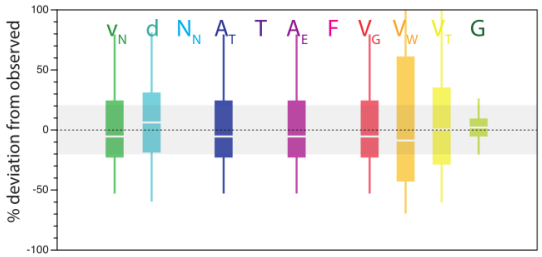


$N_N\ T\ A_E$

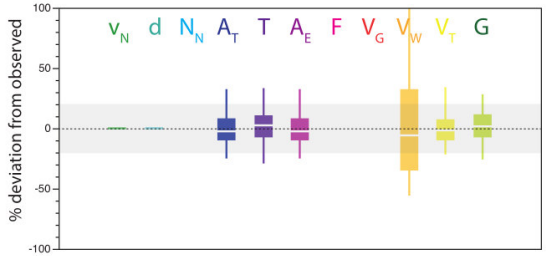


$N_N\ T\ F$

(worst predictors)

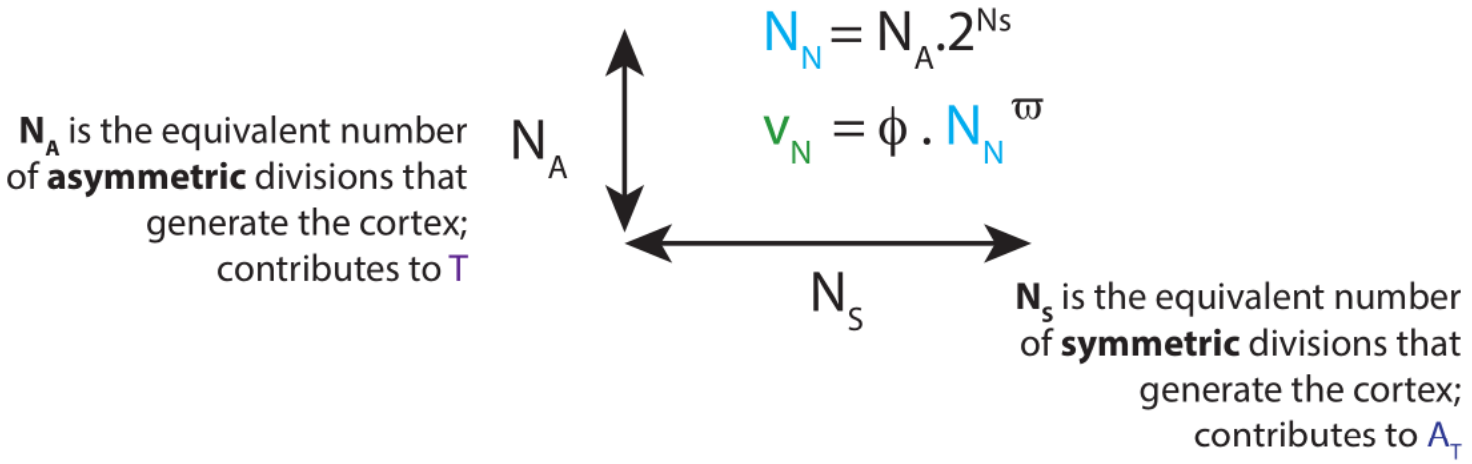


$N_N\ F\ V_G$



From morphological to developmental variables: Our model

lateral expansion, but also radial expansion and increased cell size



A system of equations to describe the cortex

$N_N = N_A.2^{Ns}$

$v_N = V_G/N_N = \phi . N_N^{\varpi}$

$d = 1/v_N$

N in stack x height of neuron: $T = \beta . v_N^{1/3}. N_A$

stacks x area of neuron: $A_T = 1/\beta . v_N^{2/3}. 2^{Ns}$

$V_G = v_N . N_A . 2^{Ns}$

from $A_T T^{1/2} = \kappa A_E^{\alpha}$: $A_E = (\beta^{-1/2\alpha})/\kappa^{1/\alpha}) . v_N^{5/6\alpha}. N_A . 2^{Ns}$

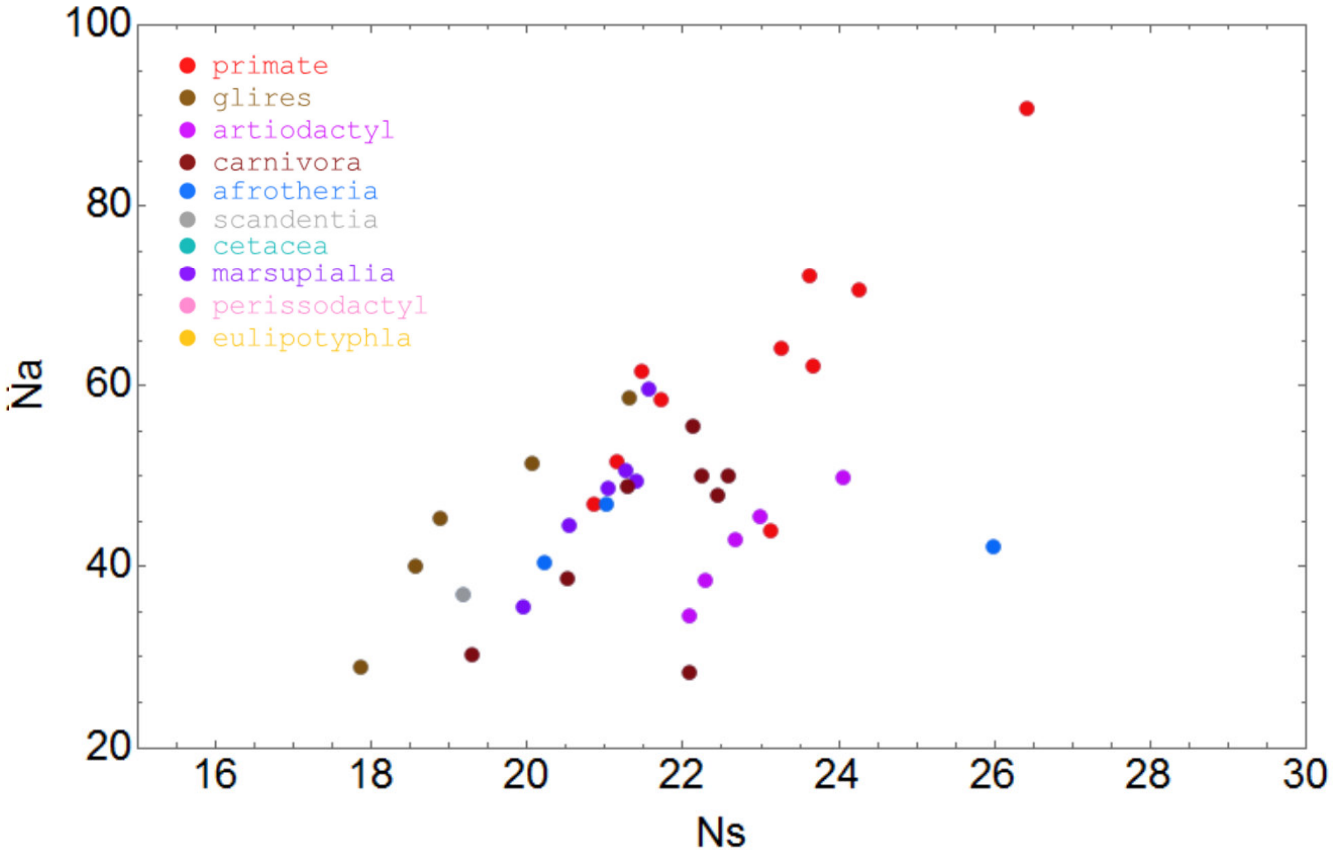
from $F = A_T/A_E$: $F = \{2^{Ns}. [(2^{Ns}. N_A . v_N^{5/6})/(\kappa . \beta^{1/2} . N_A^{1/2})]^{-1/\alpha} . v_N^{2/3}\}/\beta$

from $V_T = \sigma . A_E^{\gamma}$: $V_T = \sigma . [(2^{Ns}. N_A . v_N^{5/6})/(\kappa . \beta^{1/2} . N_A^{1/2})]^{\gamma/\alpha}$

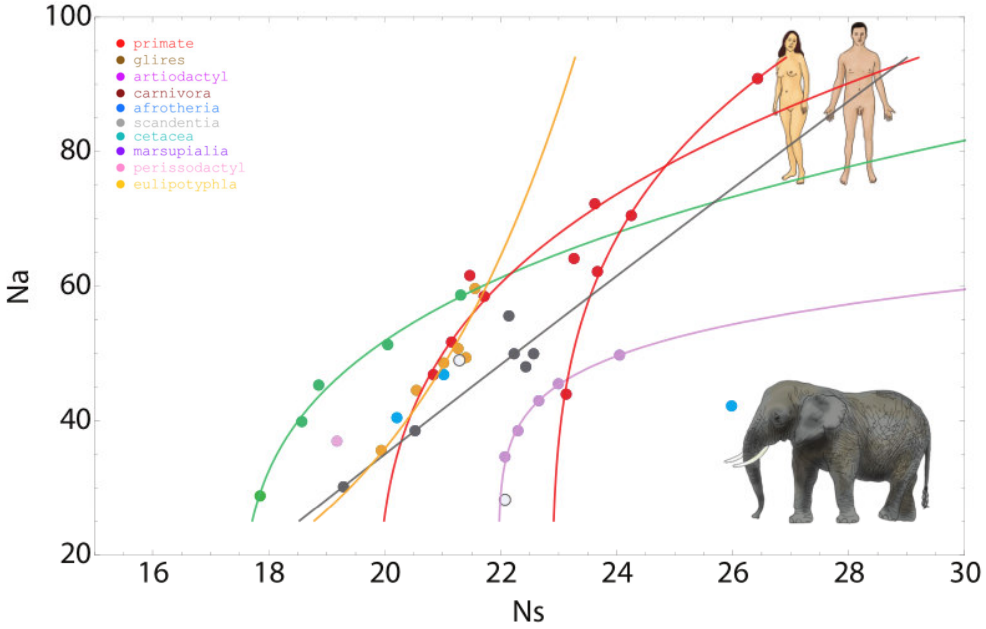
from $V_T = V_G + V_W$: $V_W = \sigma . [(2^{Ns}. N_A . v_N^{5/6})/(\kappa . \beta^{1/2} . N_A^{1/2})]^{\gamma/\alpha} - v_N . N_A . 2^{Ns}$

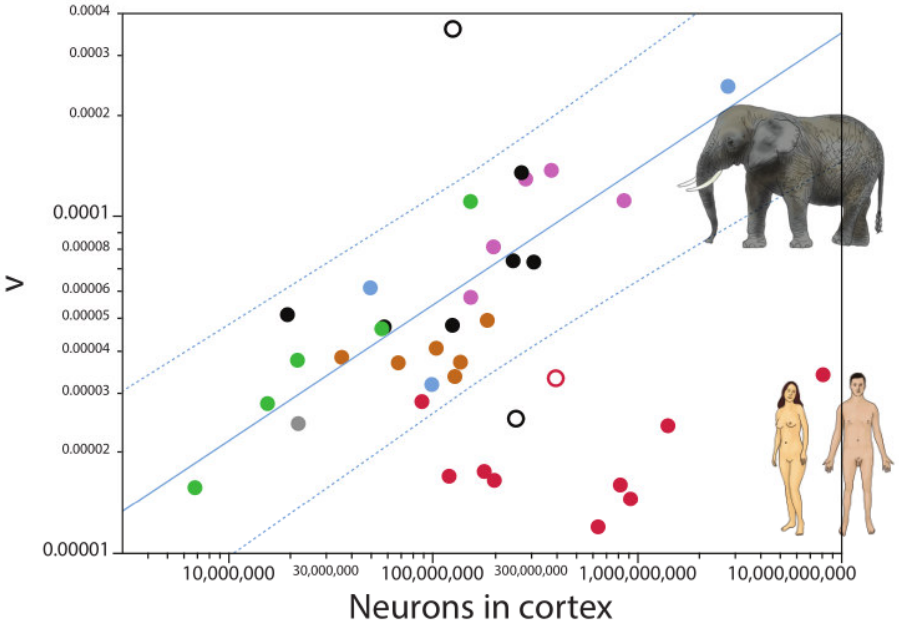
from $G = V_G / V_T$: $G = (v_N . N_A . 2^{Ns}) / \{\sigma . [(2^{Ns}. N_A . v_N^{5/6})/(\kappa . \beta^{1/2} . N_A^{1/2})]^{\gamma/\alpha}\}$

Hard constraints vs soft constraints



Soft constraints: Clade-dependent

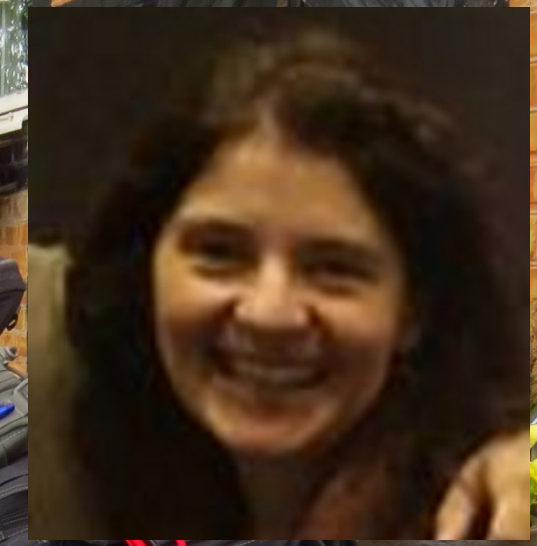




- Number of symmetric divisions varies from 17 to 27 across species
- Number of asymmetric divisions varies from 27 to 90 across species
- There is a relationship between N_S and N_A, clade-specific
- v_N increases with N_N across non-primates, not across primates

- New **clade** evolves with new relationship between N_S and N_A
- New **species** evolves with new N_S and N_A , but still obeying that relationship

Thank you!



… and caveat emptor