

Crecimiento Tumoral

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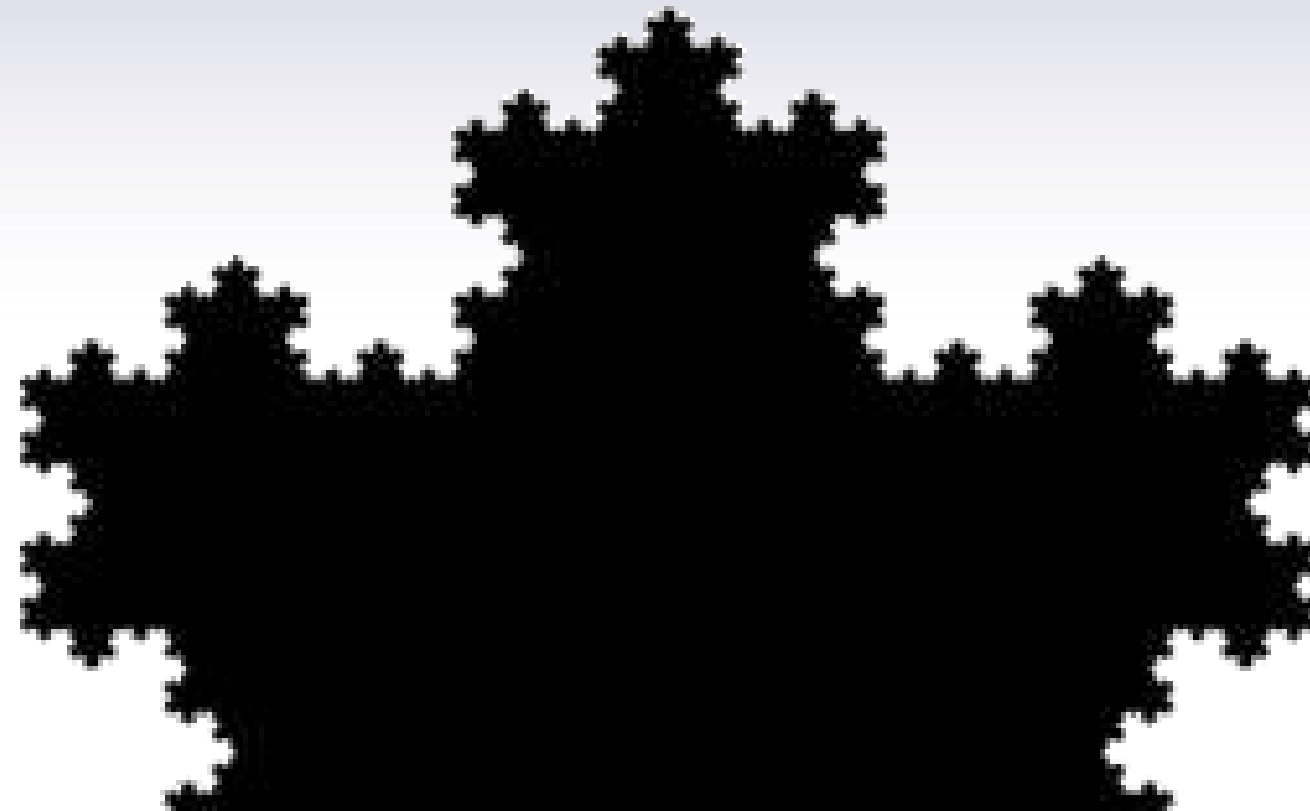


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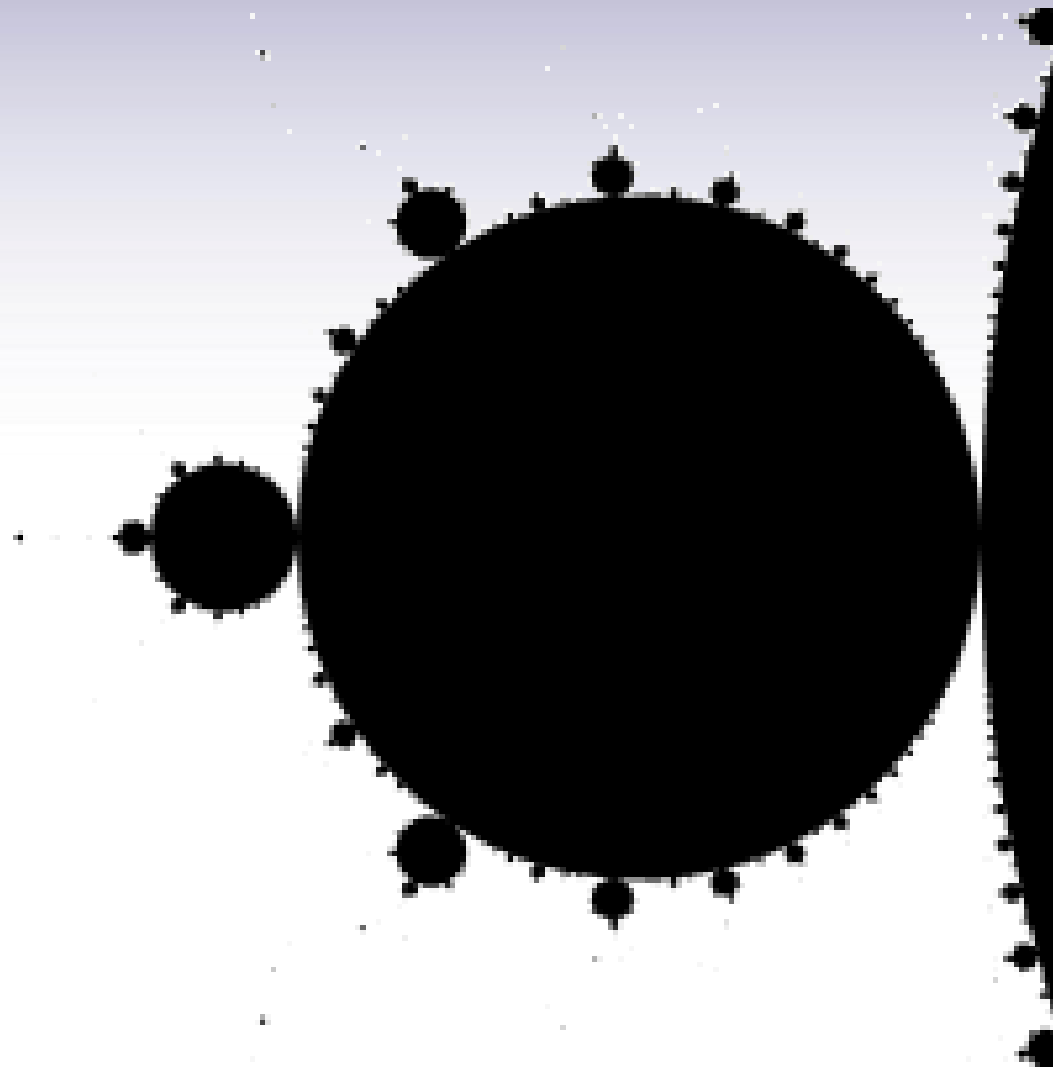




- Fractales. Dimensión fractal.
- Leyes de potencia
- Crecimiento de interfaces.
- La interfaz tumoral.
- Análisis por escalamiento de la interfaz tumoral.
- Multifractalidad.
- Análisis mediante redes complejas.
- Comportamientos universales.
- Modelos de crecimiento y simulaciones.



Curva de Koch



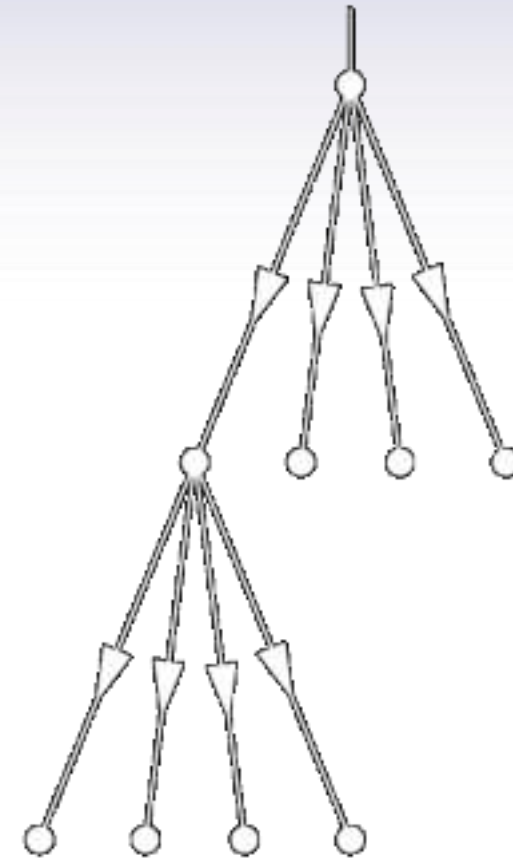
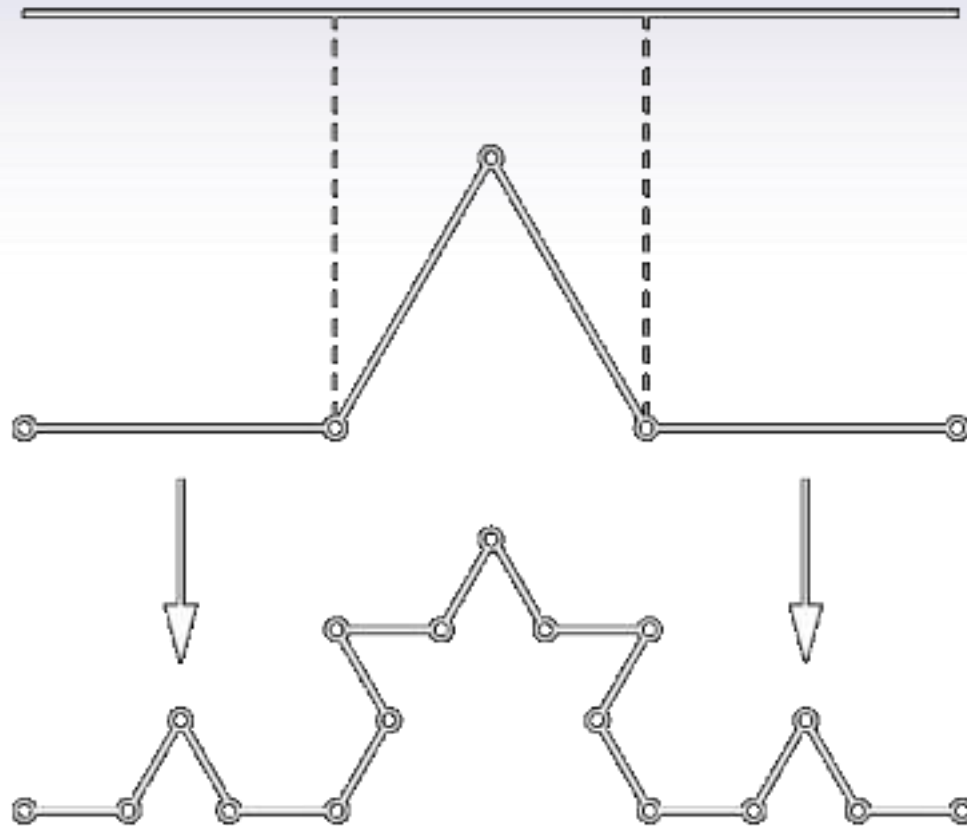
Conjunto de Mandelbrot



- Fractales auto-similares, se obtienen de una forma iniciadora, un generador, es decir, una regla para modificar la forma inicial y realizar iteraciones para generar la forma fractal. Son deterministas.
- Son invariantes bajo una transformación de escala isotrópica (idéntica en cualquier dirección espacial)



Auto-similitud





Dimensión de auto-similitud

Número de objetos similares en los que se descompone un objeto al reducir la escala isotrópicamente en un factor M esta dado por:

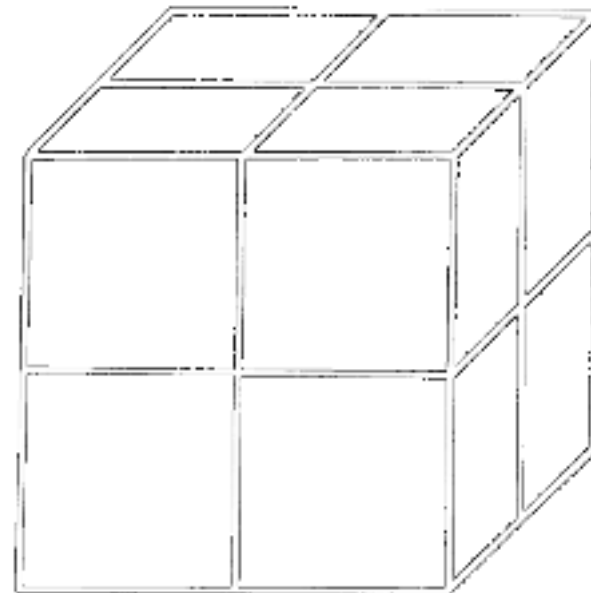
$$N(M) = M^{d_E}$$



$$2 = 2^1$$



$$4 = 2^2$$



$$8 = 2^3$$



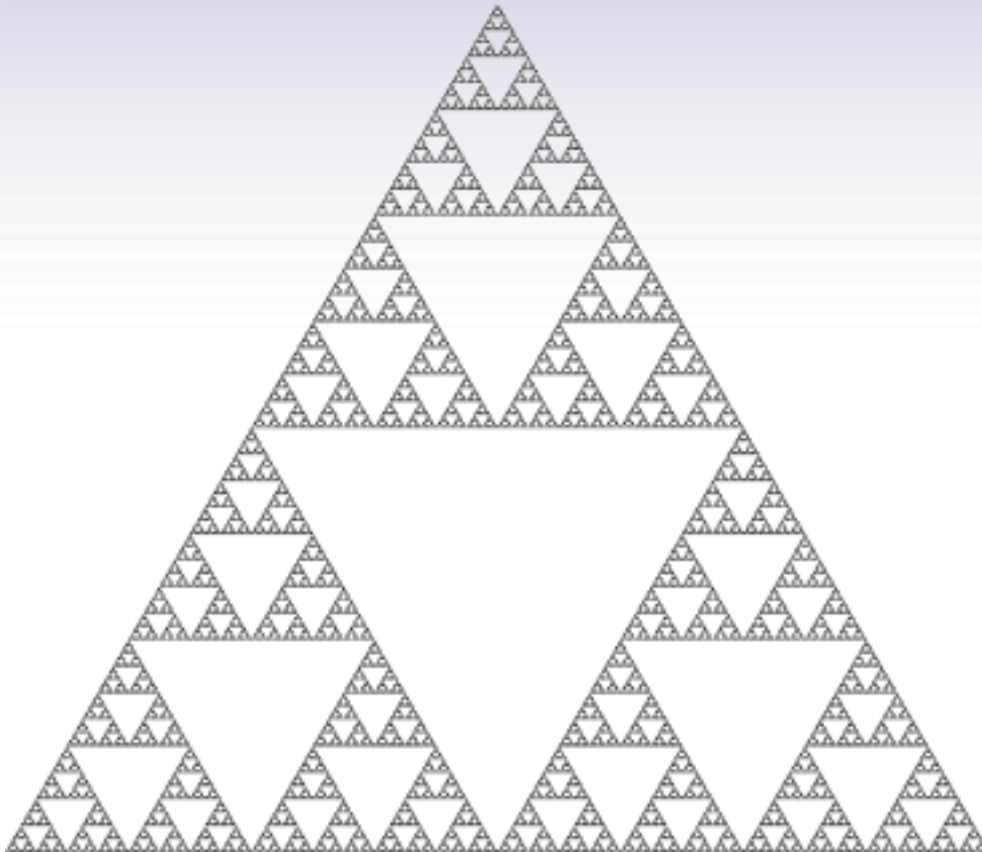
En forma análoga podemos decir, que las estructuras fractales están compuestas por $N(a)$ partes idénticas de tamaño $1/a$:

$$N(a) = a^{D_f}$$

D_f se denomina la dimensión de auto-similitud y sólo puede definirse para fractales deterministas.



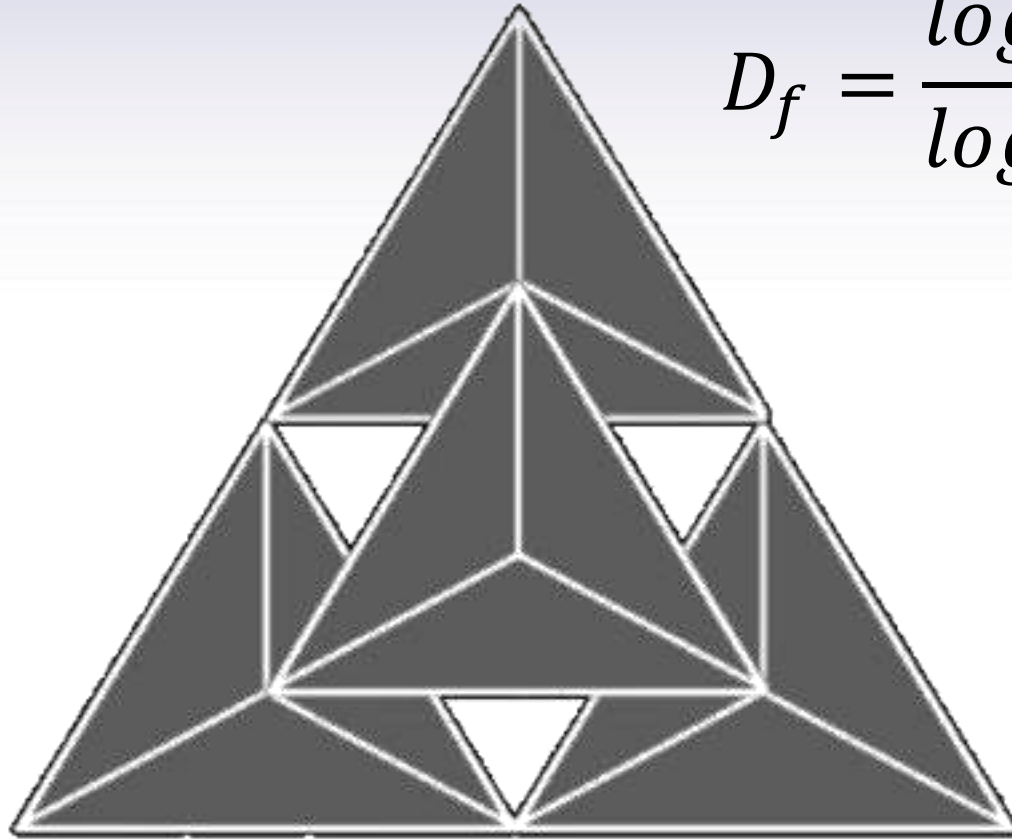
Dimensión de auto-similitud. Triángulo de Sierpinski.



$$D_f = \frac{\log(3)}{\log(2)} \cong 1.58496 \dots$$

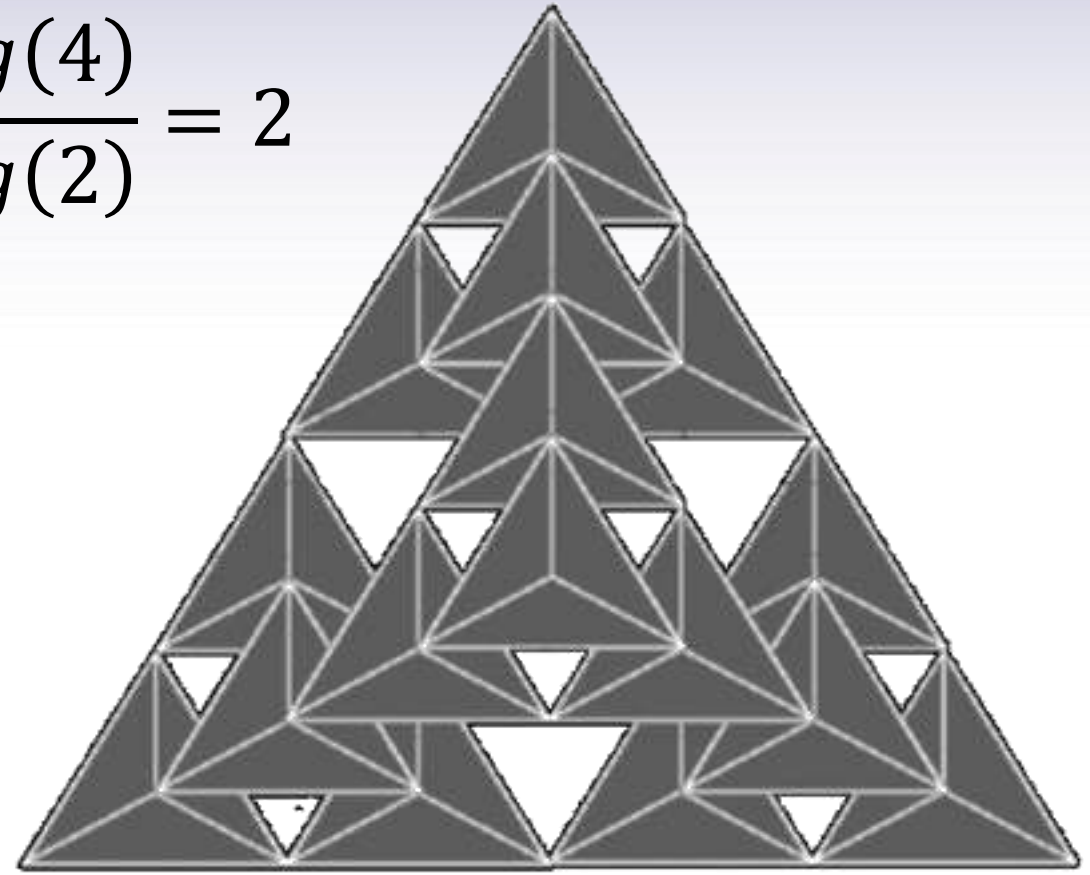


Dimensión de auto-similitud. Tetrahedro de Sierpinski.



$$4 = 2^2$$

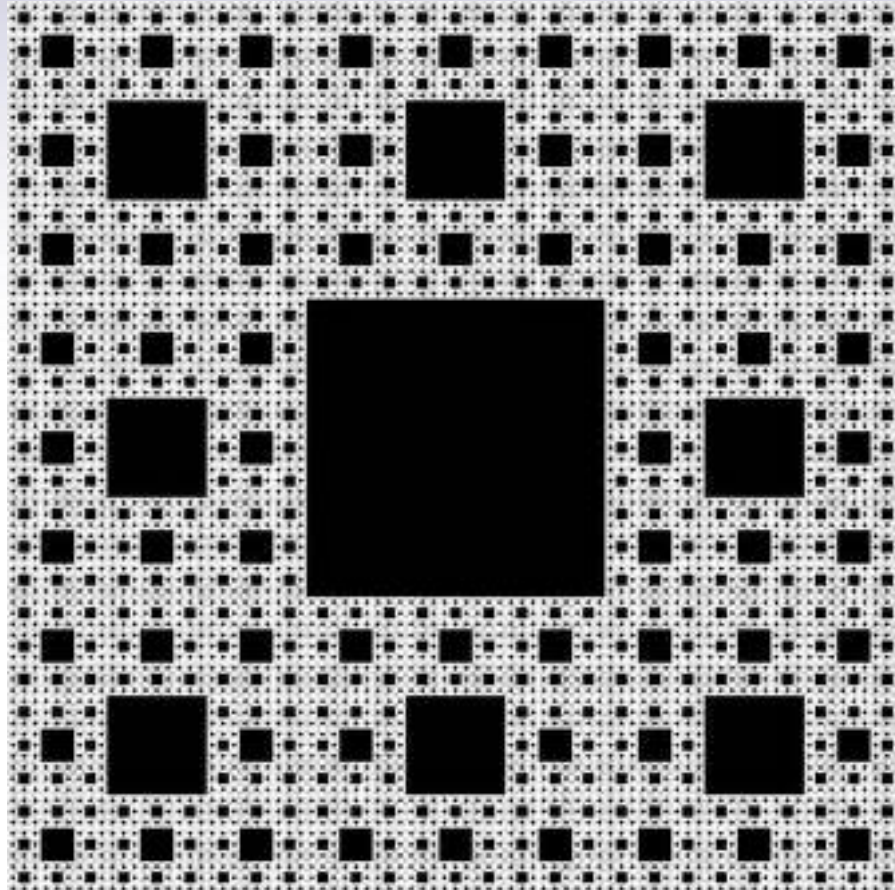
$$D_f = \frac{\log(4)}{\log(2)} = 2$$



$$16 = 4^2$$



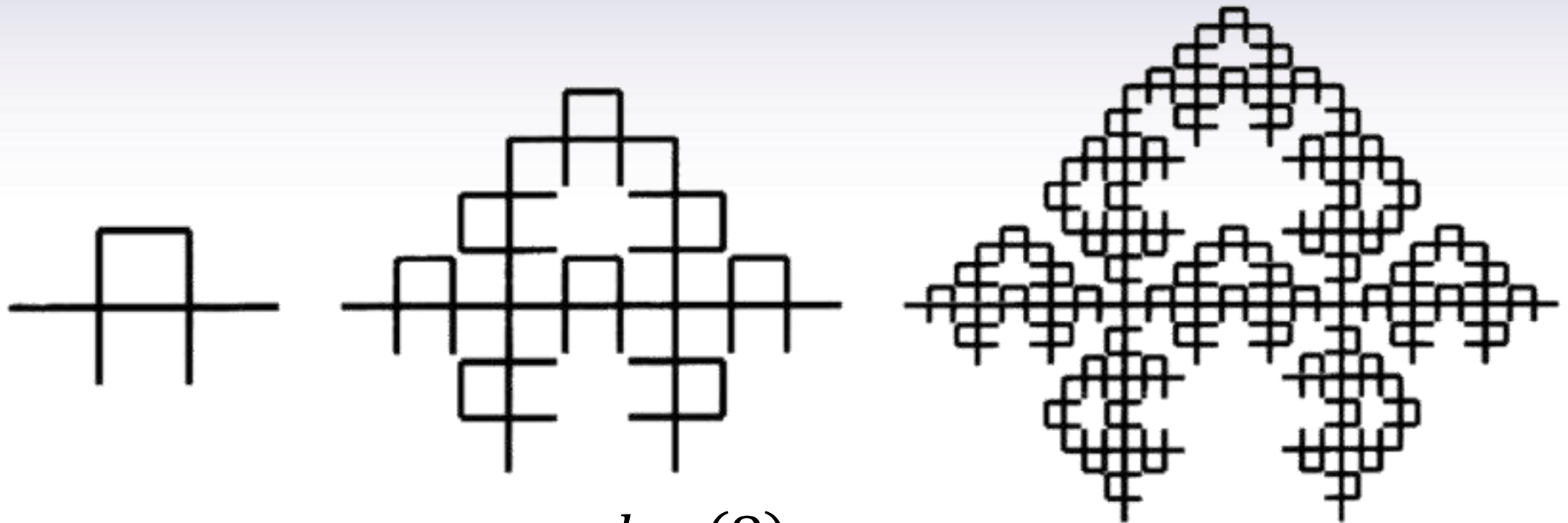
Dimensión de auto-similitud. Alfombra de Sierpinski.



$$D_f = \frac{\log(8)}{\log(3)} = 1.89279$$



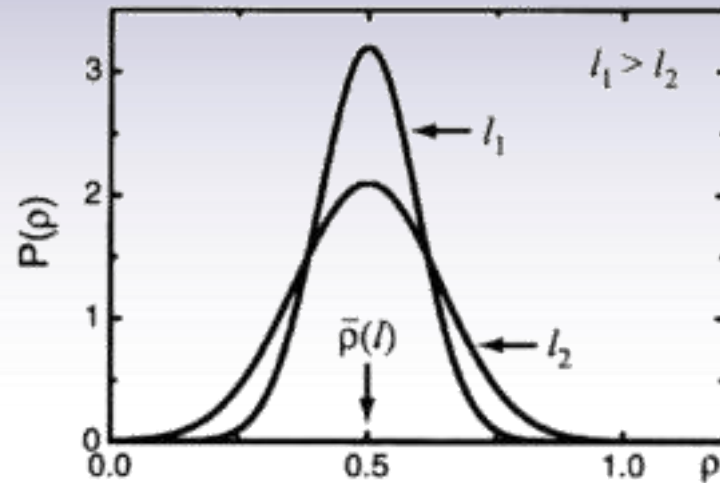
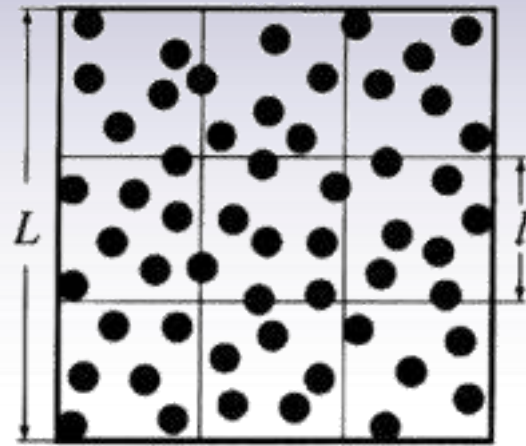
Dimensión de auto-similitud. Fractal de Mandelbrot-Given.



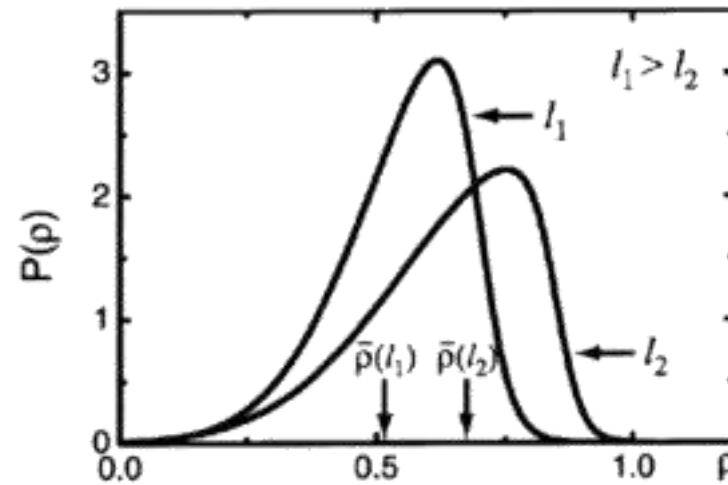
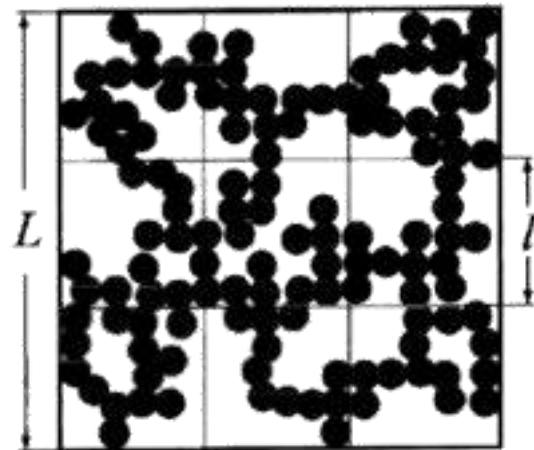
$$D_f = \frac{\log(8)}{\log(3)} \cong 1.89278 \dots$$



Fractales aleatorios.



$$\bar{q}(l) = \frac{\langle M_i(l) \rangle_i}{l^d} = \frac{m}{\bar{a}^d}$$

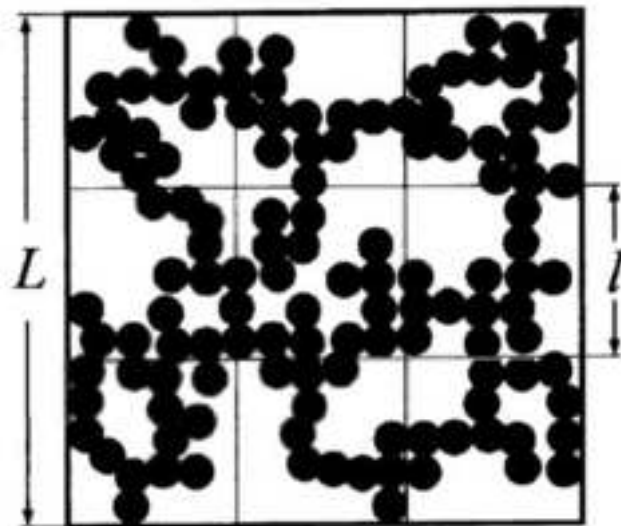


$$\bar{q}(l) = \frac{\langle M_i(l) \rangle_i}{l^d} \propto l^{D_f - d}$$



Dimensión de capacidad y dimensión de Hausdorff.

- En fractales aleatorios no es posible aplicar la definición de autosimilitud pues no existe ésta estrictamente, por lo que se hace necesario establecer una definición diferente de dimensión fractal.
- Las dimensiones de capacidad y de Hausdorff están basadas en métodos que atienden a “cubrir” la estructura a analizar. Se determina con cuantas esferas de tamaño l se cubre al sistema.



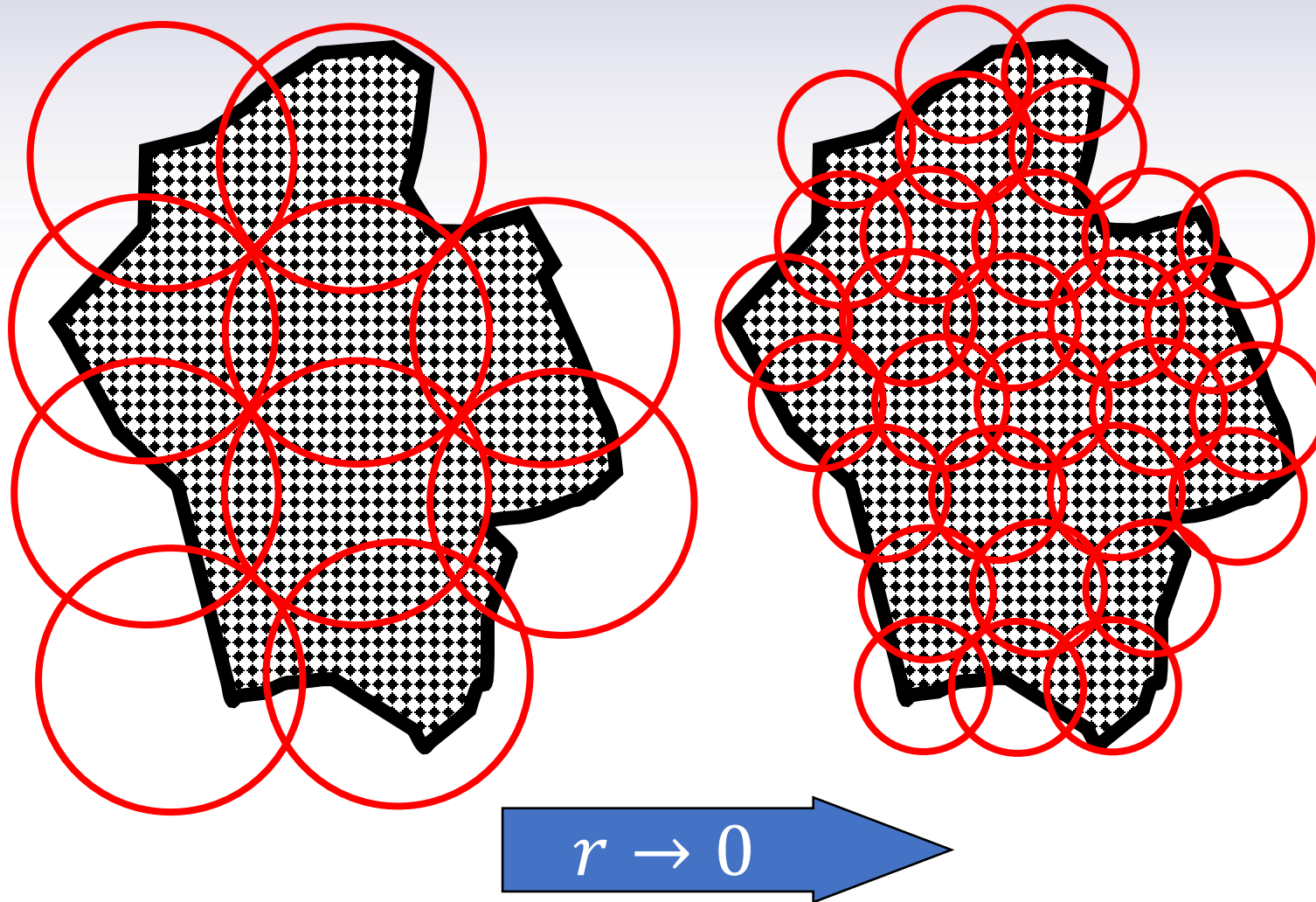
$$\langle M_i(l) \rangle_i \propto l^{D_f}$$

$$N(l) \langle M_i(l) \rangle_i = \text{número total de partículas}$$

$$N(l) \propto l^{-D_f}$$



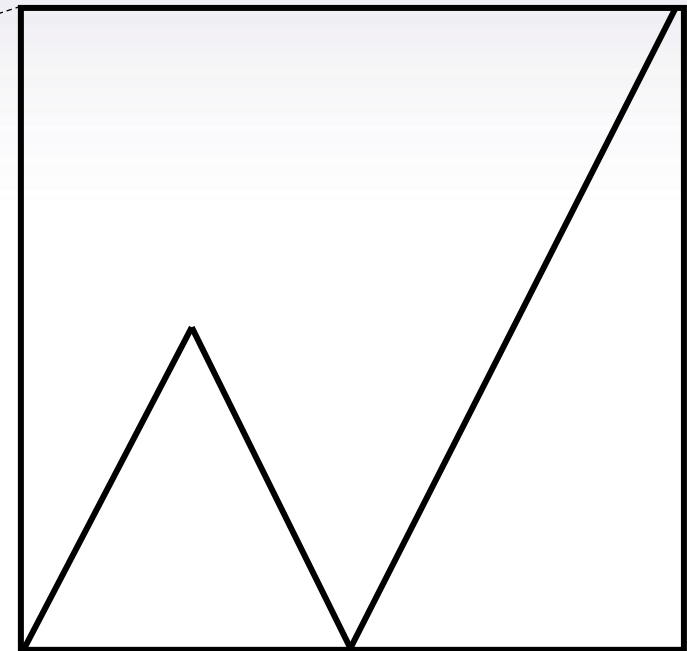
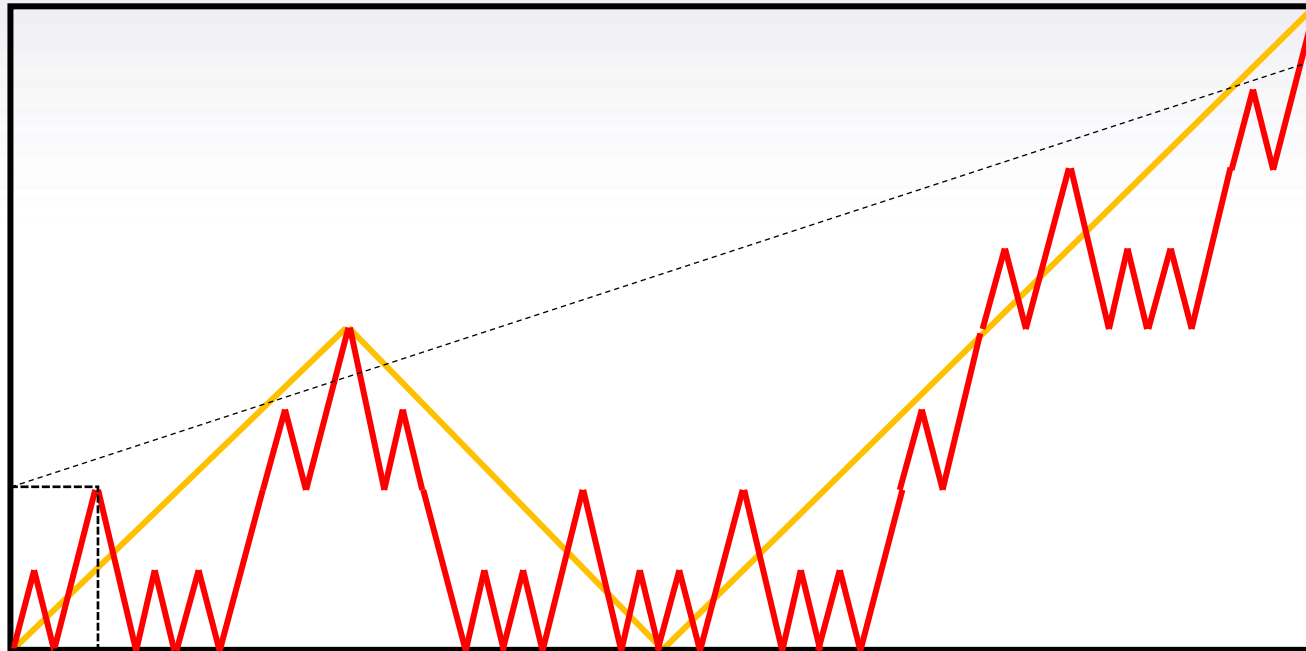
Dimensión de capacidad.



$$D_f = \lim_{r \rightarrow 0} \frac{\log N(r)}{\log \left(\frac{1}{r} \right)}$$



Auto-afinidad





El análogo a la propiedad de escalamiento en fractales auto-similares

$$N(l) \propto l^{-D_f}$$

donde D_f es la dimensión de capacidad o la dimensión de Hausdorff, esta dada por

$$h(x) \sim b^{-\alpha} h(bx), \quad h(l) \sim l^\alpha$$

donde α es un exponente denominado de Hölder o de auto-afinidad, que expresa cuantitativamente la rugosidad de la estructura fractal.



Auto-afinidad. Relación entre rugosidad y dimensión fractal.

Consideremos la función auto-afin definida en el intervalo $[0,1]$ y dividamos ese intervalo en N_s segmentos. En cada segmento el cambio de valor de la función escala cómo

$$\Delta(l) \propto l^\alpha, \quad l = \frac{1}{N_s}$$

de modo que el número de cajas que se necesitan para “cubrir” la función en cada segmento es

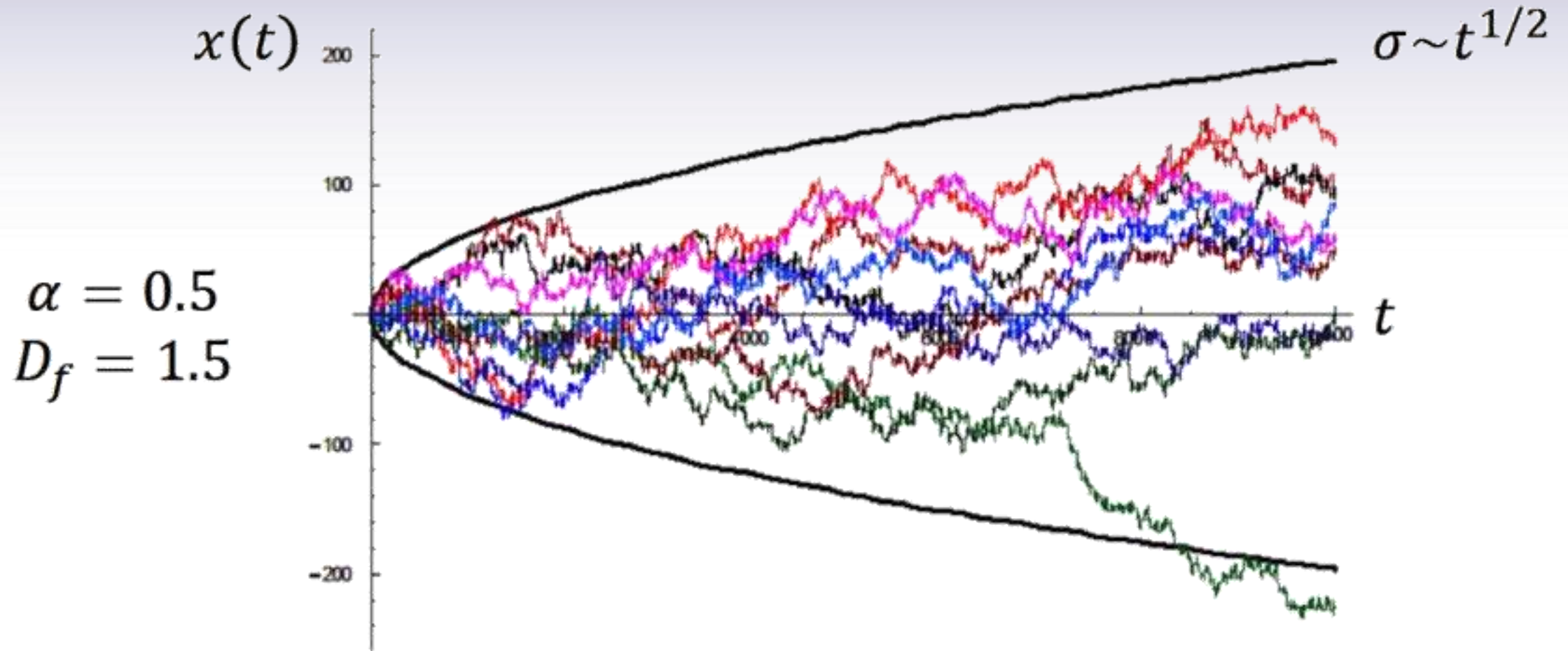
$$\frac{\Delta(l)}{l} \propto l^{\alpha-1}$$

y el número total de cajas que “cubren” toda la estructura

$$N(l) \sim N_s \times l^{\alpha-1} \sim l^{\alpha-2} \sim l^{-D_f} \quad \rightarrow \quad D_f = 2 - \alpha$$

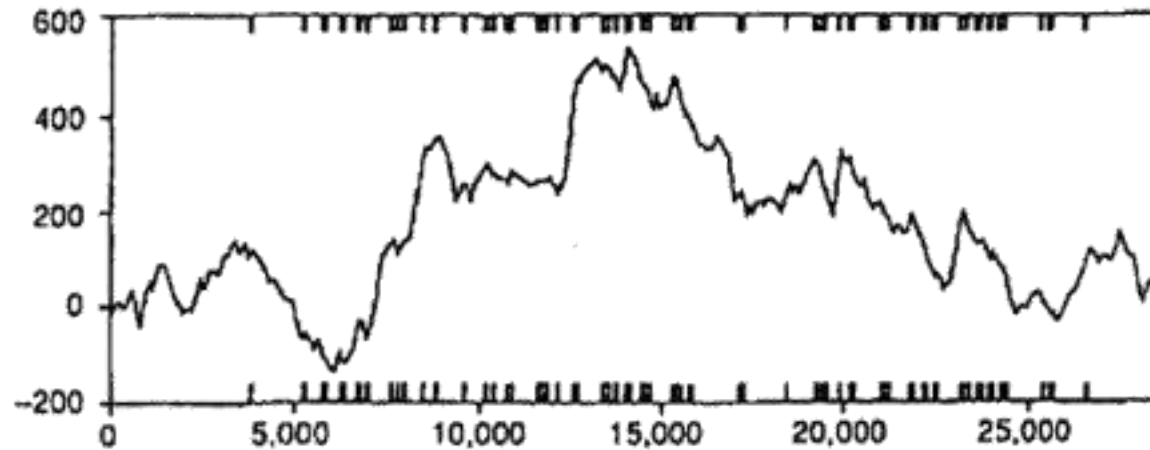
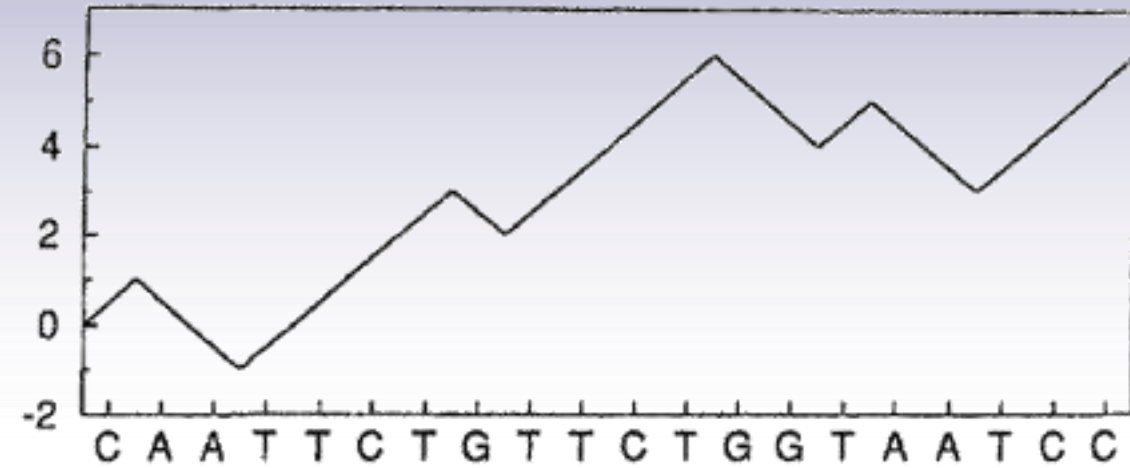


Auto-afinidad. Movimiento Browniano.



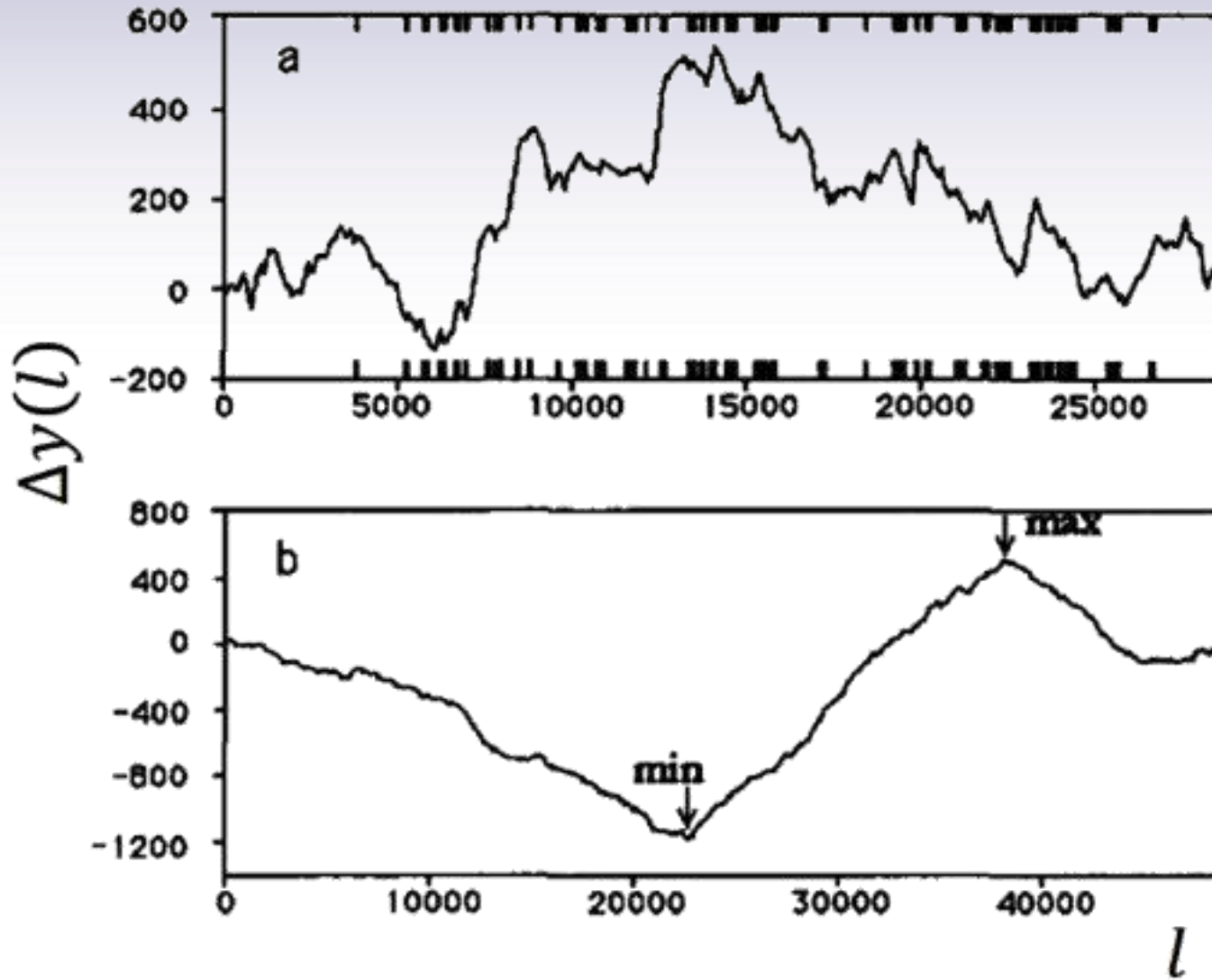


Auto-Afinidad. "DNA Walk"





Auto-Afinidad. "DNA Walk"



$$F^2(l) \equiv \overline{[\Delta y(l)]^2} - \overline{\Delta y(l)}^2$$

$$\Delta y(l) \equiv y(l_0 + l) - y(l_0)$$

$$F(l) \sim l^\alpha$$

$$\alpha \neq 0.5$$



Distribución de Probabilidad o Función de Densidad de Probabilidad (PDF)

$$P(X = x) = ax^{-\alpha}$$

Función de Distribución o Función de Distribución Acumulada (CDF)

$$P(X > x) = bx^{-(\alpha+1)}$$

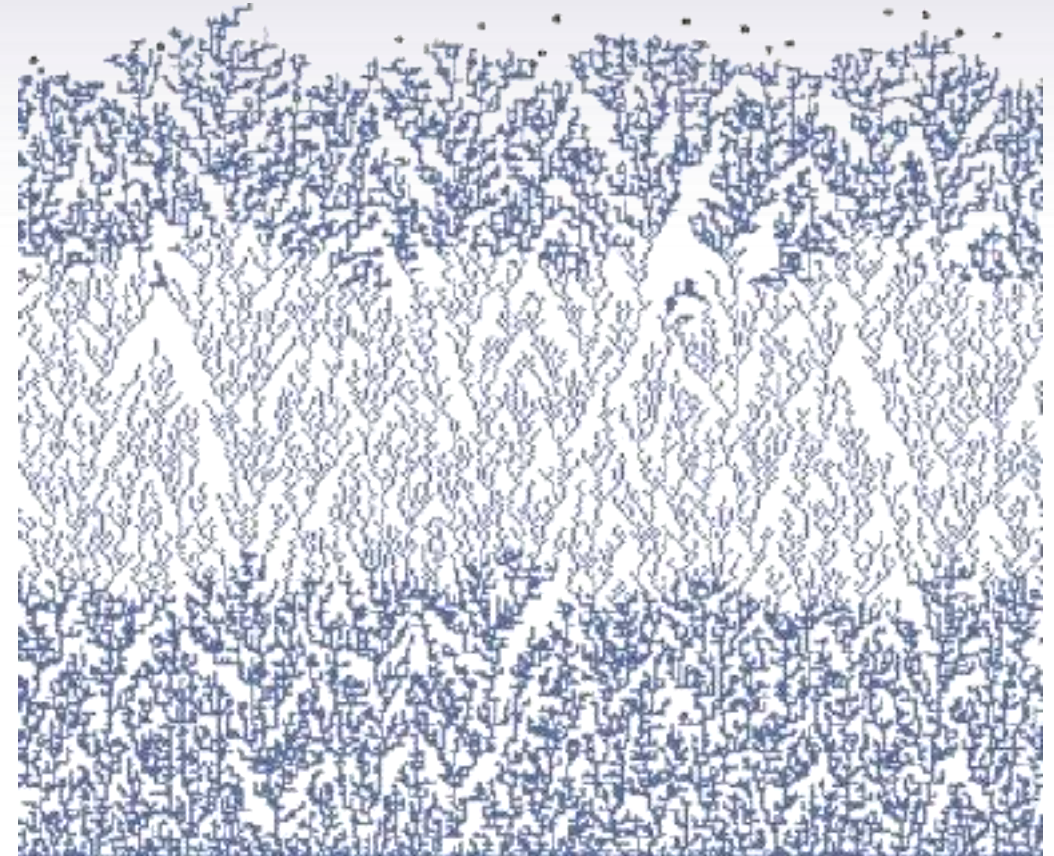
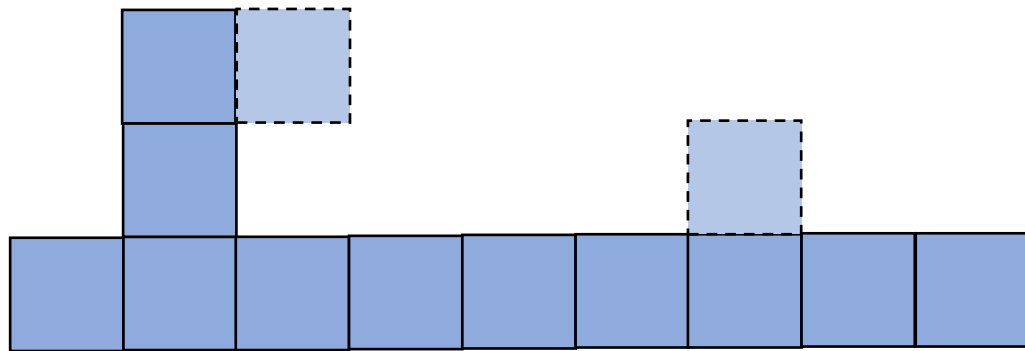


Leyes de potencia

- Representan distribuciones que no tienen una escala característica, espacial o temporal, y por lo tanto son representativas de fractalidad.
- Cuando el valor de α en una ley de potencia para la PDF se encuentra entre 0 y 2, la distribución tiene una varianza infinita y si α es menor que 1 entonces su media también es infinita.
- Las distribuciones que presentan leyes de potencia son generalmente de larga cola, lo que significa que las correlaciones decaen lentamente en el espacio o en el tiempo. Esta persistencia es también una indicación de fractalidad.

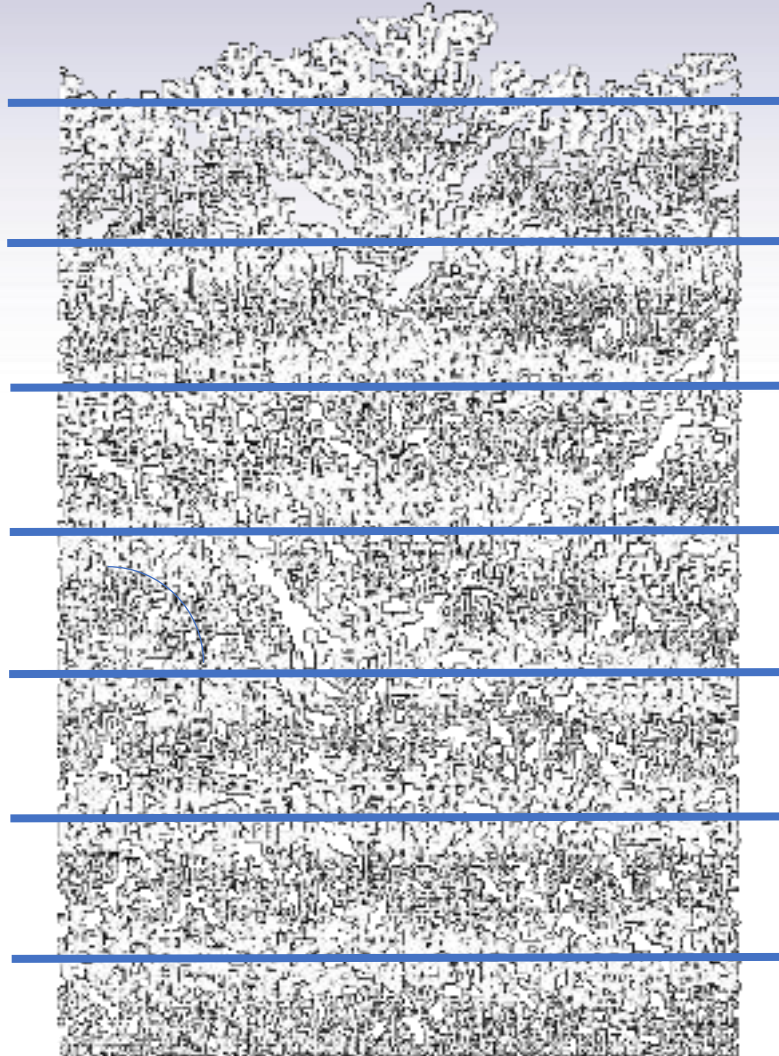


Ejemplos de Leyes de Potencia. Deposición balística.





Ejemplos de Leyes de Potencia. Deposición balística.



La altura media \bar{h} sobre la superficie es:

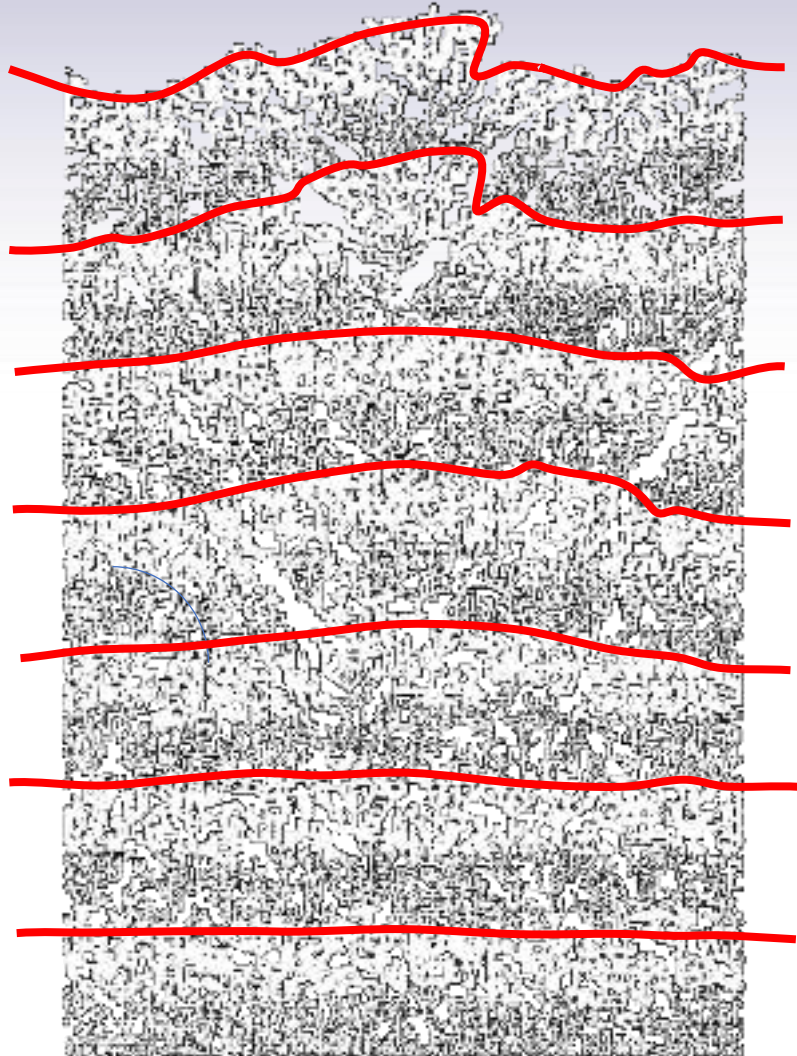
$$\bar{h} \equiv \frac{1}{L} \sum_{i=1}^L h(i, t)$$

Si la tasa de deposición es constante entonces:

$$\bar{h} \sim t$$



Ejemplos de Leyes de Potencia. Deposición balística.



La altura media \bar{h} sobre la superficie es:

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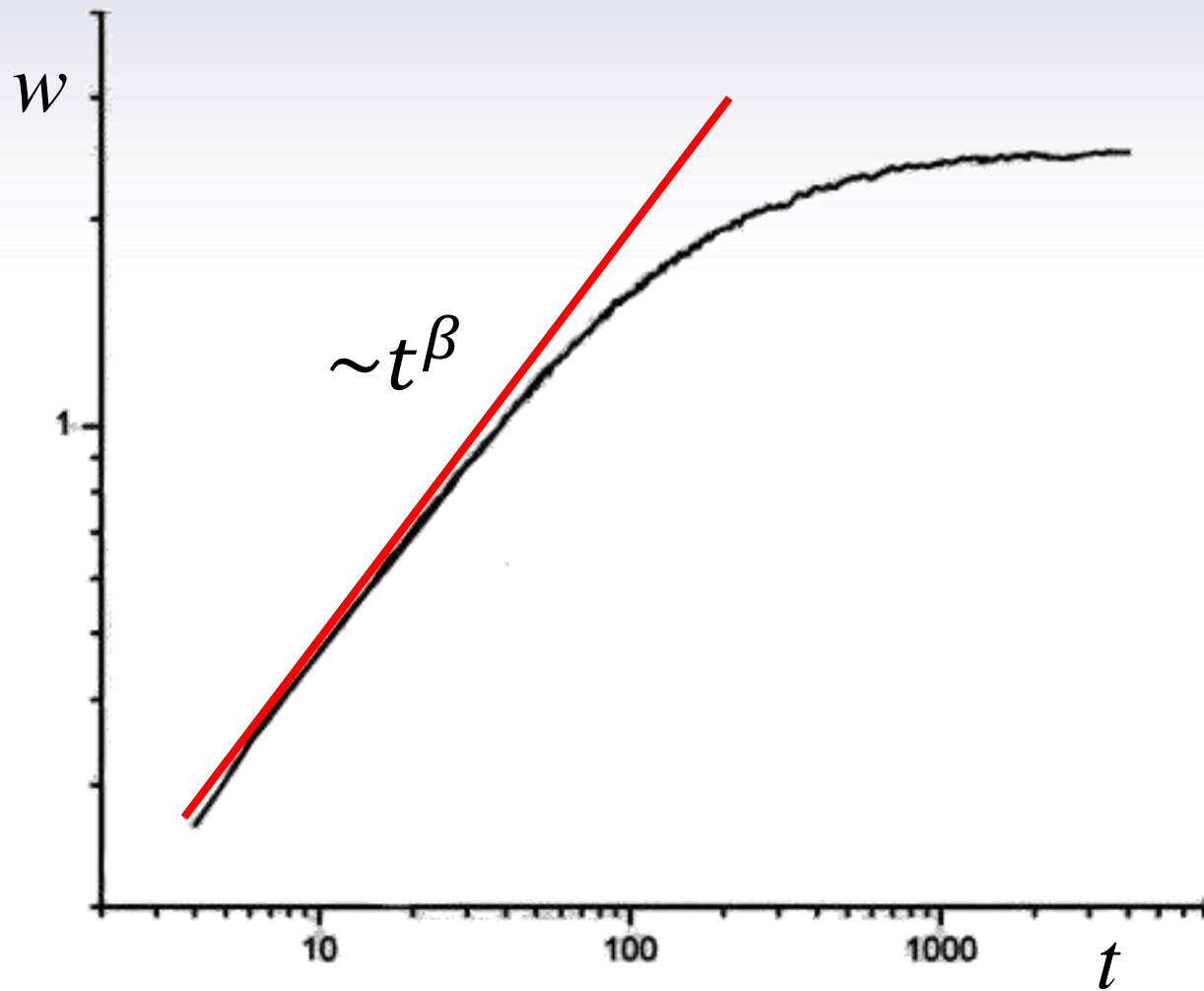
$$\bar{h} \sim t$$

El espesor de la interfaz, que caracteriza la rugosidad de la misma, se hace más rugoso a medida que progresa la deposición

$$w(L, t) \equiv \sqrt{\frac{1}{L} \sum_{i=1}^L [h(i, t) - \bar{h}(t)]^2}$$



Ejemplos de Leyes de Potencia. Deposición balística.



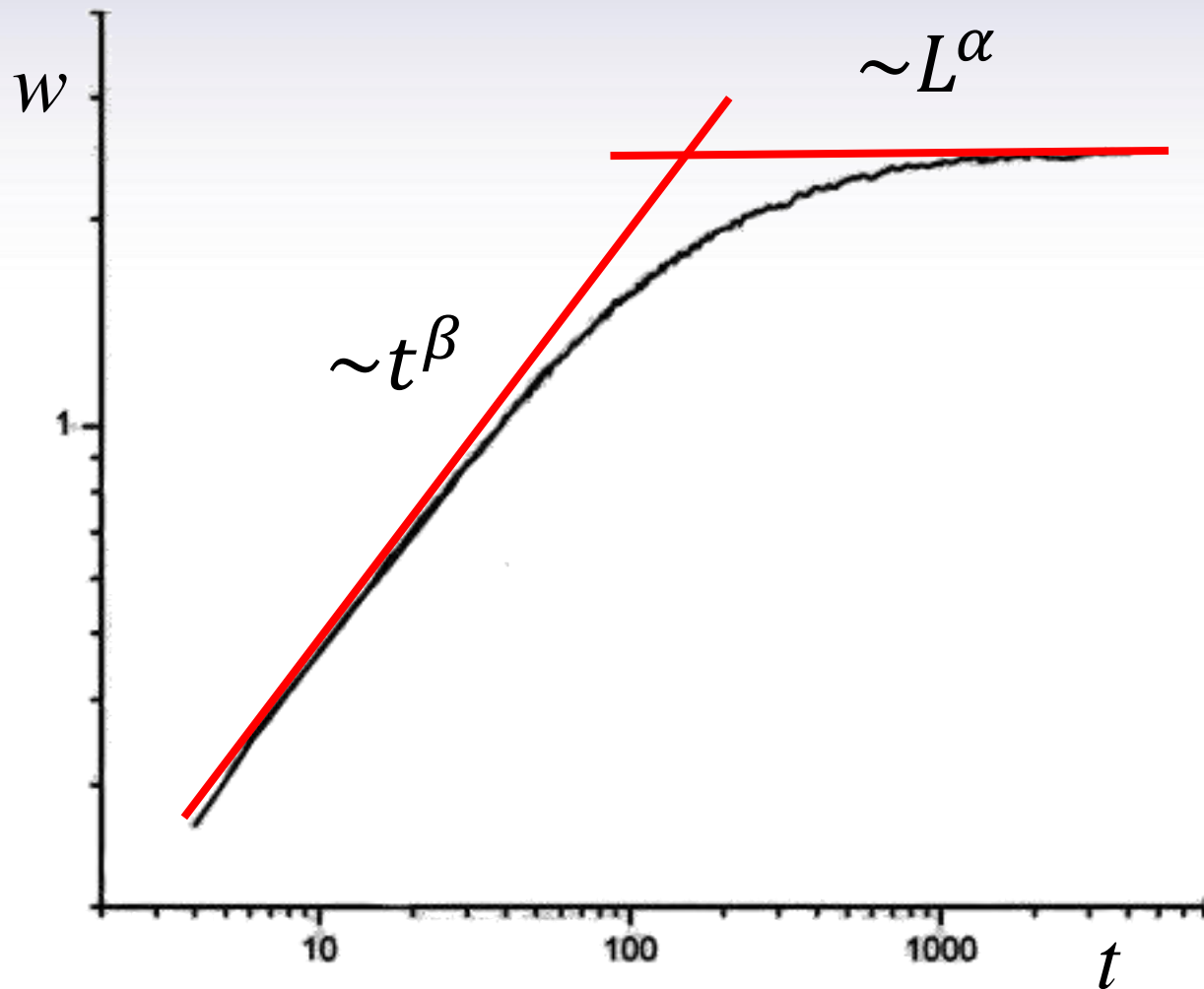
Inicialmente, el espesor de la interfaz crece cómo

$$w(L, t) \sim t^\beta$$

Este exponente se denomina exponente de crecimiento.



Ejemplos de Leyes de Potencia. Deposición balística.



Inicialmente, el espesor de la interfaz crece cómo

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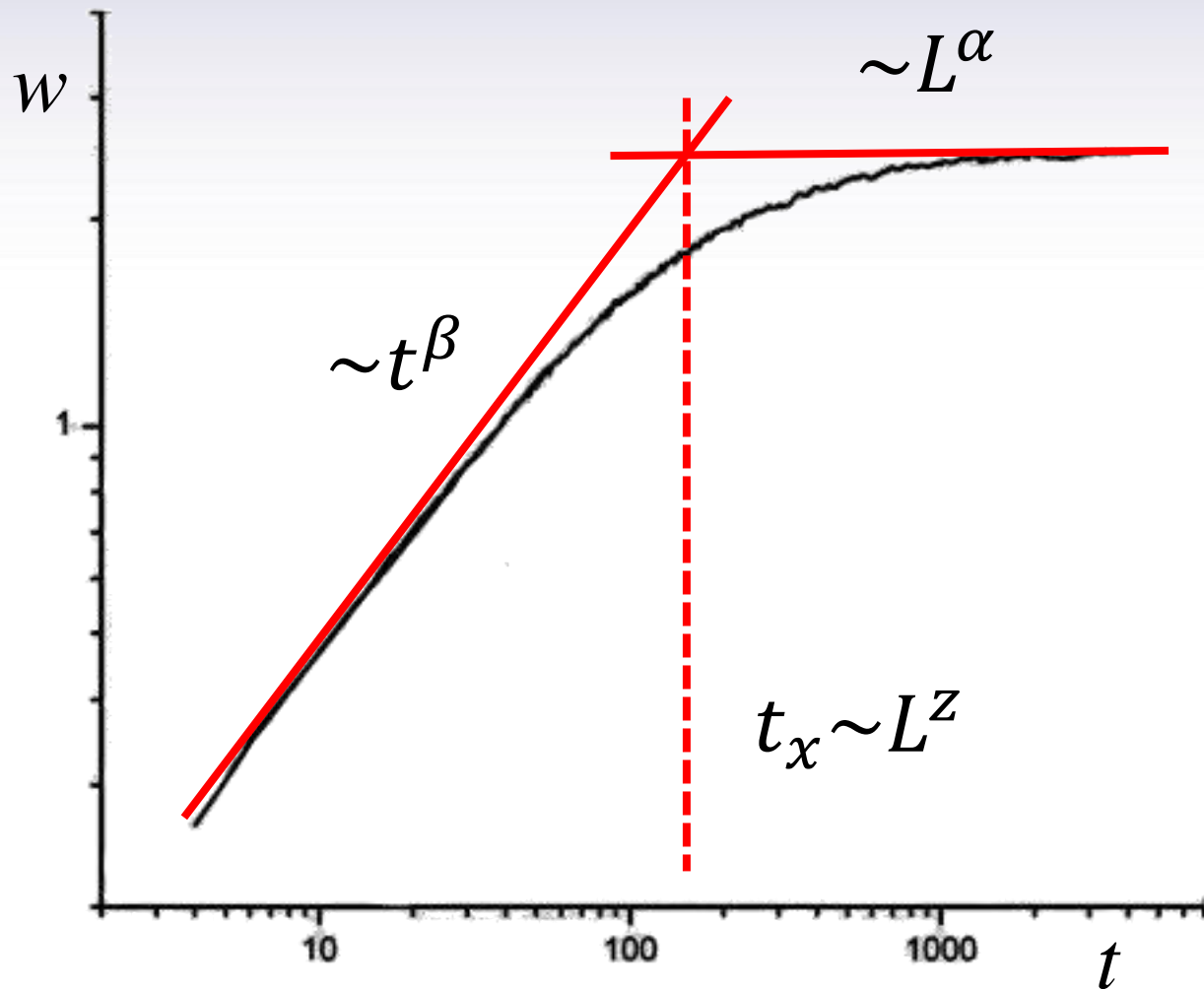
A tiempos suficientemente largos, el espesor de la interfaz alcanza un valor de saturación que presenta un comportamiento

$$w_{sat}(L) \sim L^\alpha$$

El exponente se denomina exponente de rugosidad.



Ejemplos de Leyes de Potencia. Deposición balística.



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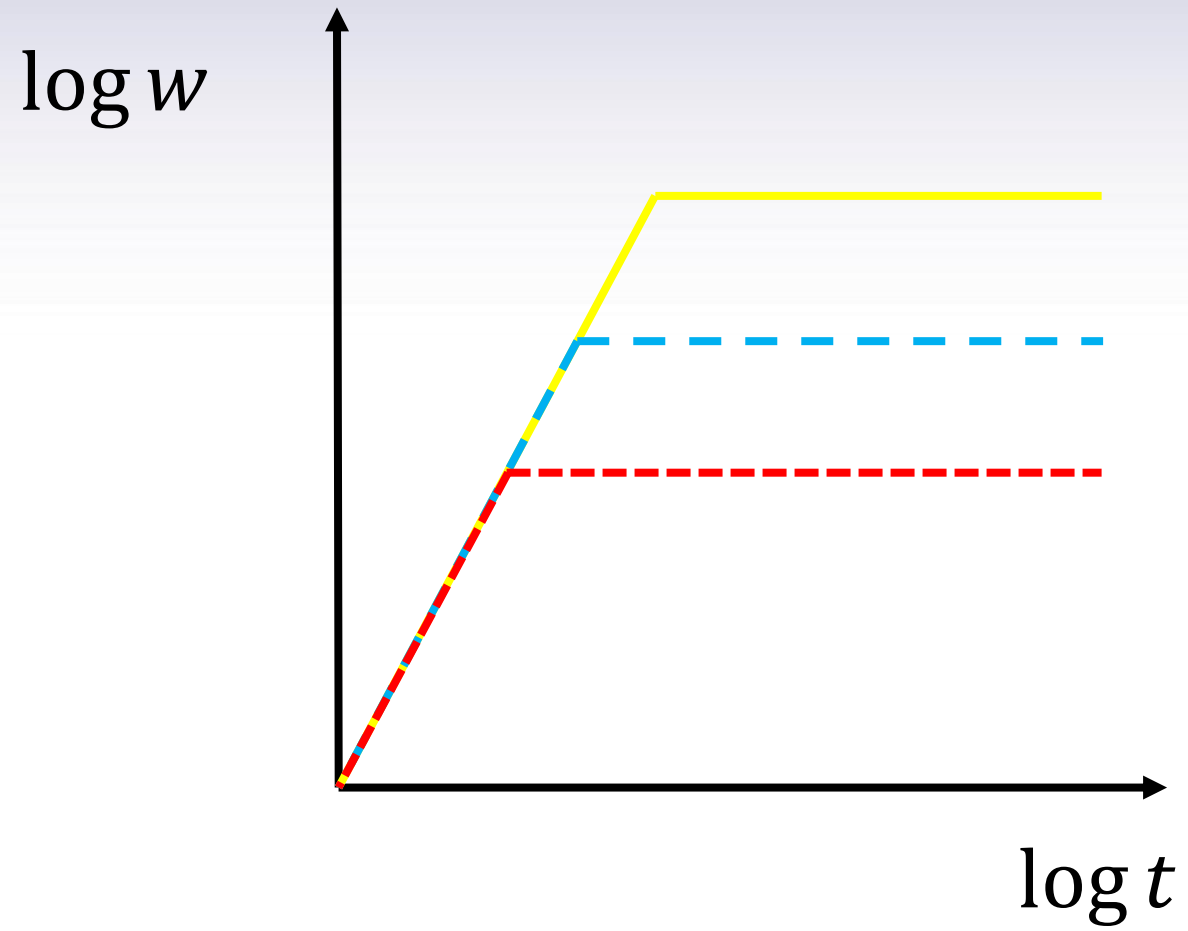
La transición ocurre a un tiempo t_x que escala con el tamaño del sistema

$$t_x \sim L^z$$

El exponente se denomina exponente dinámico.

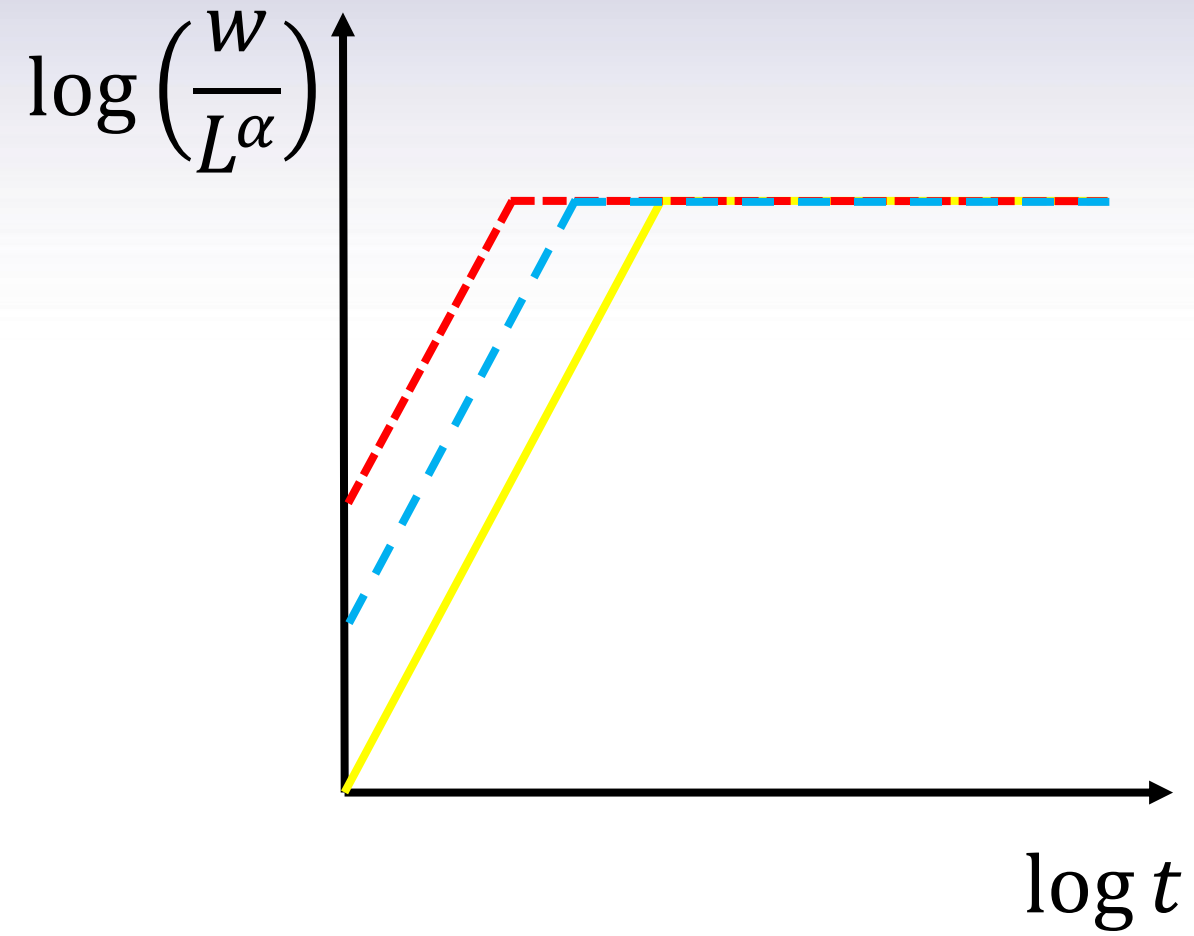


Análisis de escalamiento.



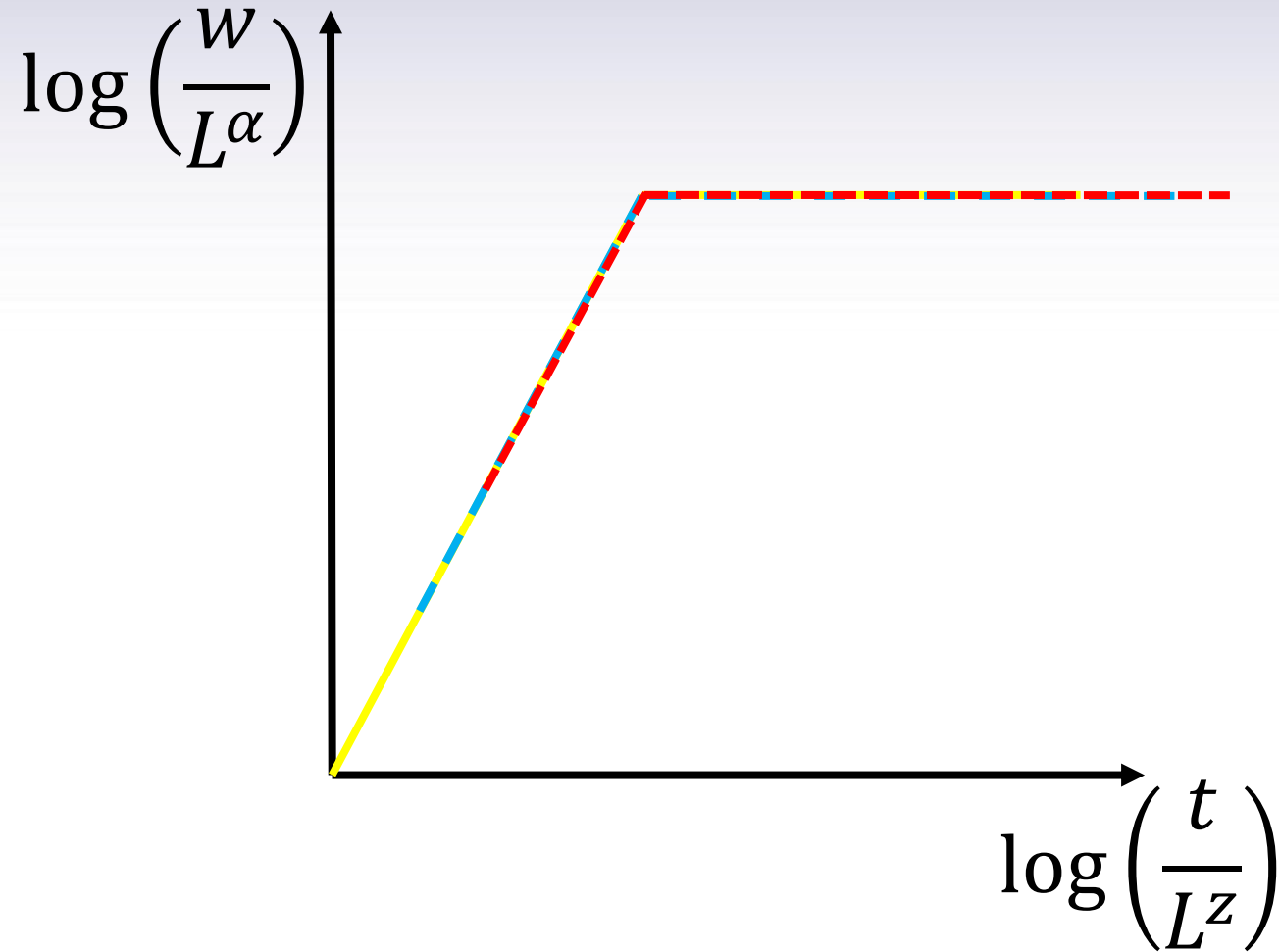


Análisis de escalamiento.





Análisis de escalamiento.



$$w(L, t) \sim L^\alpha f\left(\frac{t}{L^z}\right)$$

$$f(u) \sim u^\beta \quad (u \ll 1)$$

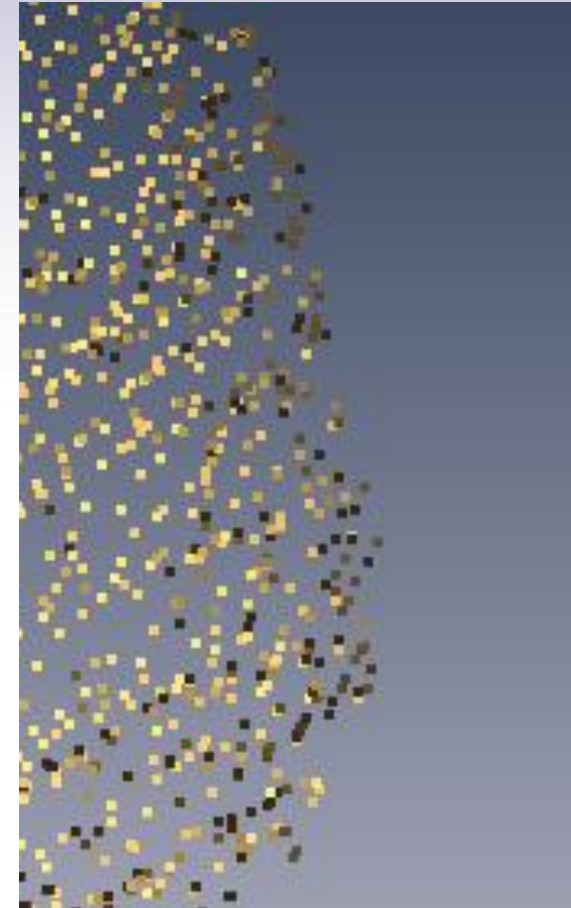
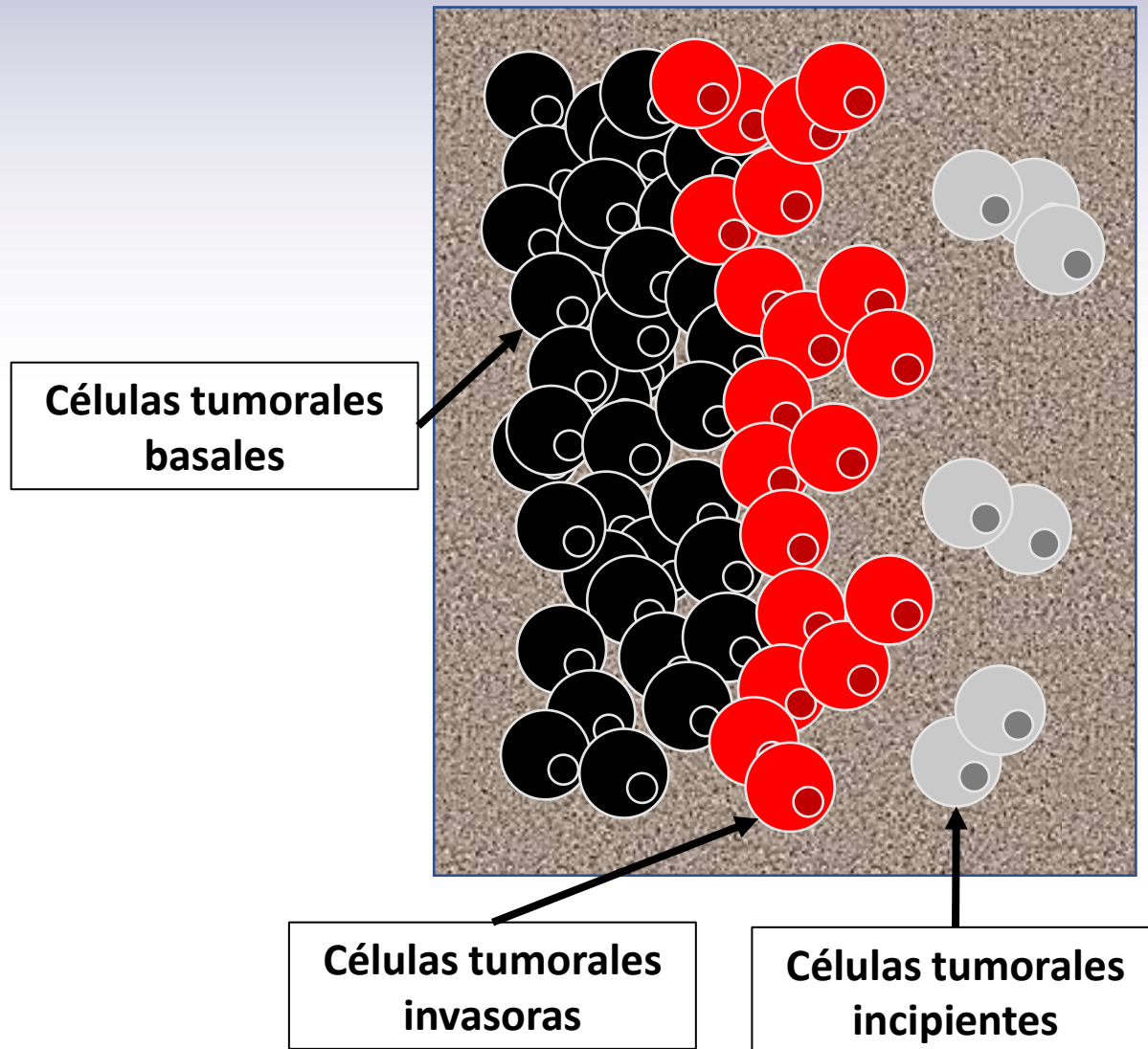
$$f(u) \sim \text{const} \quad (u \gg 1)$$

$$z = \frac{\alpha}{\beta}$$

Ansatz de Family-Vicsek

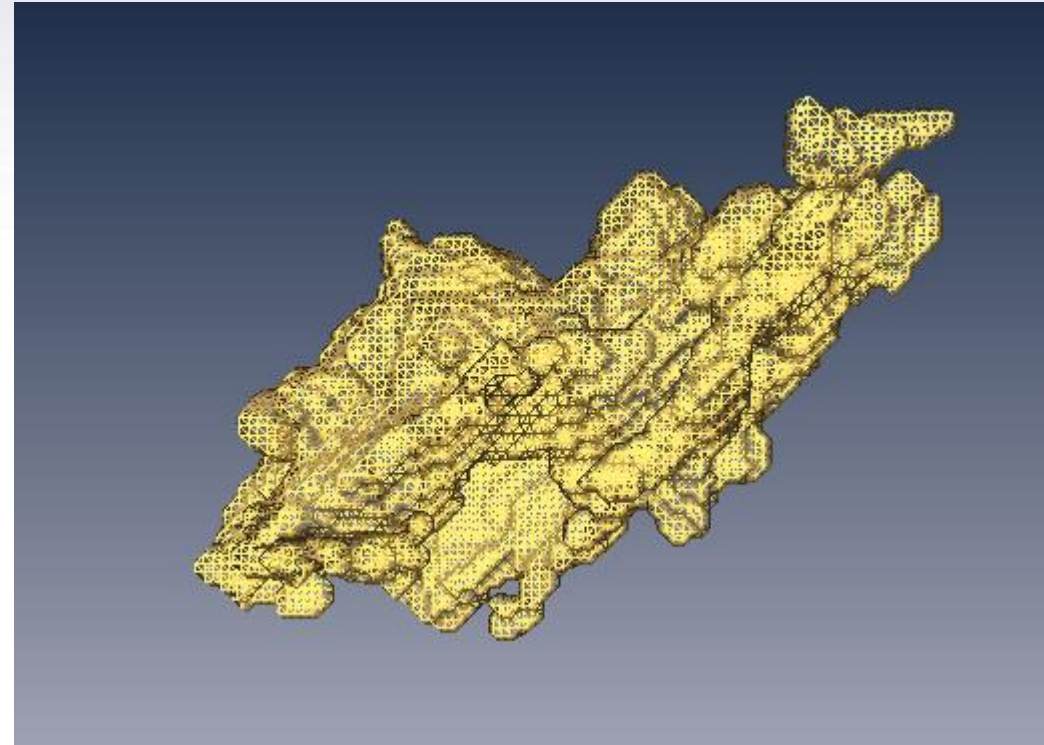
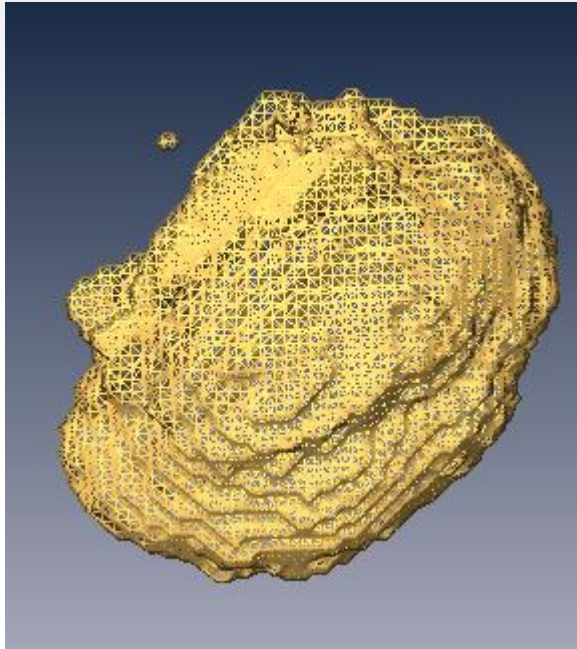


Interfaz tumoral.





Interfaz tumoral.





Crecimiento interfaz tumoral.

La generación espontánea de interfaces fractales ha sido observada en muchos procesos naturales. La hipótesis básica es que el objeto exhibe auto-similaridad y no presenta una longitud característica. Bajo estas condiciones, la interfaz escala cómo:

$$h(\bar{x}, t) \sim b^{-\alpha} h(b\bar{x}, t)$$

con $\alpha > 0$

Se propone una ecuación del tipo Langevin:

$$\frac{\partial h(\bar{x}, t)}{\partial t} = F + G(h(\bar{x}, t)) + \eta(\bar{x}, t)$$



Crecimiento interfaz tumoral.

**Variable de interfaz
promedio sobre todo el
sistema de tamaño L**

La rugosidad de la interfaz $h(\bar{x}, t)$ esta caracterizada por el espesor de la interfaz:

$$W(L, t) = \left\langle \left[(h(x, t) - \bar{h}(t))^2 \right]_L \right\rangle^{1/2}$$



Crecimiento interfaz tumoral.

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**$\langle \rangle$: Promedio
sobre n
realizaciones**



Crecimiento interfaz tumoral.

La rugosidad de la interfaz $h(\bar{x}, t)$ esta caracterizada por el espesor de la interfaz:

$$W(L, t) = \left\langle \left[(h(x, t) - \bar{h}(t))^2 \right]_L \right\rangle^{1/2}$$

La función de correlación de la variable de interfaz $h(x, t)$ esta dada por:

$$C(l, t) = \langle [(h(x, t) - h(x + l, t))^2]_L \rangle$$



Crecimiento interfaz tumoral.

El **espectro de potencia** de la variable de interfaz es:

$$S(k, t) = \langle \hat{h}(k, t) \hat{h}(-k, t) \rangle$$

donde $\hat{h}(k, t) = L^{-1/2} \int [h(x, t) - \bar{h}(t)] \exp(ikx) dx$

Se relaciona con las cantidades anteriores $C(l, t)$ y $W(L, t)$, mediante

$$C(l, t) \sim \int_{2\pi/L}^{\pi/a} \frac{dk}{2\pi} [1 - \cos(kl)] S(k, t)$$

$$W^2(L, t) = \int \frac{dk}{2\pi} S(k, t)$$

Generic Dynamic Scaling in Kinetic Roughening, J.J. Ramasco, J.M. López, M.A. Rodríguez, Phys. Rev. Lett. **84**, 2199-2202 (2000)



Crecimiento interfaz tumoral.

Ansatz de Family-Vicsek.

$$W(L, t) = t^{\alpha/z} f\left(\frac{L}{\zeta(t)}\right), \quad f(u) \sim \begin{cases} u^\alpha & \text{si } u \ll 1 \\ \text{const} & \text{si } u \gg 1 \end{cases}$$

$\zeta(t) \sim t^{1/z}$ **comportamiento de la longitud de correlación lateral en estado estacionario**

Lo que reproduce:

$$W(L, t) \sim t^\beta \text{ para tiempos pequeños, } \frac{L}{\zeta(t)} \gg 1$$

$$W(L, t) \sim L^\alpha \text{ para estado estacionario, } \zeta(t) \gg L$$

Además, $\alpha + d_f = d_E$, donde d_f es la dimensión fractal de la interfaz y d_E es la dimensión Euclídea del espacio que contiene la interfaz.



Crecimiento interfaz tumoral.

La existencia de un escalamiento dinámico, mediante el ansatz de Family-Vicsek y la ausencia de una longitud de escala característica permite establecer en forma similar el espesor local $w(l, t)$ que mide las fluctuaciones de la interfaz para $l \ll L$. Igualmente para $t_c(l) \sim l_c^z$ donde l_c es la longitud de coherencia para la fluctuación local, tenemos $w(l, t \gg t_c)_{sat} \sim l^{\alpha_{loc}}$ y para $t \ll t_c$, $w(l, t) \sim t^\beta$.

$$w(l, t) = \langle [(r(x, t) - \bar{r}(t))^2]_l \rangle_L^{1/2}$$

donde en este caso, $[]_l$ representa un promedio sobre un subconjunto l , $\bar{r}(t)$ el promedio del radio de la interfaz en ese mismo subconjunto y $\langle \rangle_L$ el promedio sobre el tamaño total, L .



Crecimiento interfaz tumoral.

Cuando $w(l, t)$ difiere de $W(L, t)$, entonces:

$$w(l, t) \sim l^{\alpha_{loc}}, \quad W(L, t) \sim L^{\alpha}, \quad t \gg t_C$$

Los sistemas con $\alpha > 1$ se denominan **super-rugosos**. Para estos sistemas no se cumplen las relaciones anteriores, sino un nuevo comportamiento en un régimen temporal intermedio $l^z \ll t \ll L^z$, caracterizado por un exponente de crecimiento, β^* , tal que

$$w(l, t \gg l^z) \sim lt^{\beta^*}, \quad \beta^* = \beta - \frac{\alpha_{loc}}{z}$$

Igualmente debe cumplirse $\alpha_{loc} + d_f = d_E$



Dynamics of fractal surfaces, F. Family and T. Viseck, World Scientific, Singapore, 1991.



Super-Rough Dynamics on Tumor Growth

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²*Departamento de Física Fundamental, UNED, c/Senda del Rey s/n, 28040 Madrid, Spain*

³*Instituto Ramón y Cajal, CSIC, Madrid, Spain*

⁴*Hospital SS Ntra. del Prado, Talavera de la Reina, 45600, Spain*

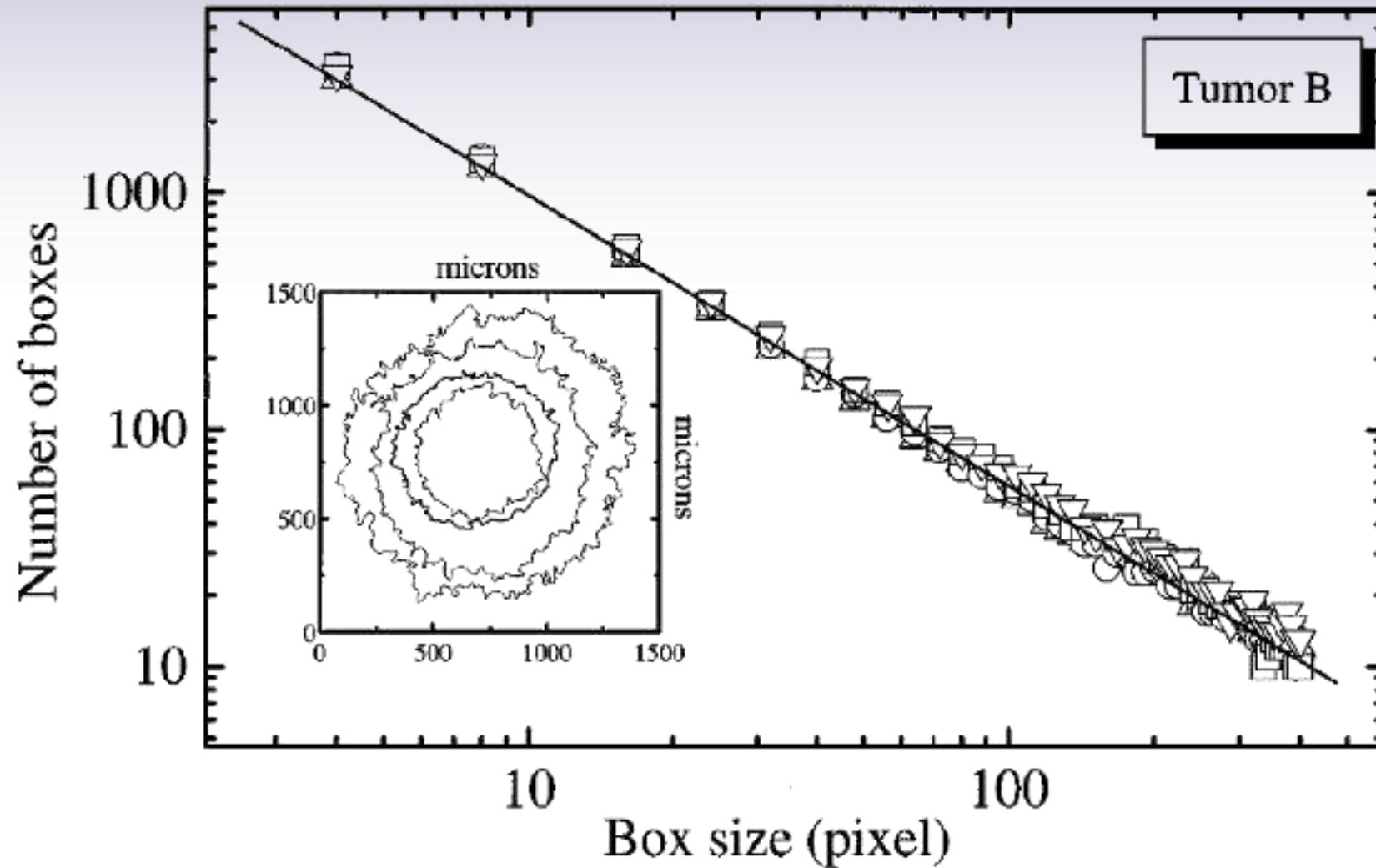
⁵*Facultad de Ciencias, Universidad de Alicante, 03690 Alicante, Spain*

(Received 22 May 1998)

The growth of a cultivated typical brain tumor is studied in this work. The tumor is analyzed both dynamically and morphologically. We have measured its fractal dimension to be $d_f = 1.21 \pm 0.05$. From its dynamical behavior we determine the scaling critical exponents of this circular symmetry system which are compatible with the linear molecular beam epitaxy universality class. A very important feature of tumor profiles is that they are *super-rough*, which constitutes the first (1 + 1)-dimensional experiment in literature with super-roughness. The results obtained from the dynamics study make manifest two very surprising features of tumor growth: Its dynamics is mainly due to contour cells and the tendency of an interface cell to duplicate is a function of the local curvature. [S0031-9007(98)07545-0]

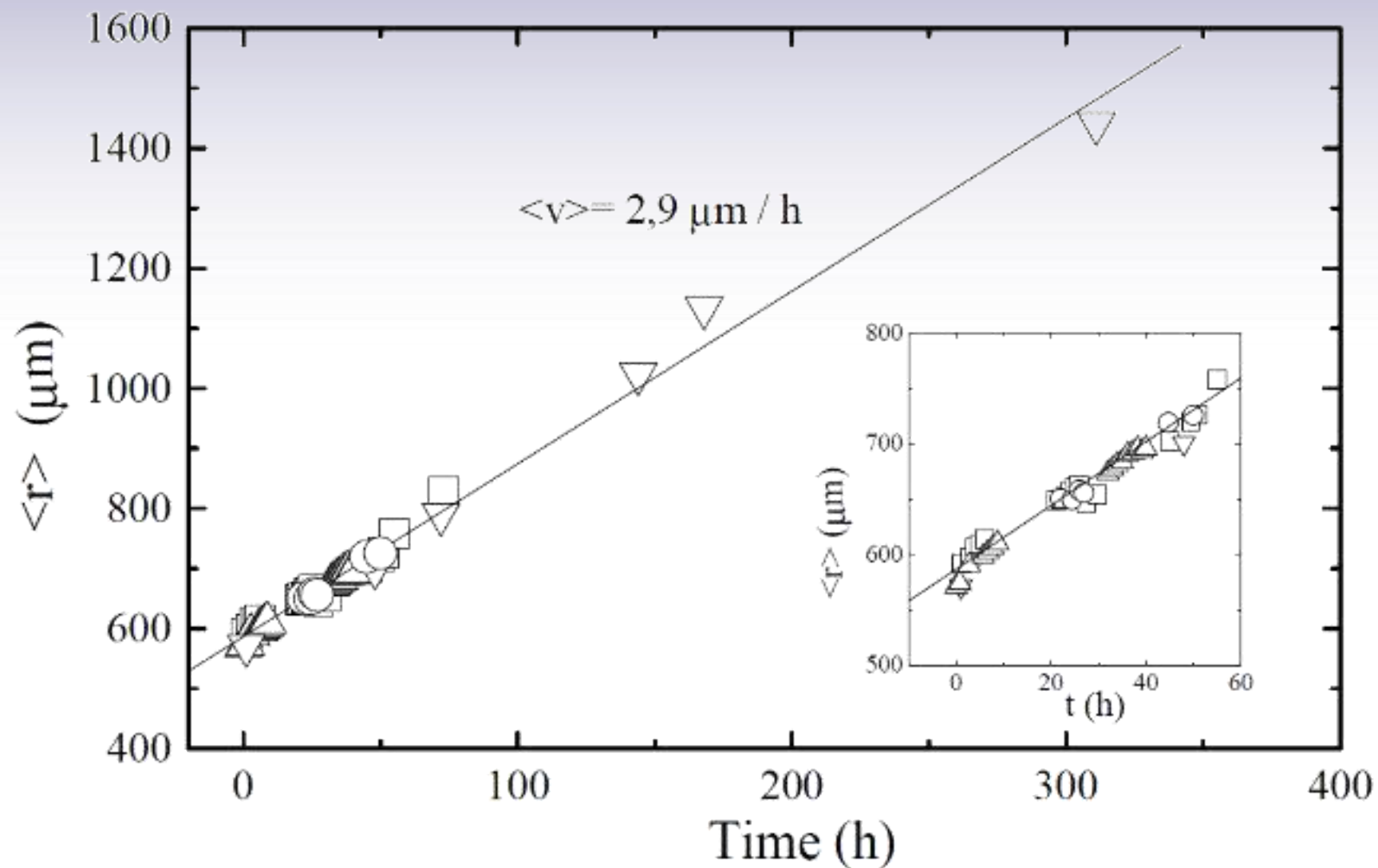


Crecimiento tumoral *in vitro*.



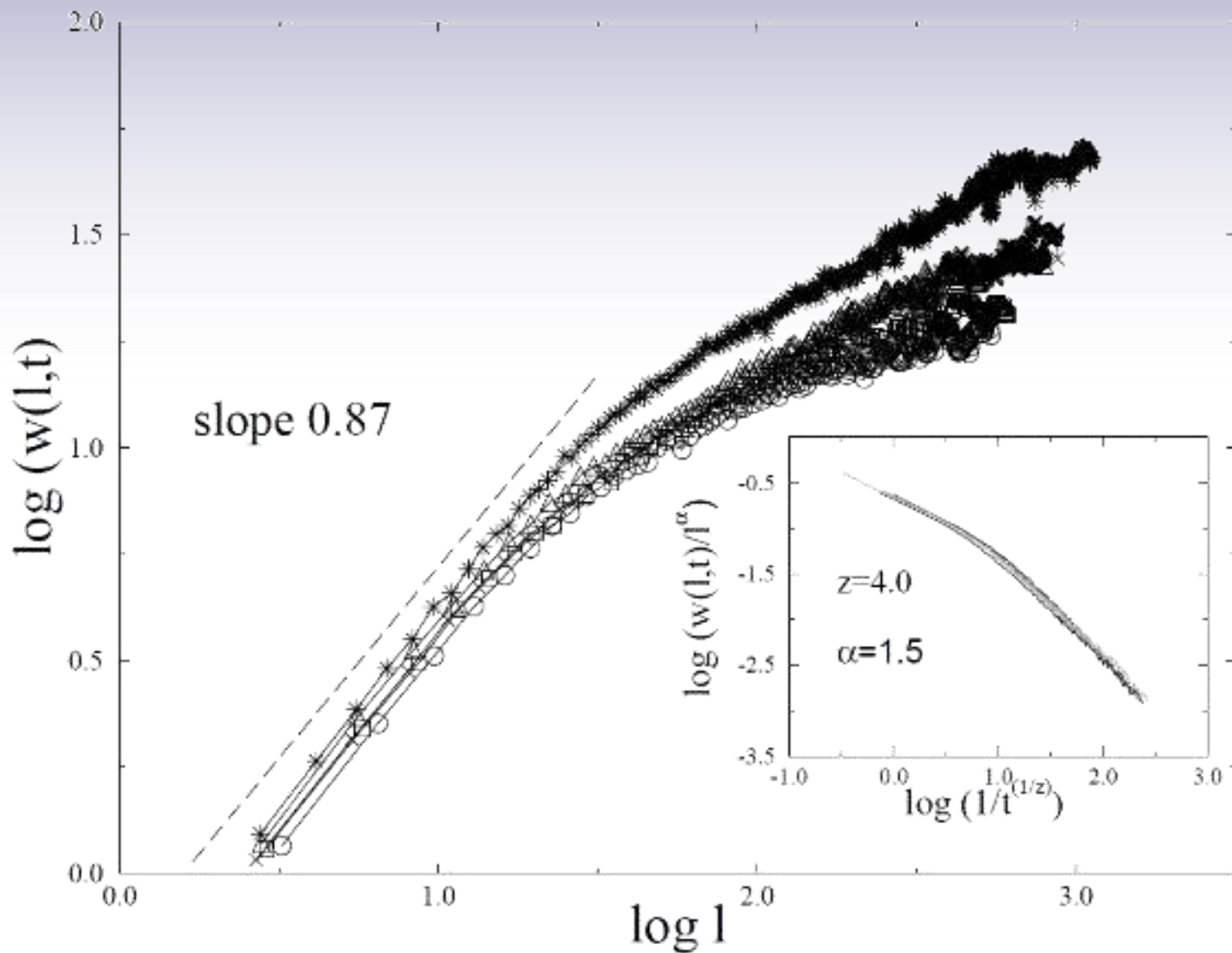


Crecimiento tumoral *in vitro*.





Crecimiento tumoral *in vitro*.



$$W(l, t) \sim l^{\alpha_{loc}}, \quad t \gg t_S$$

$$\beta^* = \frac{\alpha - \alpha_{loc}}{z}$$



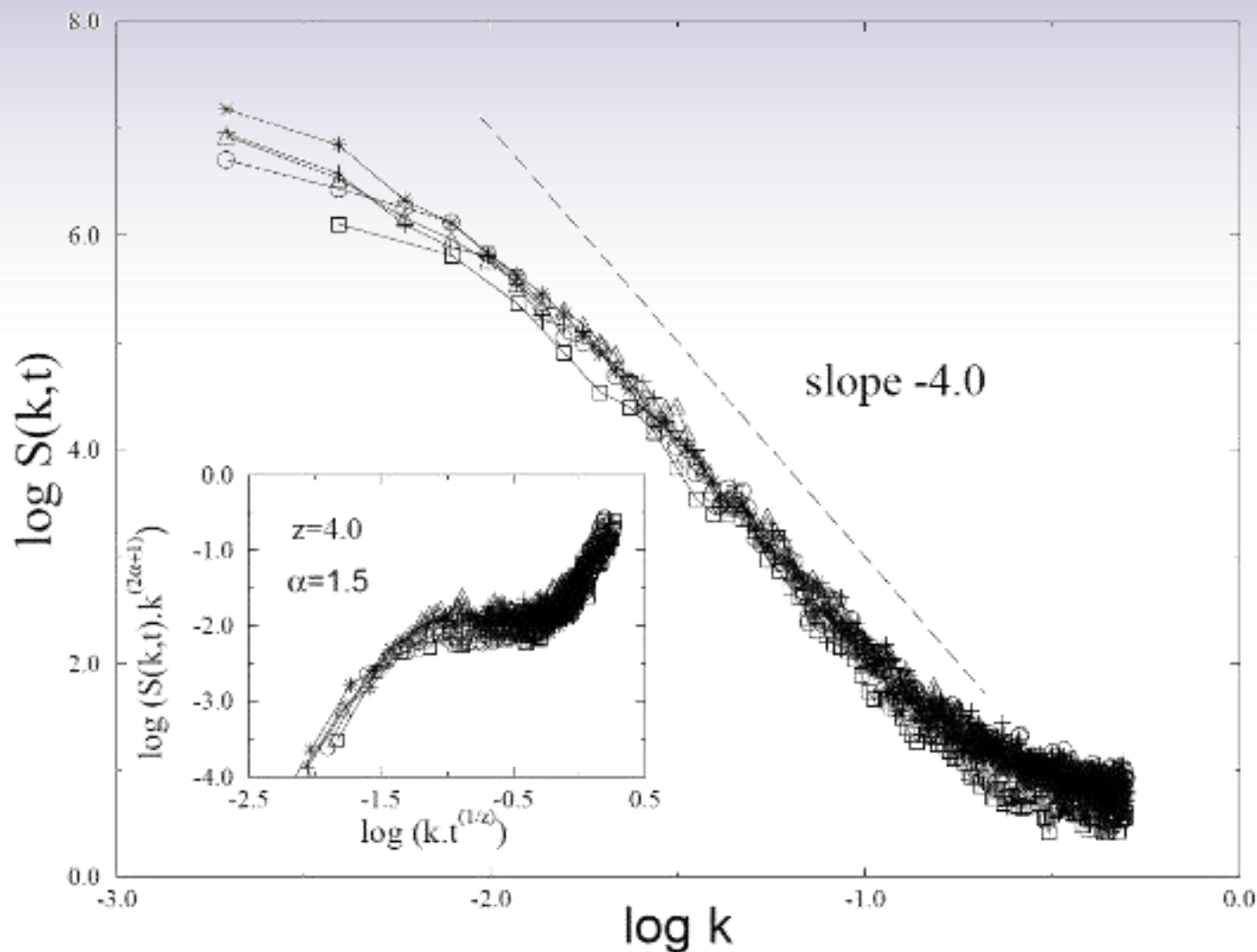
Crecimiento tumoral *in vitro*.

$$S(k, t) = k^{-(2\alpha+1)} s(kt^{1/z})$$

$$s(u) = \begin{cases} \text{constante} & \text{si } u \gg 1 \\ u^{2\alpha+1} & \text{si } u \ll 1 \end{cases}$$



Crecimiento tumoral *in vitro*.



$$\alpha = 1.5 \pm 0.1$$
$$\beta = 0.375 \pm 0.03$$
$$z = 4.0 \pm 0.2$$

$$\beta^* = 0.15 \pm 0.05$$
$$\alpha_{loc} = 0.87 \pm 0.05$$

MBE



The Universal Dynamics of Tumor Growth

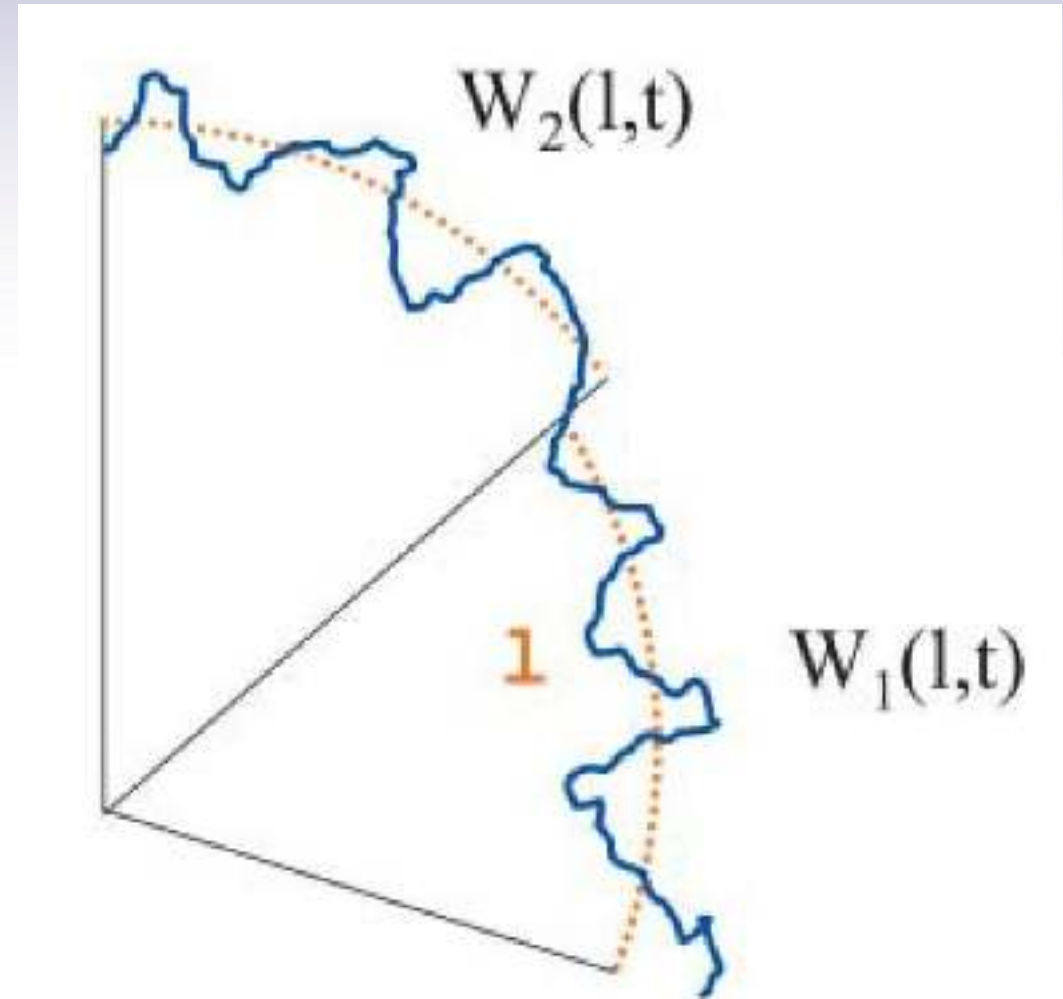
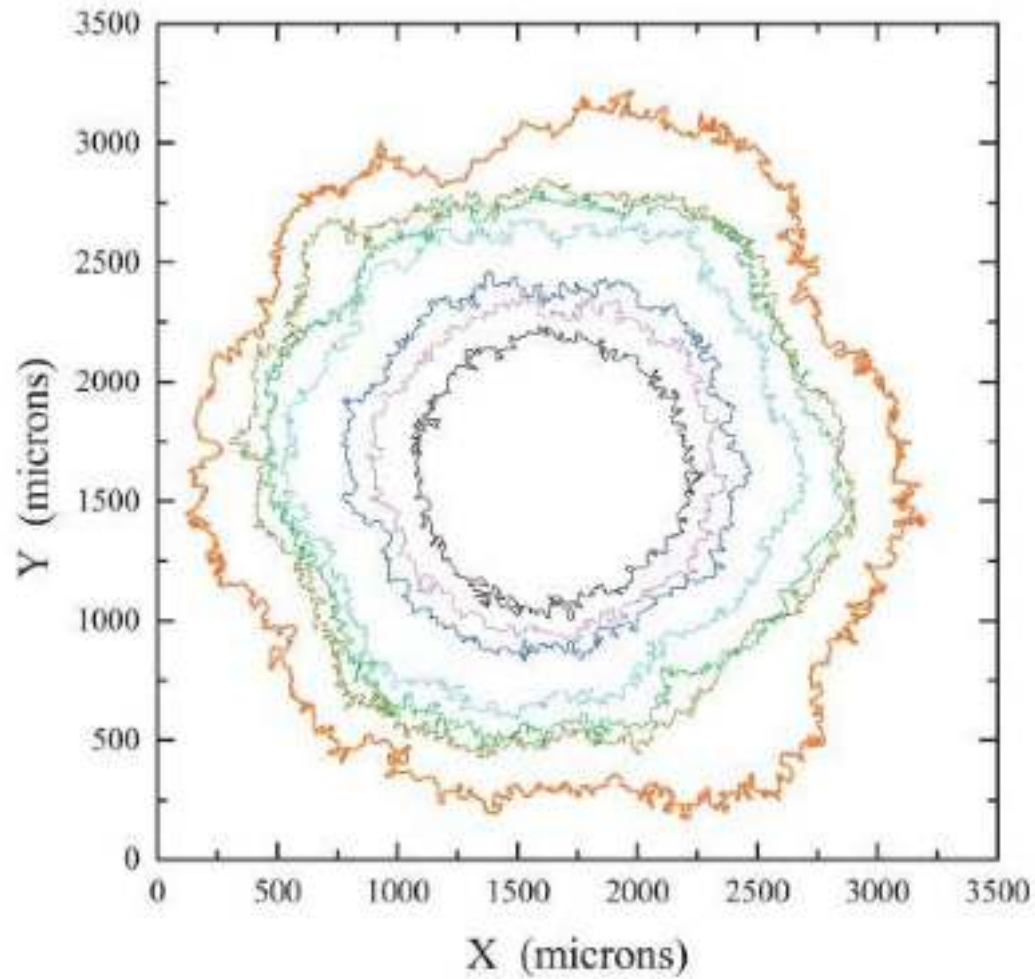
Antonio Brú,^{*} Sonia Albertos,[†] José Luis Subiza,[‡] José López García-Asenjo,[§] and Isabel Brú[¶]

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ABSTRACT Scaling techniques were used to analyze the fractal nature of colonies of 15 cell lines growing *in vitro* as well as of 16 types of tumor developing *in vivo*. All cell colonies were found to exhibit exactly the same growth dynamics—which correspond to the molecular beam epitaxy (MBE) universality class. MBE dynamics are characterized by 1), a linear growth rate, 2), the constraint of cell proliferation to the colony/tumor border, and 3), surface diffusion of cells at the growing edge. These characteristics were experimentally verified in the studied colonies. That these should show MBE dynamics is in strong contrast with the currently established concept of tumor growth: the kinetics of this type of proliferation rules out exponential or Gompertzian growth. Rather, a clear linear growth regime is followed. The importance of new cell movements—cell diffusion at the tumor border—lies in the fact that tumor growth must be conceived as a competition for space between the tumor and the host, and not for nutrients or other factors. Strong experimental evidence is presented for 16 types of tumor, the growth of which cell surface diffusion may be the main mechanism responsible *in vivo*. These results explain most of the clinical and biological features of colonies and tumors, offer new theoretical frameworks, and challenge the wisdom of some current clinical strategies.



Crecimiento tumoral *in vitro* y *ex vivo*.





Crecimiento tumoral *in vitro* y *ex vivo*.

TABLE 1 In vitro cell lines

Cell line	Type	Origin	d_f	α_{loc}	α_{glob}	β	z	β^*	Growth rate ($\mu\text{m/h}$)
HT-29	Colon adenocarcinoma	Human	1.13	0.91	1.51	0.38	3.9	0.15	1.93
HT-29 M6	Mucus secreting HT-29 cells	Human	1.12	0.91	1.47	0.37	3.9	0.14	1.85
C-33 ^a	Cervix carcinoma	Human	1.25	0.89	1.48	0.36	4.1	0.14	6.40
Saos-2	Osteosarcoma	Human	1.34	0.92	1.50	0.37	4.0	0.14	0.94
AT5	Primary human foreskin fibroblasts	Human	1.23	0.91	1.48	0.37	4.0	0.14	8.72
HeLa	Cervix carcinoma	Human	1.30	0.90	1.47	0.39	3.7	0.15	1.34
3T3	Mouse fibroblasts	Animal	1.20	0.90	1.51	0.37	4.0	0.15	1.10
3T3 K-ras	Transformed mouse fibroblasts	Animal	1.32	0.91	1.52	0.39	3.8	0.16	1.89
3T3 V-src	Transformed mouse fibroblasts	Animal	1.34	0.90	1.50	0.38	3.9	0.15	1.35
VERO C	African green monkey kidney cells	Animal	1.18	0.92	1.50	0.38	3.9	0.15	5.10
Car B	Mouse spindle carcinoma	Animal	1.20	0.93	1.51	0.37	4.1	0.14	2.06
MCA3D	Mouse keratinocytes	Animal	1.09	0.89	1.52	0.39	3.9	0.16	3.73
Mv1Lu	Mink, lung epithelial cells	Animal	1.23	0.90	1.52	0.36	4.2	0.15	11.50
B16	Mouse melanoma	Animal	1.13	0.93	1.55	0.37	4.2	0.13	5.83
C6	Rat astrocytoma	Animal	1.21	0.91	1.49	0.37	4.0	0.14	2.90



Crecimiento tumoral *in vitro* y *ex vivo*.

TABLE 2 Human and animal tumors

Type	Origin	d_f	α_{loc}	α_{glob}
Colorectal adenocarcinoma (protruded)	Human	1.29	0.90	1.57
Colorectal adenocarcinoma (excavated)	Human	1.17	0.89	1.39
Thyroid carcinoma	Human	1.05	0.90	1.34
Melanoma	Human	1.35	0.78	1.40
Lung epidermoid carcinoma	Human	1.19	0.94	1.40
Mammary adenocarcinoma	Human	1.31	0.89	1.41
Mammary nodal metastases	Human	1.31	0.89	1.43
Melanoma nodal metastases	Human	1.06	0.89	1.42
Gallbladder adenocarcinoma	Human	1.27	0.95	1.37
Basocellular carcinoma	Human	1.25	0.93	1.45
Colorectal adenoma	Human	1.10	0.95	1.53
Gastric adenocarcinoma	Human	1.21	0.95	1.33
Vocal chord epidermoid	Human	1.23	0.93	1.42
Esophagus adenocarcinoma	Human	1.20	0.91	1.30
FibroEhrlicht	Animal	1.27	0.94	1.47
Colon adenocarcinoma	Animal	1.19	0.91	1.43



Crecimiento tumoral *in vivo*.

Physica A 537 (2020) 122696



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Complexity of brain tumors

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ARTICLE INFO

Article history:
Received 7 April 2019
Available online 18 September 2019

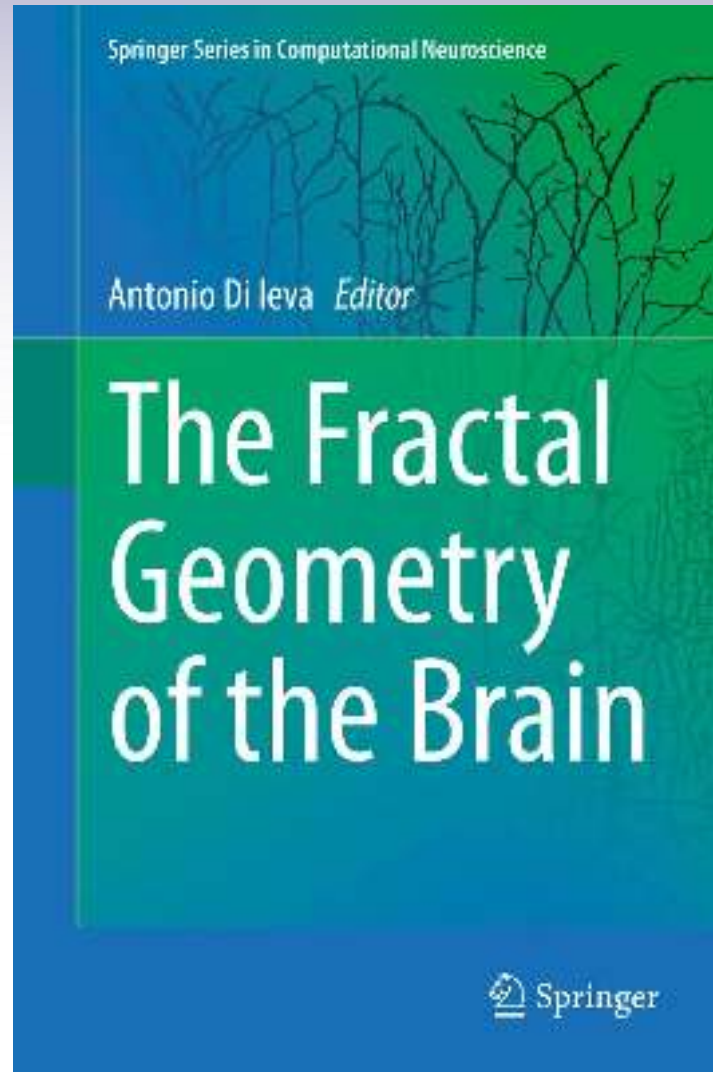
Keywords:
Scaling analysis
Multifractal systems
Complex networks

ABSTRACT

Tumor growth is a complex process characterized by uncontrolled cell proliferation and invasion of neighboring tissues. The understanding of these phenomena is of vital importance to establish the appropriate diagnosis and therapeutic strategies and starts with the evaluation of their complex morphology with suitable descriptors, such as those produced by scaling analysis. In the present work, scaling analysis is used for the extraction of dynamic parameters that characterize tumor growth processes in brain tumors. The emphasis in the analysis is on the assessment of general properties of tumor growth, such as the Family Vicsek ansatz, which includes a great variety of ballistic growth models. Results indicate in a definitive way that gliomas strictly behave as it is proposed by the ansatz, while benign tumors behave quite differently. As a complementary view, complex visibility networks derived from the tumor interface support these results and its use is introduced as a possible descriptor in the understanding of tumor growth dynamics.

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Tipo	α_{loc}	d_f	$\alpha_{loc} + d_f$
Benignos	0.77 ± 0.07	2.02 ± 0.09	2.79 ± 0.13
Gliomas Grados II y III	0.89 ± 0.07	2.10 ± 0.11	2.99 ± 0.13
Glioblastoma multiforme	0.88 ± 0.06	2.17 ± 0.07	3.05 ± 0.10



Chapter 22 Tumor Growth in the Brain: Complexity and Fractality

Miguel Martín-Landrove, Antonio Brú, Antonio Rueda-Toicen,
and Francisco Torres-Hoyos

Abstract Tumor growth is a complex process characterized by uncontrolled cell proliferation and invasion of neighboring tissues. The understanding of these phenomena is of vital importance to establish appropriate diagnosis and therapy strategies and starts with the evaluation of their complexity with suitable descriptors produced by scaling analysis. There has been considerable effort in the evaluation of fractal dimension as a suitable parameter to describe differences between normal and pathological tissues, and it has been used for brain tumor grading with great success. In the present work, several contributions, which exploit scaling analysis in the context of brain tumors, are reviewed. These include very promising results in tumor segmentation, grading, and therapy monitoring. Emphasis is done on scaling analysis techniques applicable to multifractal systems, proposing new descriptors to advance the understanding of tumor growth dynamics in brain. These techniques serve as a starting point to develop innovative practical growth models for therapy simulation and optimization, drug delivery, and the evaluation of related neurological disorders.

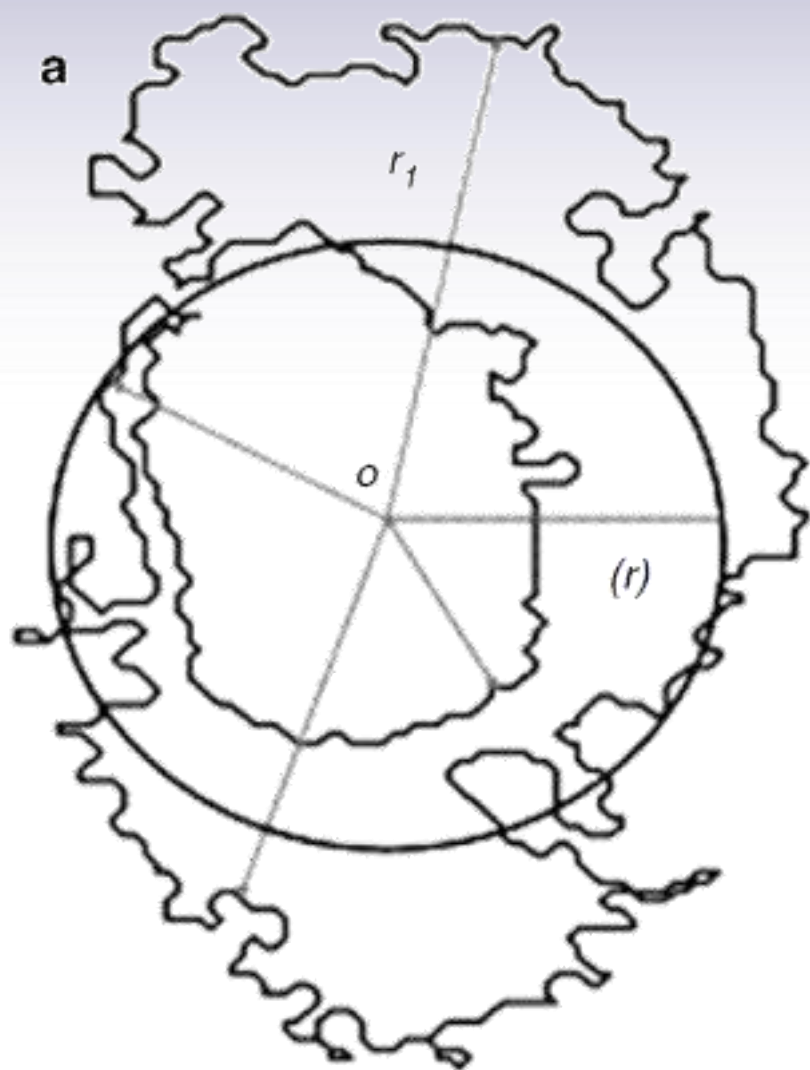


Crecimiento tumoral *in vivo*.



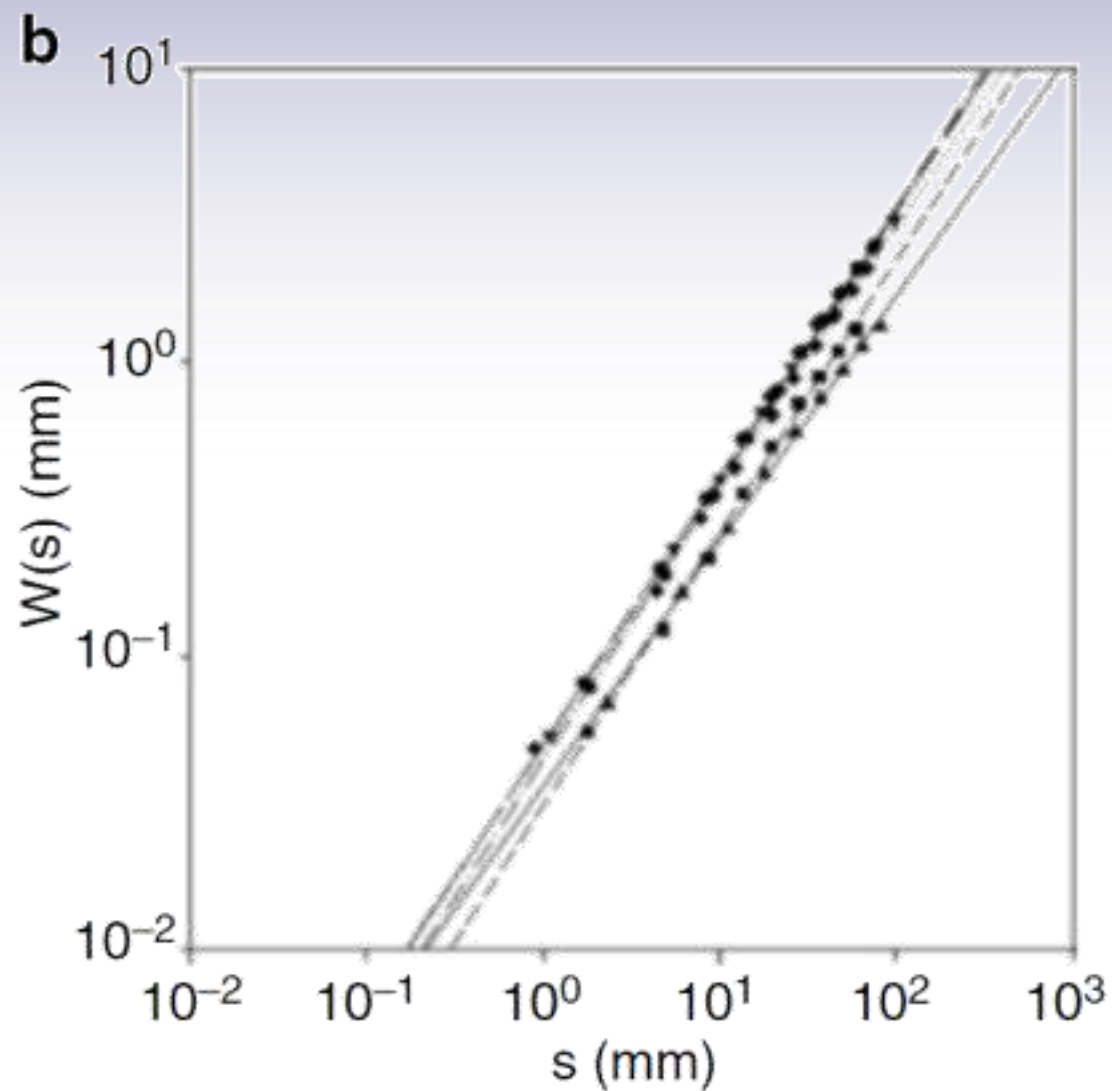
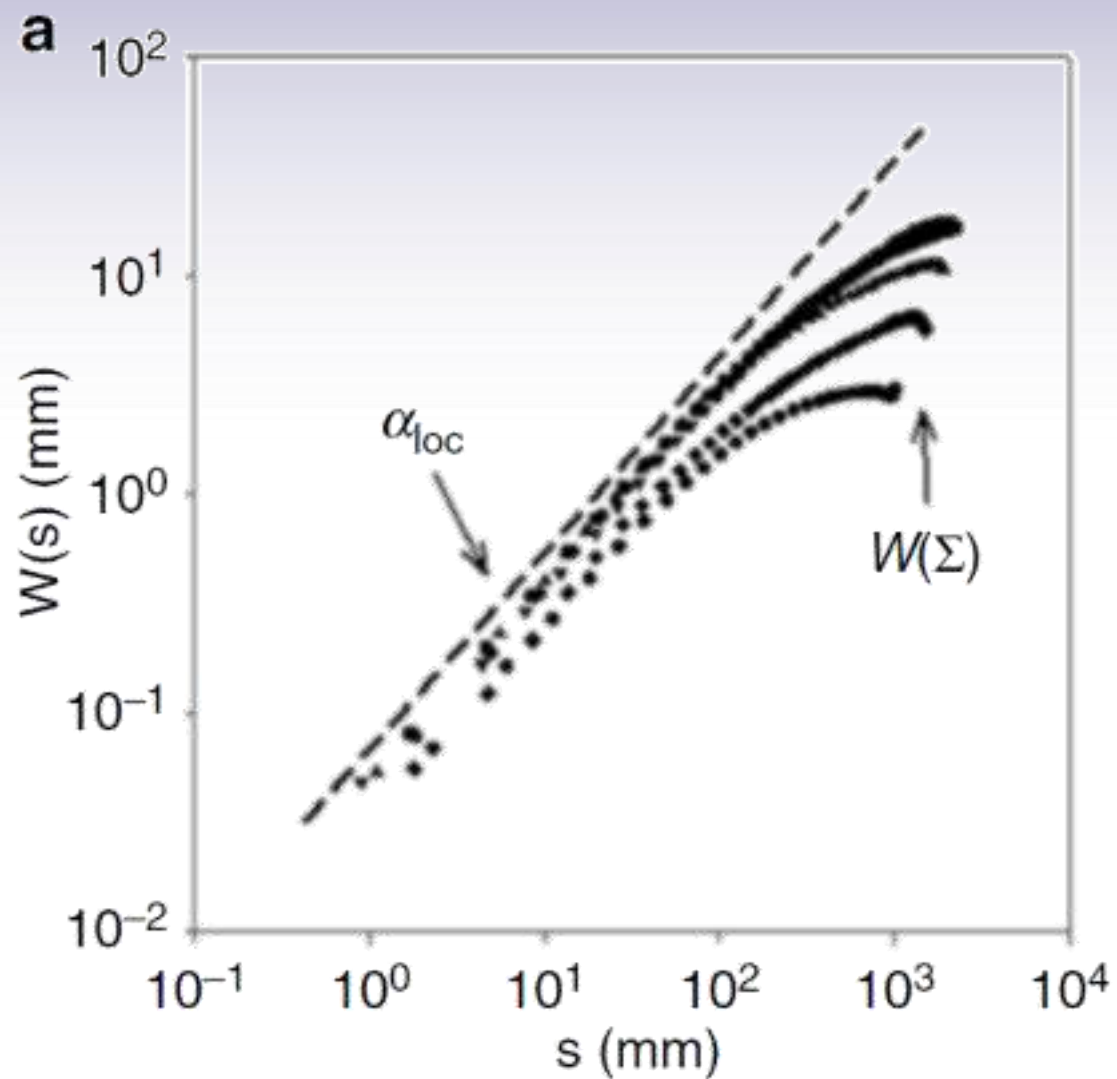


Crecimiento tumoral *in vivo*.





Crecimiento tumoral *in vivo*.





Crecimiento tumoral *in vivo*.

Type	# Cases	α_{loc}
Glioblastoma ^b	107	0.89 ± 0.08
Grade I glioma ^b	19	0.81 ± 0.08
Grade II glioma ^b	11	0.86 ± 0.07
Grade III glioma ^b	7	0.86 ± 0.10
Metastasis ^a	47	0.81 ± 0.11
Vestibular schwannoma ^a	64	0.74 ± 0.10
Meningioma ^a	118	0.76 ± 0.08
Craniopharyngioma ^a	1	0.71
Pituitary adenoma ^a	9	0.76 ± 0.08
Space-occupying lesion ^a	42	0.80 ± 0.09

^aBenign tumor information was obtained by analyzing local image databases

^bGlioma and glioblastoma information was obtained through the image analysis of The Cancer Imaging Archive, National Cancer Institute [7, 8]



*Sánchez J and Martín-Landrove M
(2022) Morphological and Fractal
Properties of Brain Tumors.
Front. Physiol. 13:878391.*

Morphological and Fractal Properties of Brain Tumors

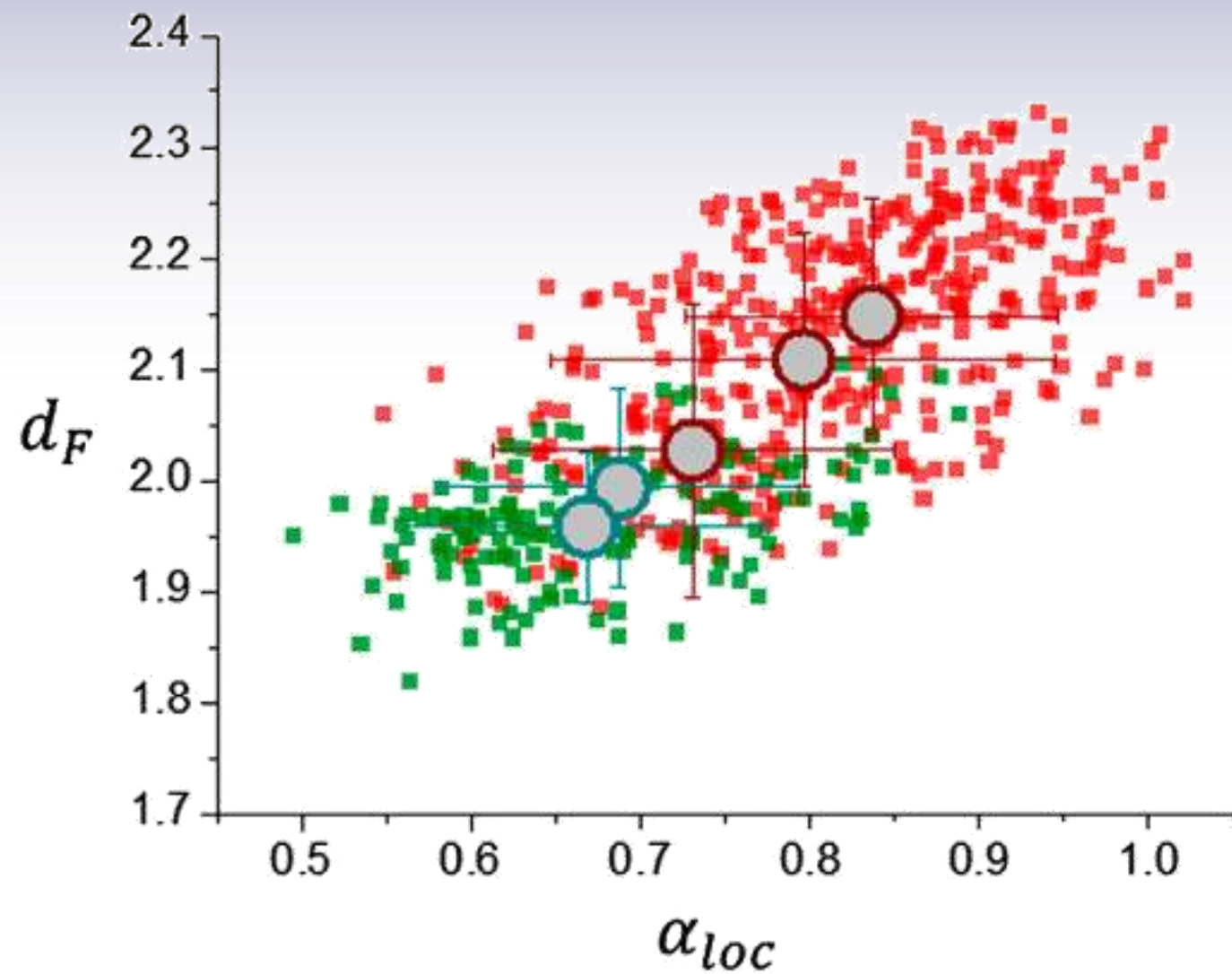
Jacksson Sánchez^{1†} and Miguel Martín-Landrove^{2,3,†}

¹Faculty of Science and Technology, Physics Department, Universidad Nacional Pedro Henríquez Ureña, Santo Domingo, Dominican Republic, ²Centre for Medical Visualization, National Institute for Bioengineering, INABIO, Universidad Central de Venezuela, Caracas, Venezuela, ³Centro de Diagnóstico Docente Las Mercedes, Caracas, Venezuela

Tumor interface dynamics is a complex process determined by cell proliferation and invasion to neighboring tissues. Parameters extracted from the tumor interface fluctuations allow for the characterization of the particular growth model, which could be relevant for an appropriate diagnosis and the correspondent therapeutic strategy. Previous work, based on scaling analysis of the tumor interface, demonstrated that gliomas strictly behave as it is proposed by the Family-Vicsek ansatz, which corresponds to a proliferative-invasive growth model, while for meningiomas and acoustic schwannomas, a proliferative growth model is more suitable. In the present work, other morphological and dynamical descriptors are used as a complementary view, such as surface regularity, one-dimensional fluctuations represented as ordered series and bi-dimensional fluctuations of the tumor interface. These fluctuations were analyzed by Detrended Fluctuation Analysis to determine generalized fractal dimensions. Results indicate that tumor interface fractal dimension, local roughness exponent and surface regularity are parameters that discriminate between gliomas and meningiomas/schwannomas.



Crecimiento tumoral *in vivo*.





Crecimiento tumoral *in vivo*.

TABLE 1 | Scaling analysis results for dynamical parameters.

Tumor type	d_F	α_{loc}	$d_F + \alpha_{loc}$	λ
Acoustic Schwannoma	1.99 ± 0.11	0.69 ± 0.03	2.68 ± 0.18	0.46 ± 0.21
Meningioma	1.96 ± 0.11	0.67 ± 0.03	2.63 ± 0.15	0.46 ± 0.21
Grade II and Grade III Glioma*	2.03 ± 0.13	0.73 ± 0.03	2.76 ± 0.23	0.52 ± 0.25
Glioblastoma multiforme [†]	2.15 ± 0.10	0.84 ± 0.04	2.98 ± 0.18	0.50 ± 0.24
Glioblastoma multiforme [‡]	2.11 ± 0.12	0.80 ± 0.04	2.90 ± 0.23	0.49 ± 0.24

Databases are: (*) TCGA-LGG and REMBRANDT, (†) TCGA-GBM and (‡) BraTS Challenge 2021.



Crecimiento tumoral *in vivo*.

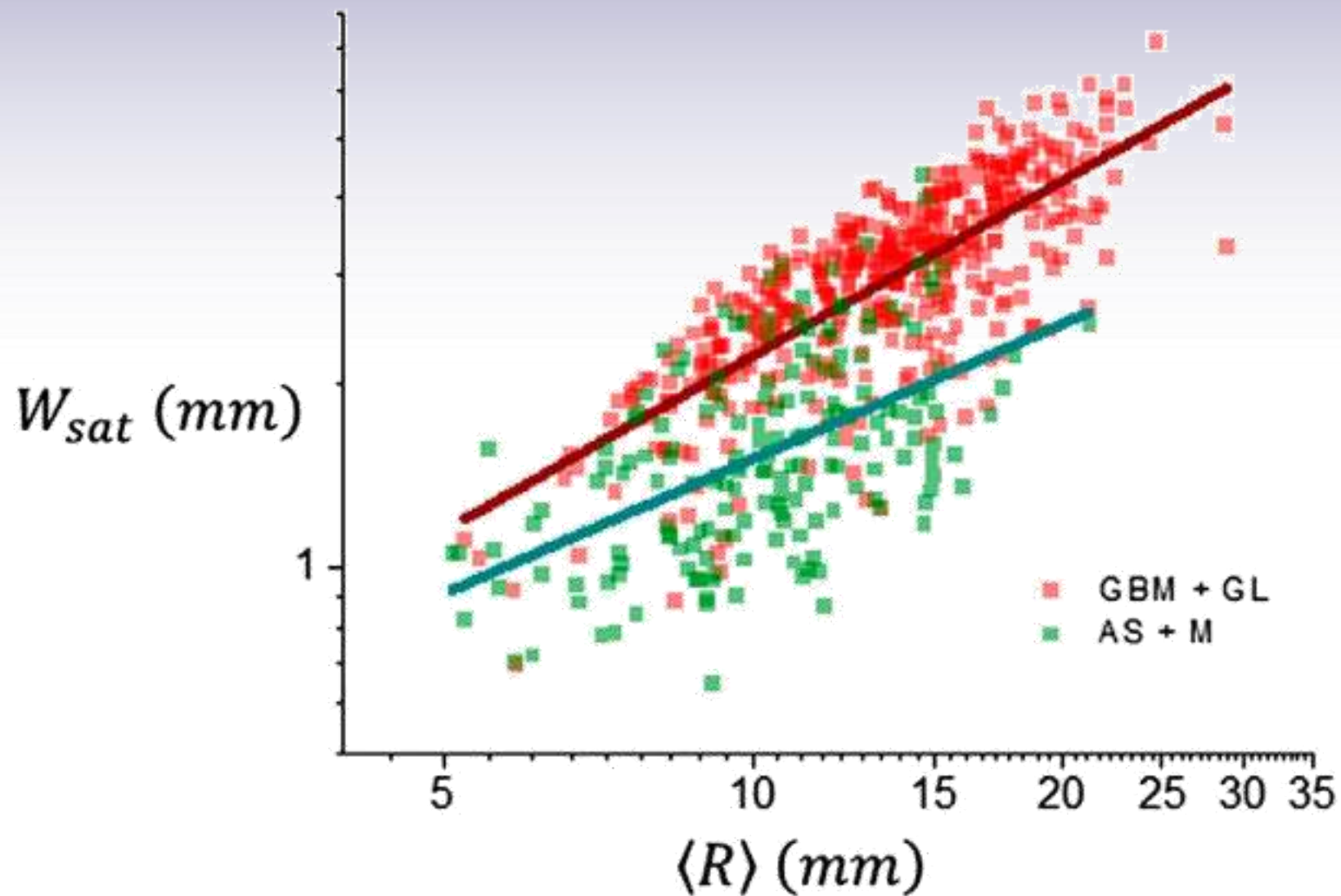




TABLE 2 | Scaling analysis results for global dynamics of the tumor interface width.

Tumor type	W_{sat} (mm)	$\langle R \rangle$ (mm)	α
Acoustic Schwannoma	1.64 ± 0.65	10.07 ± 2.48	0.73 ± 0.15
Meningioma	1.67 ± 0.65	11.19 ± 2.96	0.76 ± 0.11
Grade II and Grade III Glioma*	3.02 ± 1.23	13.21 ± 3.89	1.08 ± 0.15
Glioblastoma multiforme [†]	3.35 ± 1.00	15.08 ± 3.99	0.91 ± 0.06
Glioblastoma multiforme [‡]	2.94 ± 0.98	13.27 ± 3.70	0.93 ± 0.06

Databases are: (*) TCGA-LGG and REMBRANDT, (†) TCGA-GBM and (‡) BraTS Challenge 2021.



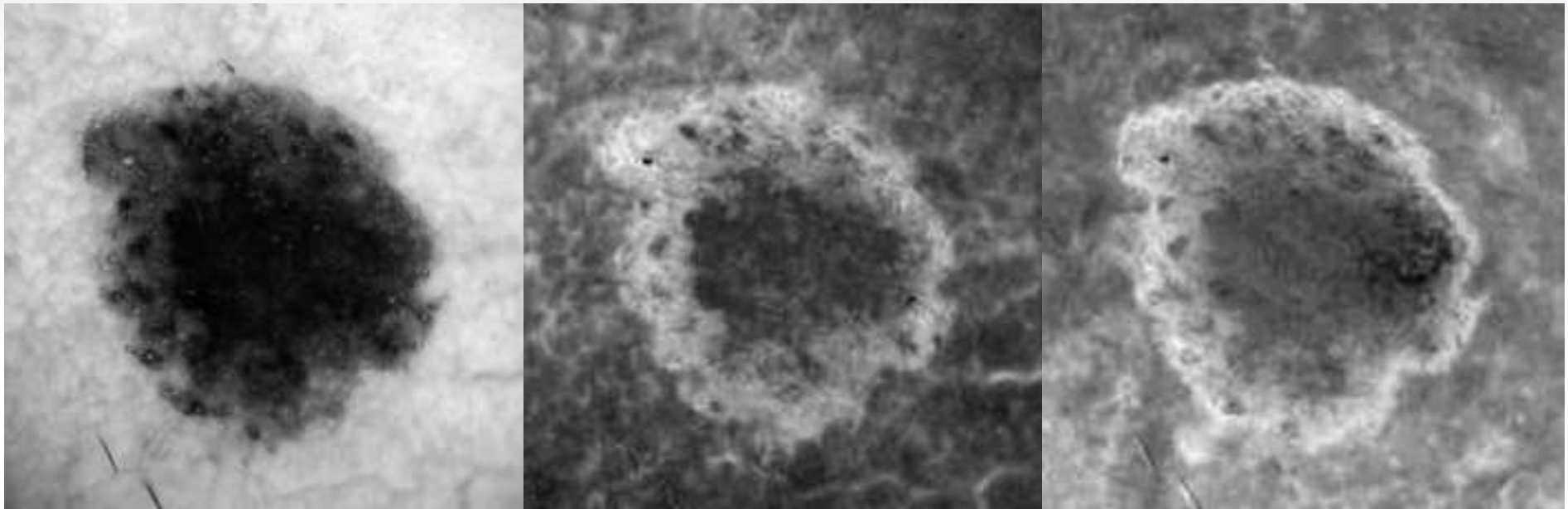
Crecimiento tumoral *in vivo*.

Tipo	α_{loc}	d_f	$\alpha_{loc} + d_f$
SCC IA	0.71 ± 0.03	2.28 ± 0.02	2.99 ± 0.03
SCC IB	0.78 ± 0.01	2.20 ± 0.02	2.98 ± 0.02
SCC IIB	0.84 ± 0.05	2.12 ± 0.04	2.96 ± 0.05
Adenocarcinoma IIIB	0.88 ± 0.01	2.09 ± 0.02	2.97 ± 0.02
Adenocarcinoma IVB	0.98 ± 0.01	2.01 ± 0.01	2.99 ± 0.01

F. Torres Hoyos, M. Martín-Landrove, R. Baena Navarro, J. Vergara Villadiego, J. Causil Cardenas, Study of cervical cancer through fractals and a method of clustering based on quantum mechanics, Applied Radiation and Isotopes 150 (2019) 182–191



Crecimiento tumoral *in vivo*.



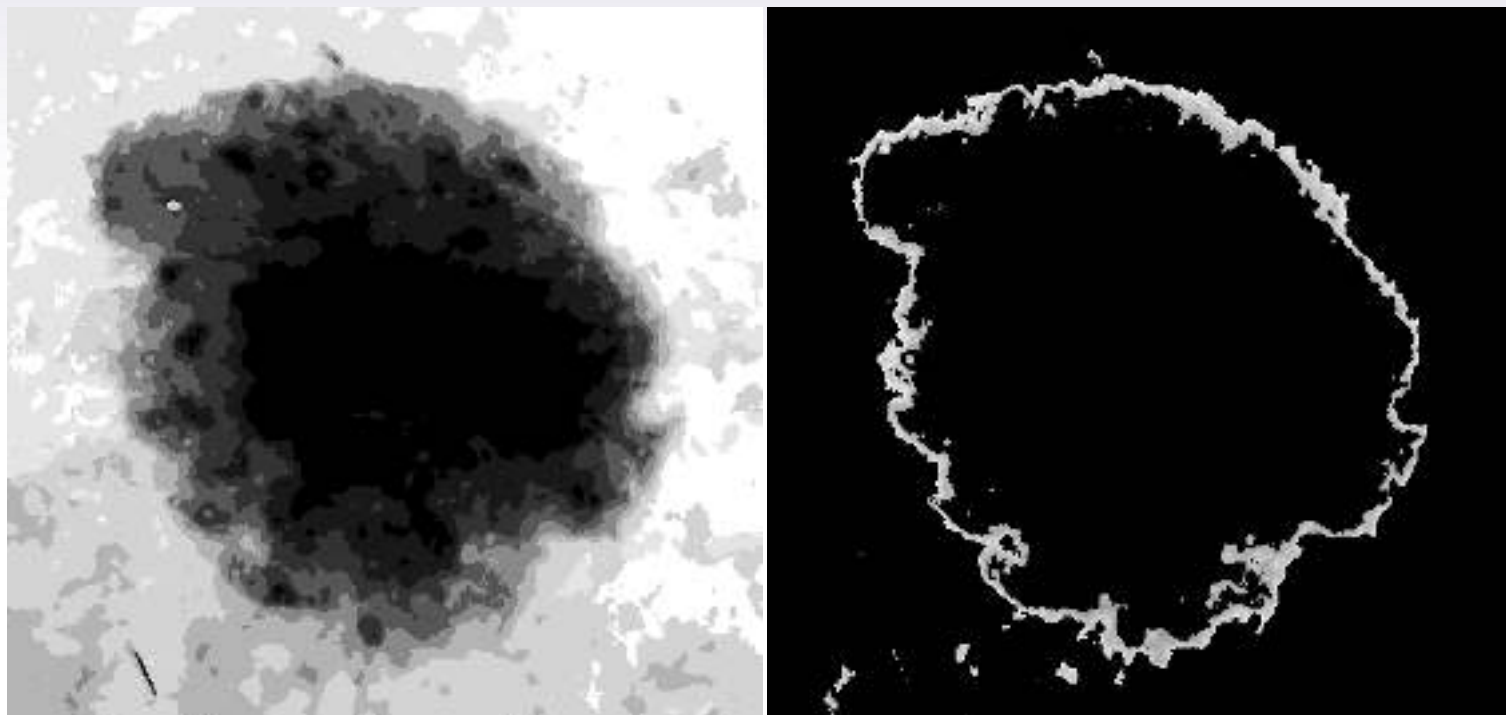
L

a

b

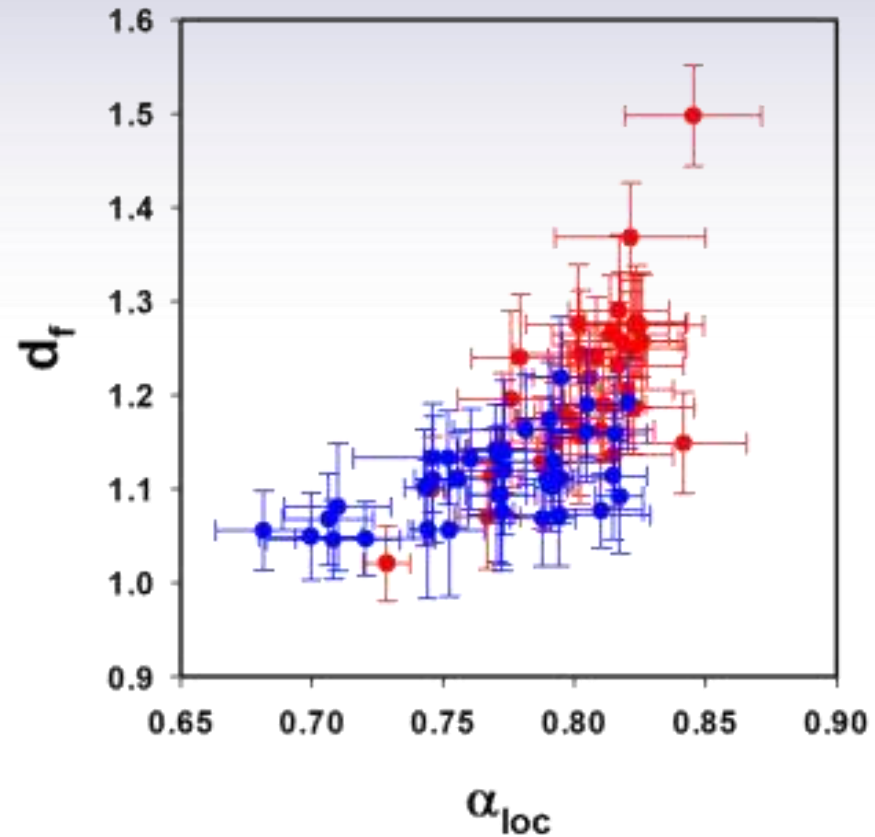


Crecimiento tumoral *in vivo*.





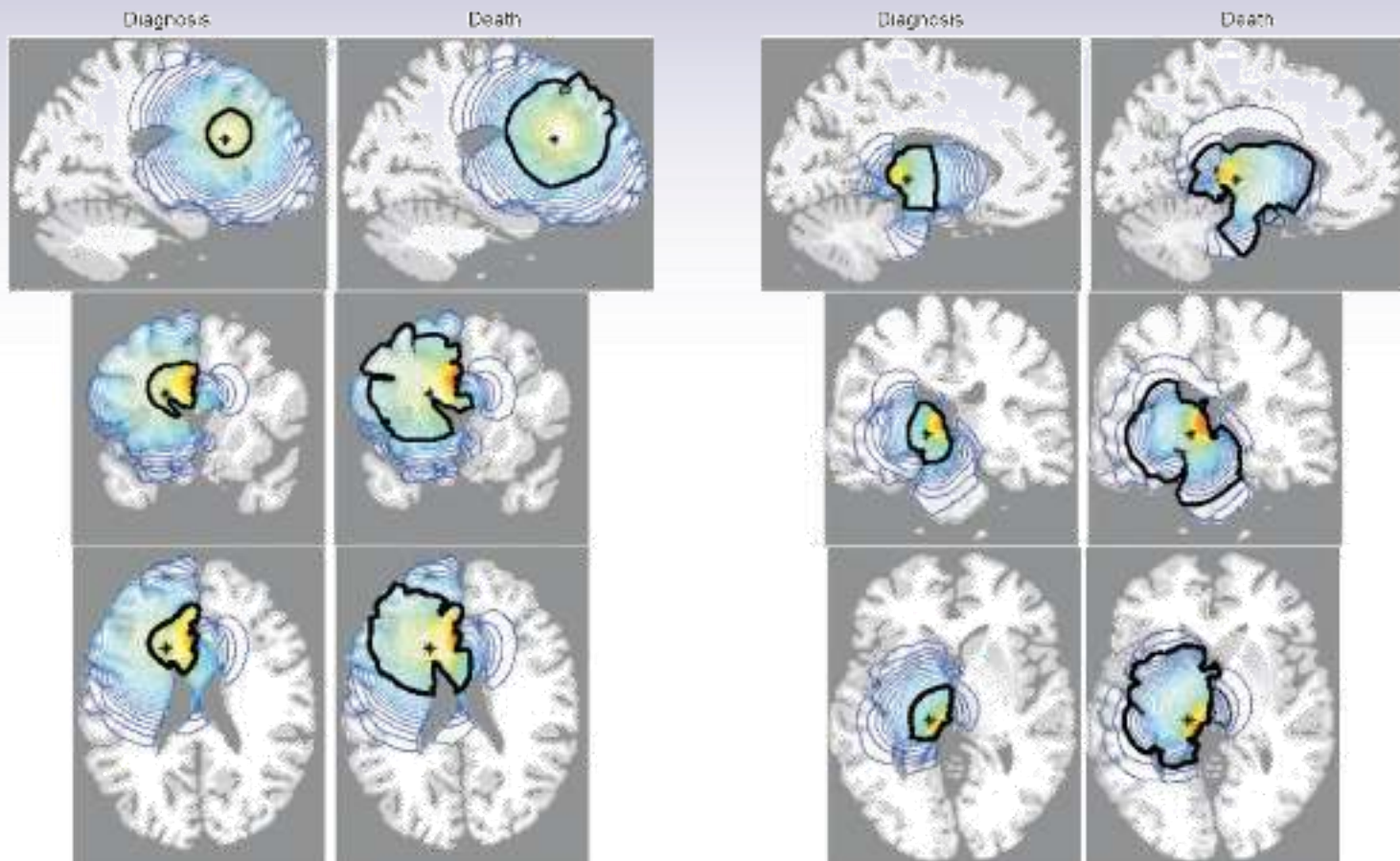
Crecimiento tumoral *in vivo*.



Tipo	α_{loc}	d_f	$\alpha_{loc} + d_f$
Nevus	0.77 ± 0.04	1.11 ± 0.04	1.88 ± 0.04
Melanoma	0.80 ± 0.03	1.21 ± 0.09	2.01 ± 0.09



Crecimiento tumoral. Simulación.

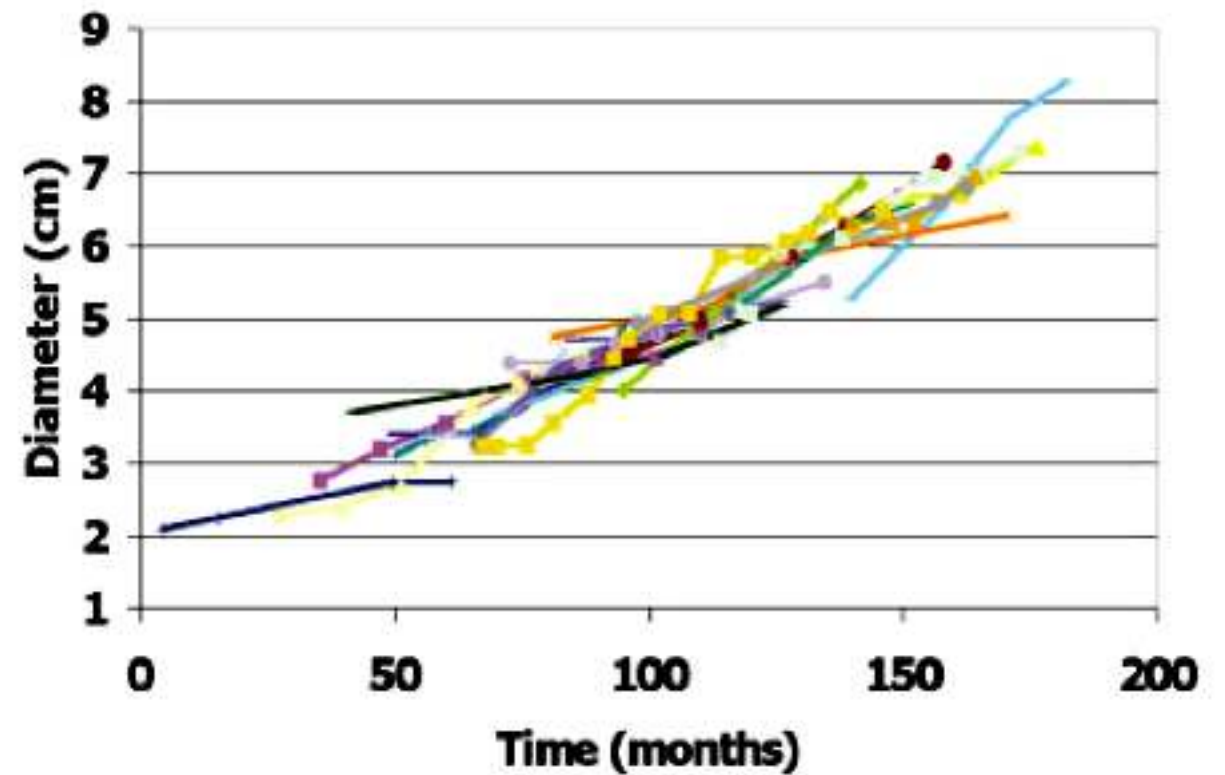
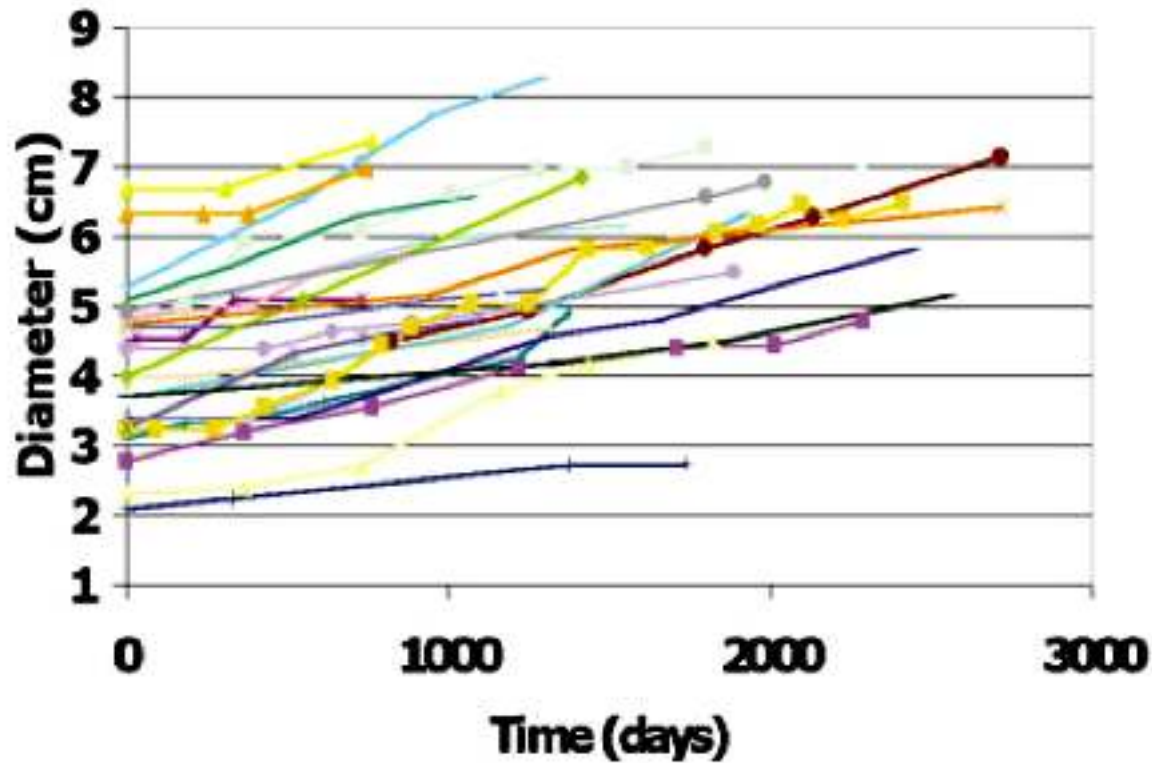


$$\frac{\partial c}{\partial t} = \nabla \cdot (D(\vec{r}) \nabla c) + \rho c$$

Virtual brain tumours (gliomas) enhance the reality of medical imaging and highlight inadequacies of current therapy, K.R. Swanson, E.C. Alvord Jr., J.D. Murray, *British Journal of Cancer* **86**, 14–18 (2002).



Crecimiento tumoral. Simulación.

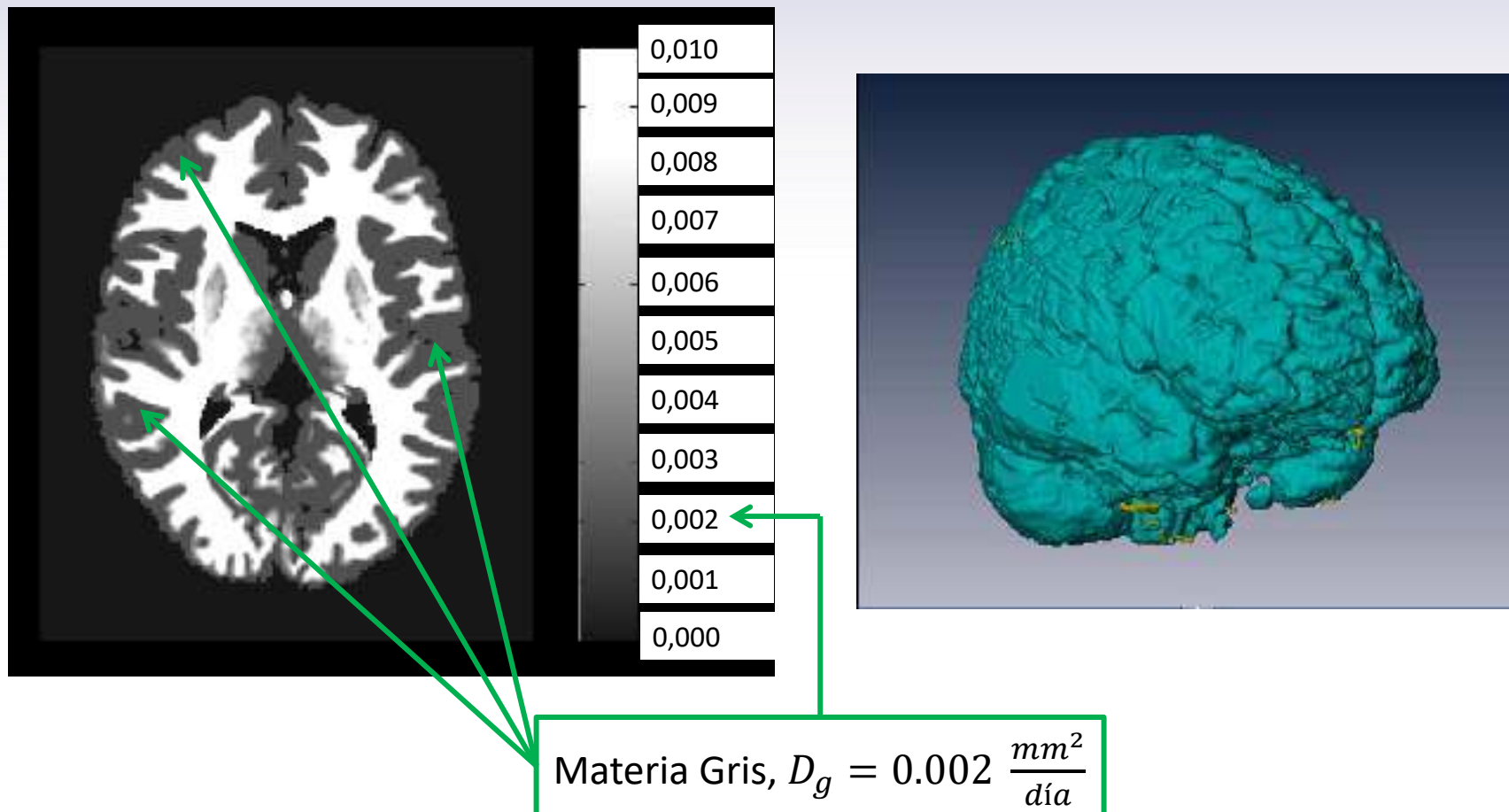


$$0.00113 \frac{cm}{día}, \quad 3.8 - 4.4 \frac{mm}{año}$$

Continuous growth of mean tumor diameter in a subset of Grade II gliomas, E. Mandonnet, J.-Y. Delattre, M.-L. Tanguy, K.R. Swanson, A.F. Carpentier, H. Duffau, P. Cornu, R. Van Effenterre, E.C. Alvord, Jr., L. Capelle, Ann Neurol 53, 524–528 (2003).



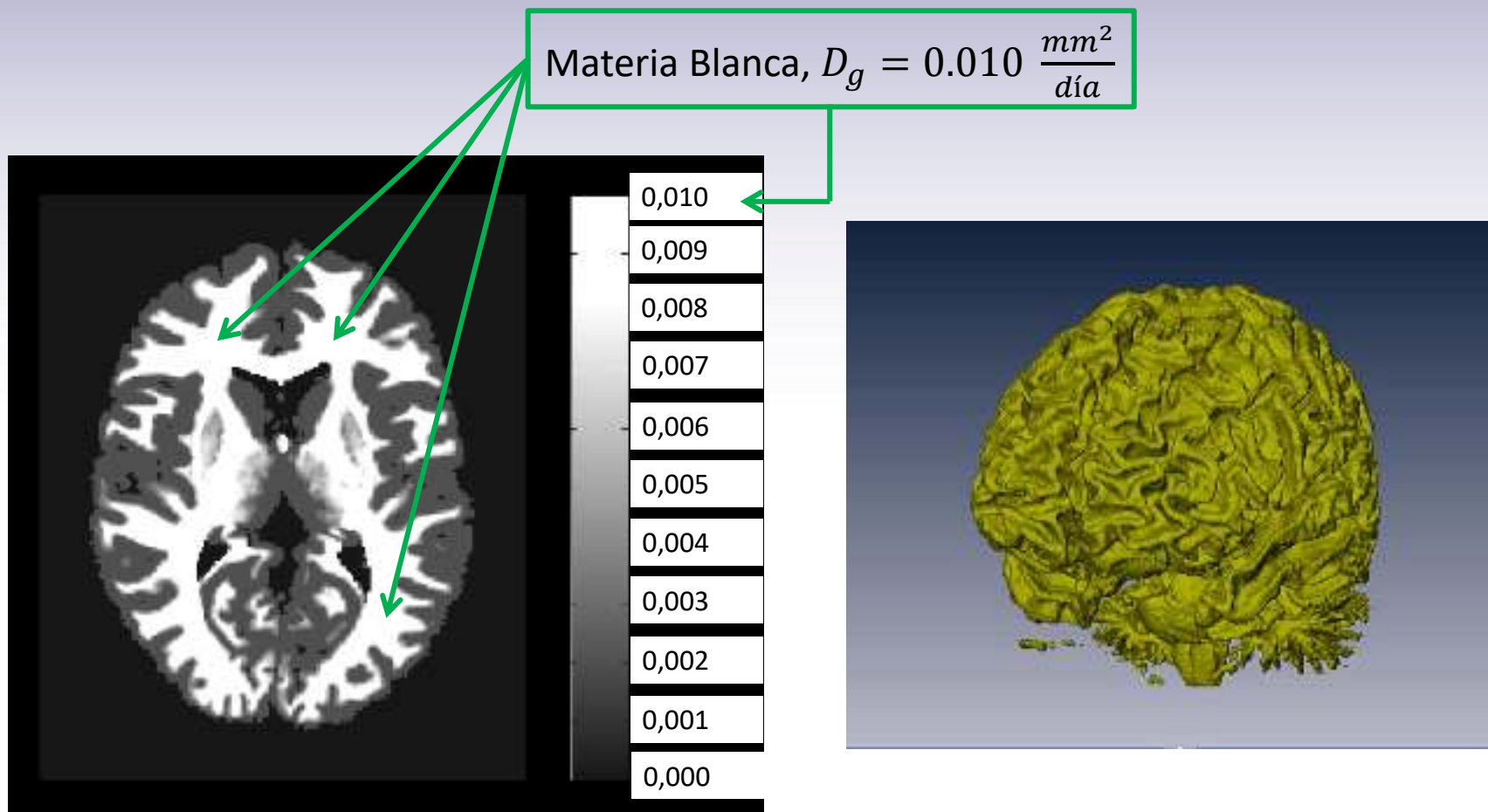
Crecimiento tumoral. Simulación.



Brainweb : On line interface to a 3d mri simulated brain database, C. Cocosco, V. Kollokian, R. Kwan, and A. Evans, in Neuroimage, Proceedings of the Third International Conference on the Funtional Mapping of the Human Brain, volume 5, Copenhagen, 1997.



Crecimiento tumoral. Simulación.



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GEOMETRÍA DEL CRECIMIENTO DE LESIONES TUMORALES EN CEREBRO

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Recibido: febrero 2013

Recibido en forma final revisado: octubre 2013

RESUMEN

El crecimiento tumoral puede ser caracterizado a través del análisis por escalamiento de la interfaz tumoral, el cual proporciona parámetros clave para definir la geometría de su crecimiento de acuerdo con diferentes clases de universalidad. En el presente trabajo se muestran resultados obtenidos mediante un análisis para lesiones tumorales en cerebro bien sean de carácter primario, de naturaleza maligna o benigna y metástasis. Para evaluar los diferentes modelos propuestos para el crecimiento tumoral, se realizaron diversas simulaciones del crecimiento de tumores primarios del cerebro o gliomas mediante la suposición de un modelo descrito por una ecuación diferencial de reacción-difusión o, en este contexto, proliferación-invasión. El término de proliferación fue del tipo logístico para considerar la limitación de nutrientes y oxígeno sobre las células tumorales. Las simulaciones corrieron sobre una base de datos del cerebro humano proporcionada por BrainWeb, y así tomar en cuenta las diferencias de difusión (invasión) entre materia gris y blanca. Las simulaciones fueron realizadas para diferentes relaciones entre los parámetros de difusión (invasión) y reacción (proliferación) cubriendo situaciones desde gliomas de bajo grado hasta gliomas de alto grado (glioblastoma multiforme). Los resultados del análisis por escalamiento de las simulaciones muestran una elevada concordancia con resultados previamente obtenidos en imágenes de resonancia magnética, lo cual sugiere que este simple modelo puede usarse para describir en forma apropiada el crecimiento tumoral de gliomas en el cerebro y potencialmente su extensión a metástasis cerebrales.



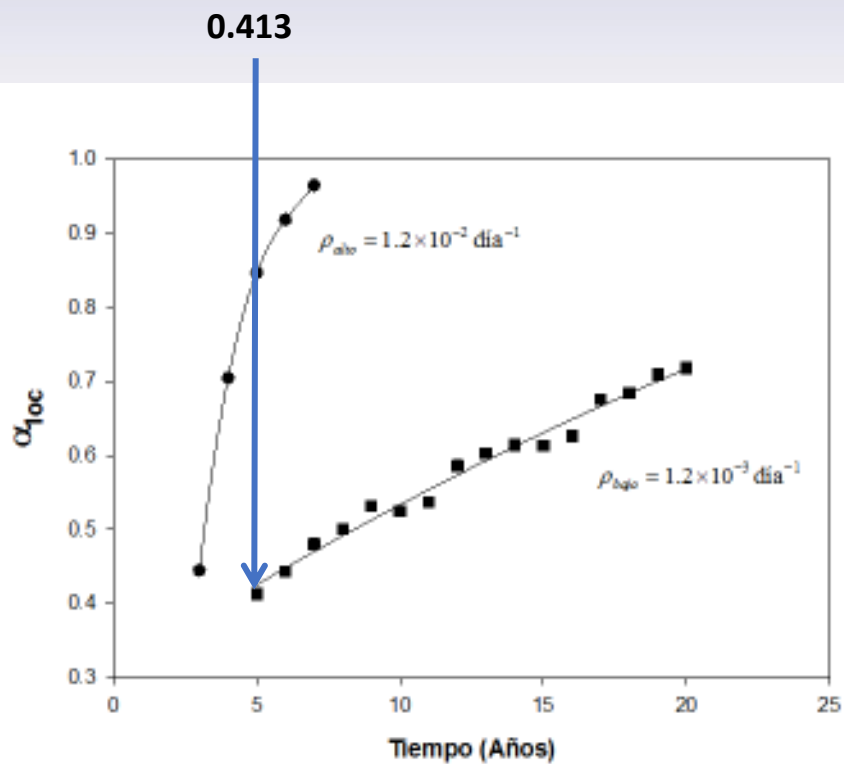
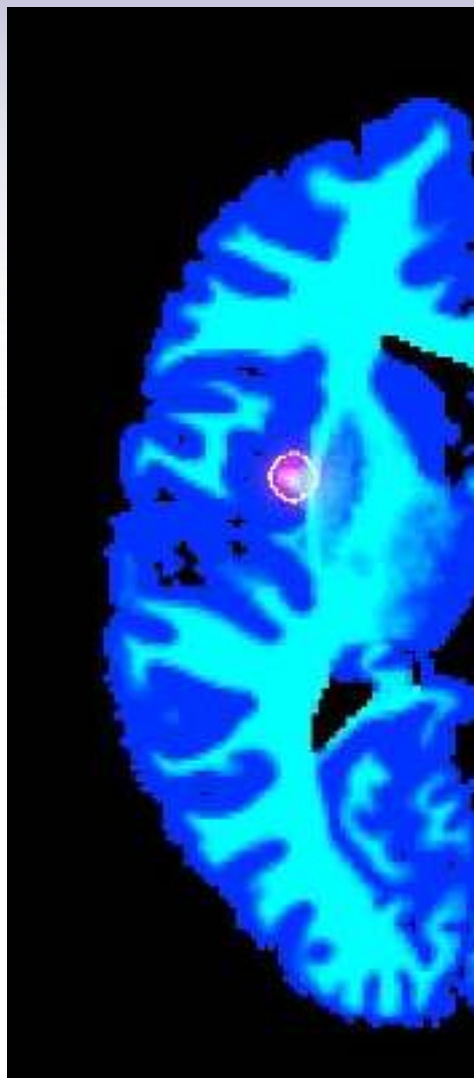
Crecimiento tumoral. Simulación.

$$\frac{\partial c}{\partial t} = \nabla \cdot (D(\vec{r})\nabla c) + \rho c \left(1 - \frac{c}{c_m}\right)$$

Parámetros	Valor	Referencia
c_m	$10^5 \text{ células} / \text{mm}^3$	Jbabdi et al. 2005
ρ_{bajo}	$1.2 \times 10^{-3} \text{ días}^{-1}$	Swanson 1999
ρ_{alto}	$1.2 \times 10^{-2} \text{ días}^{-1}$	Swanson 1999
D_g	$2.0 \times 10^{-3} \text{ mm}^2 / \text{día}$	Tracqui et al. 1995
D_w	$10^{-2} \text{ mm}^2 / \text{día}$	Tracqui et al. 1995
c_0	$200 \text{ células} / \text{mm}^3$	Jbabdi et al. 2005

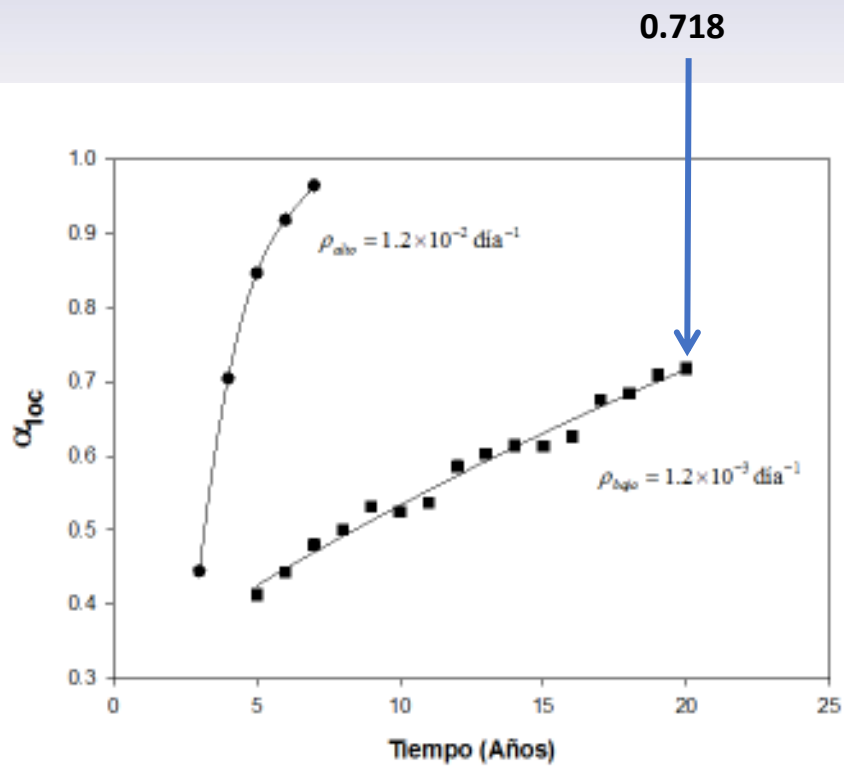
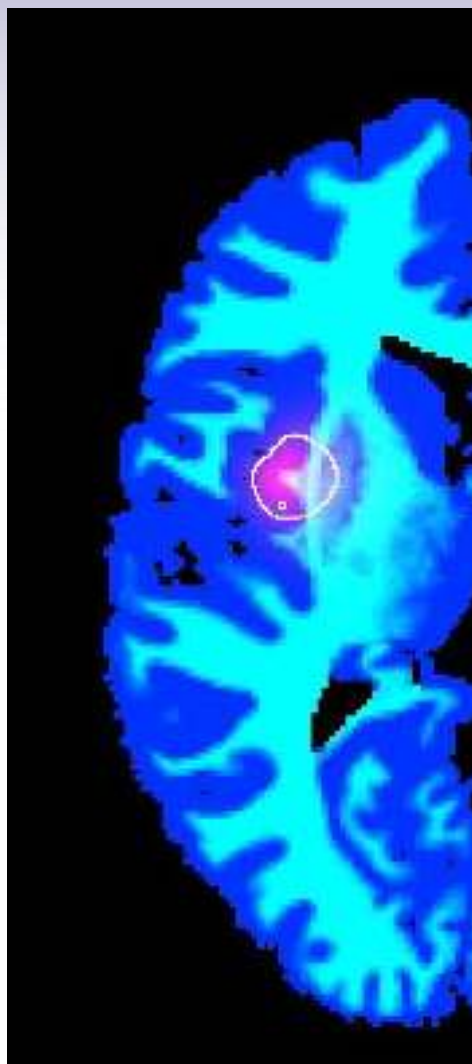


Crecimiento tumoral. Simulación.



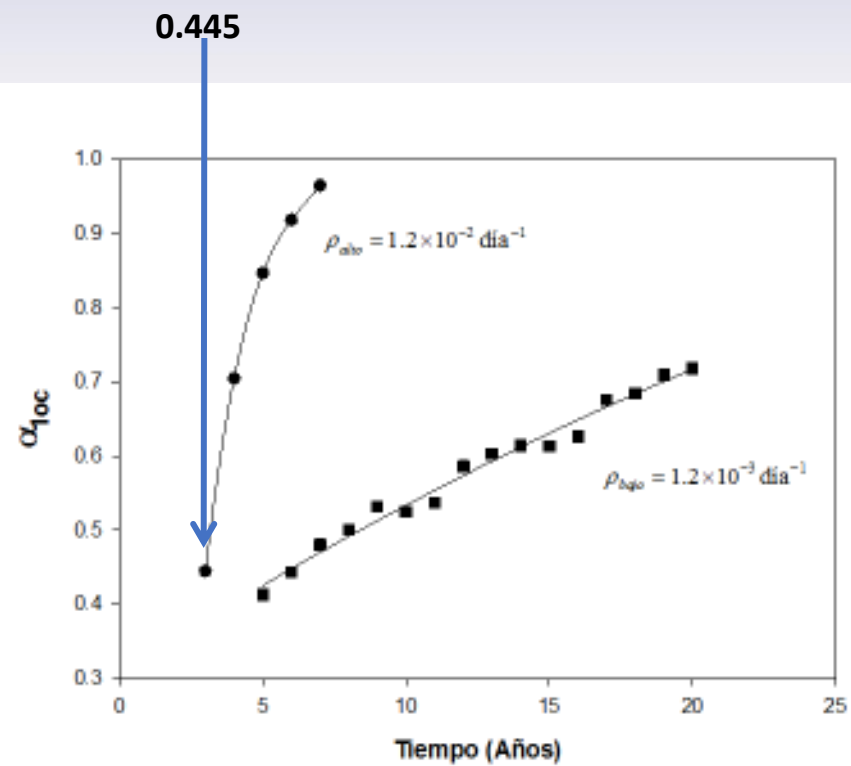
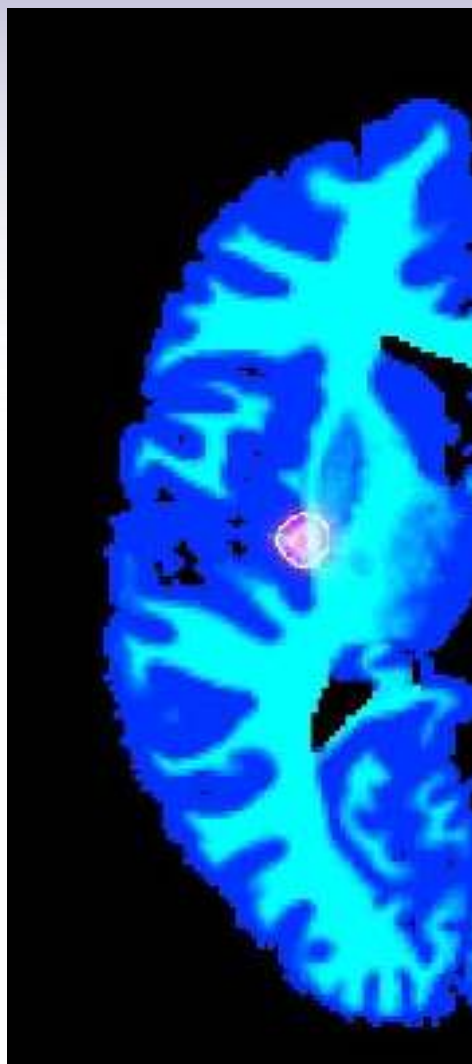


Crecimiento tumoral. Simulación.



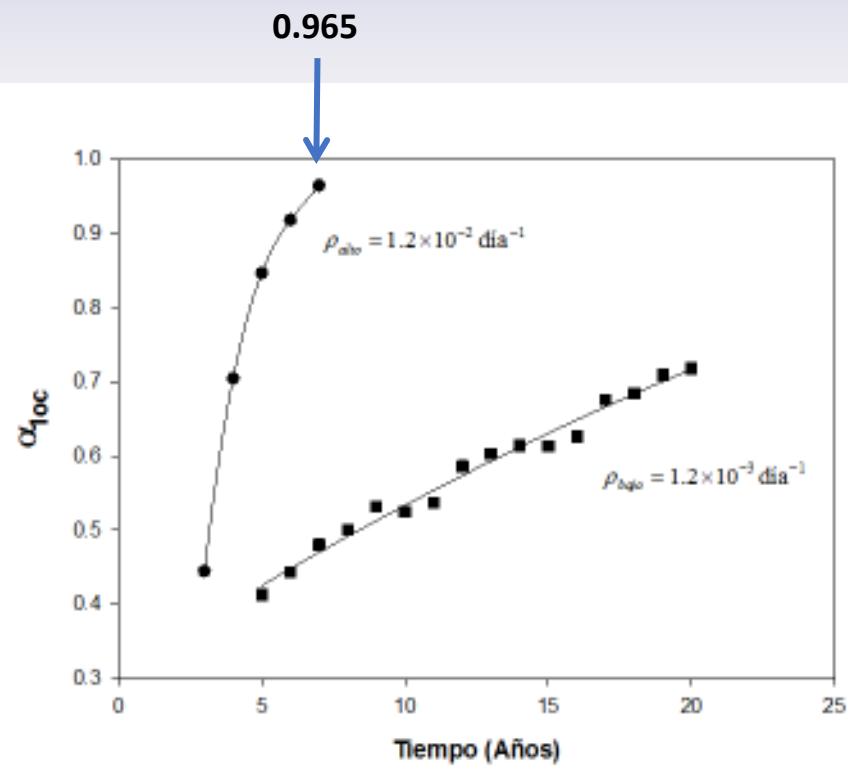
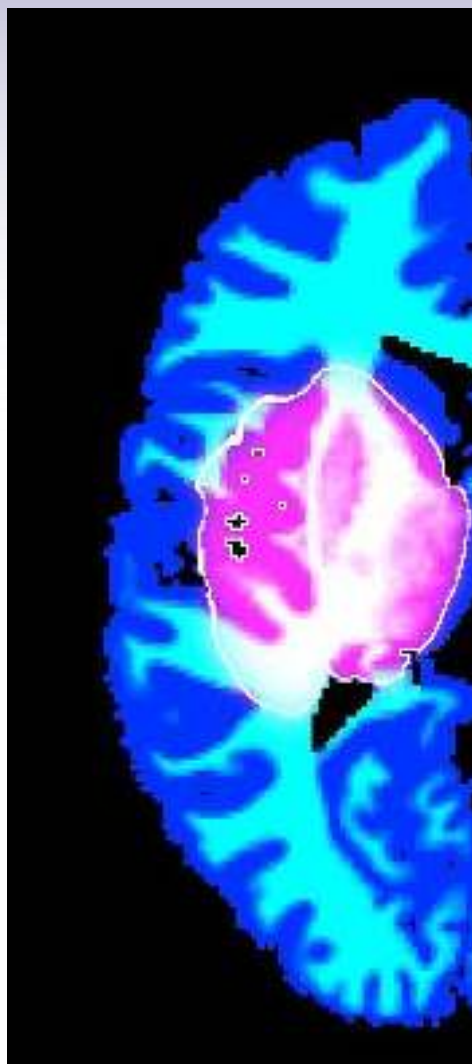


Crecimiento tumoral. Simulación.



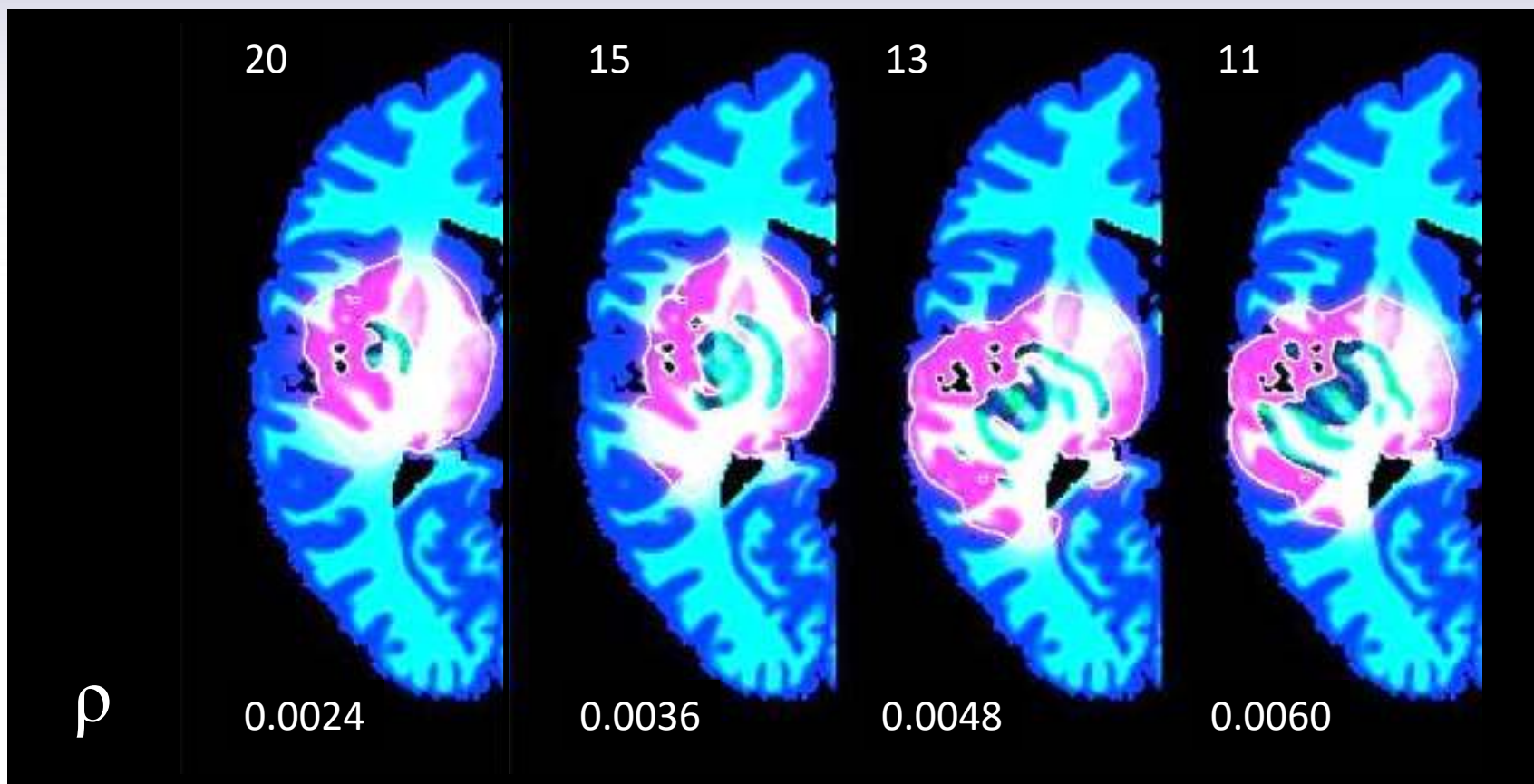


Crecimiento tumoral. Simulación.



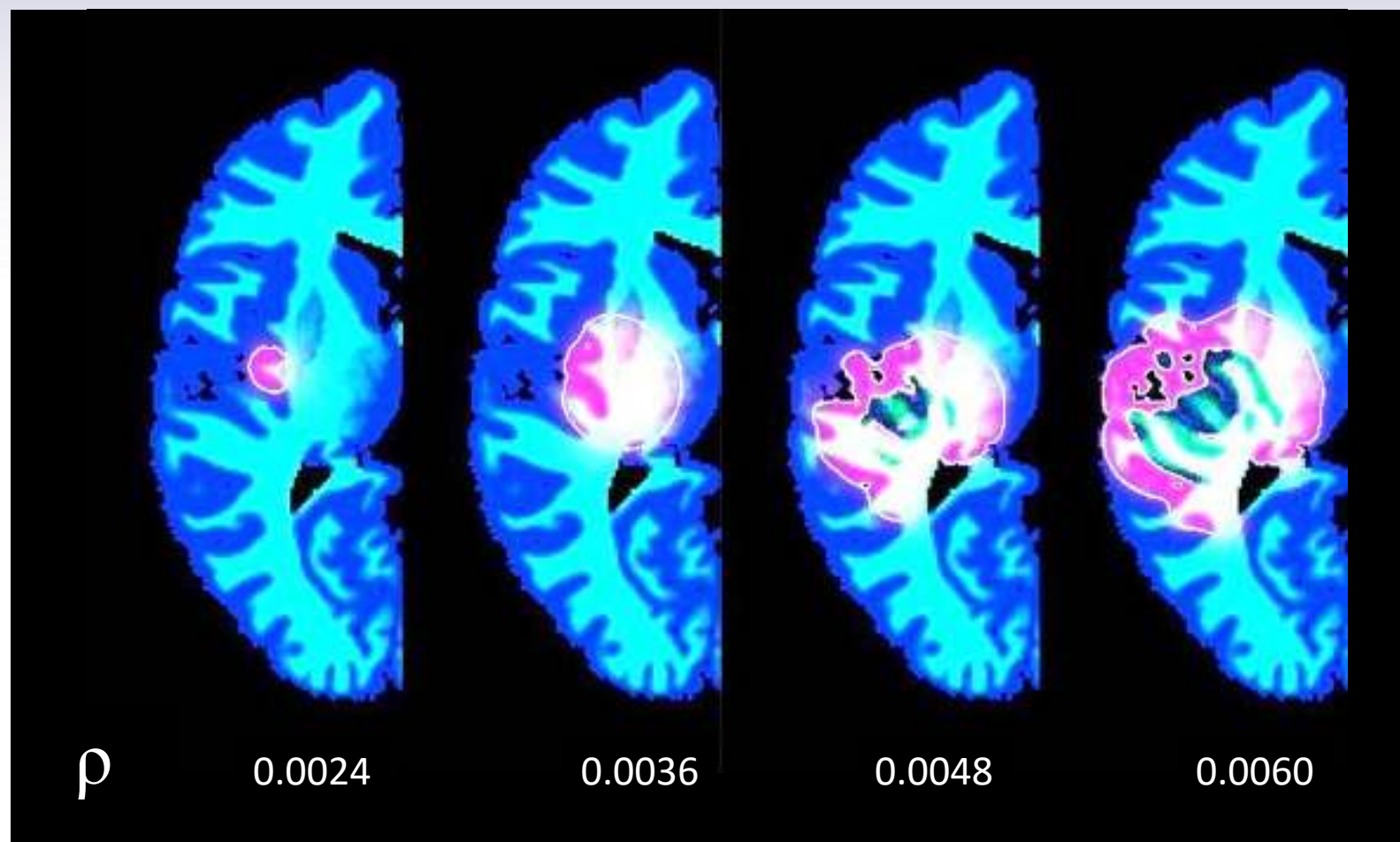


Crecimiento tumoral. Simulación.



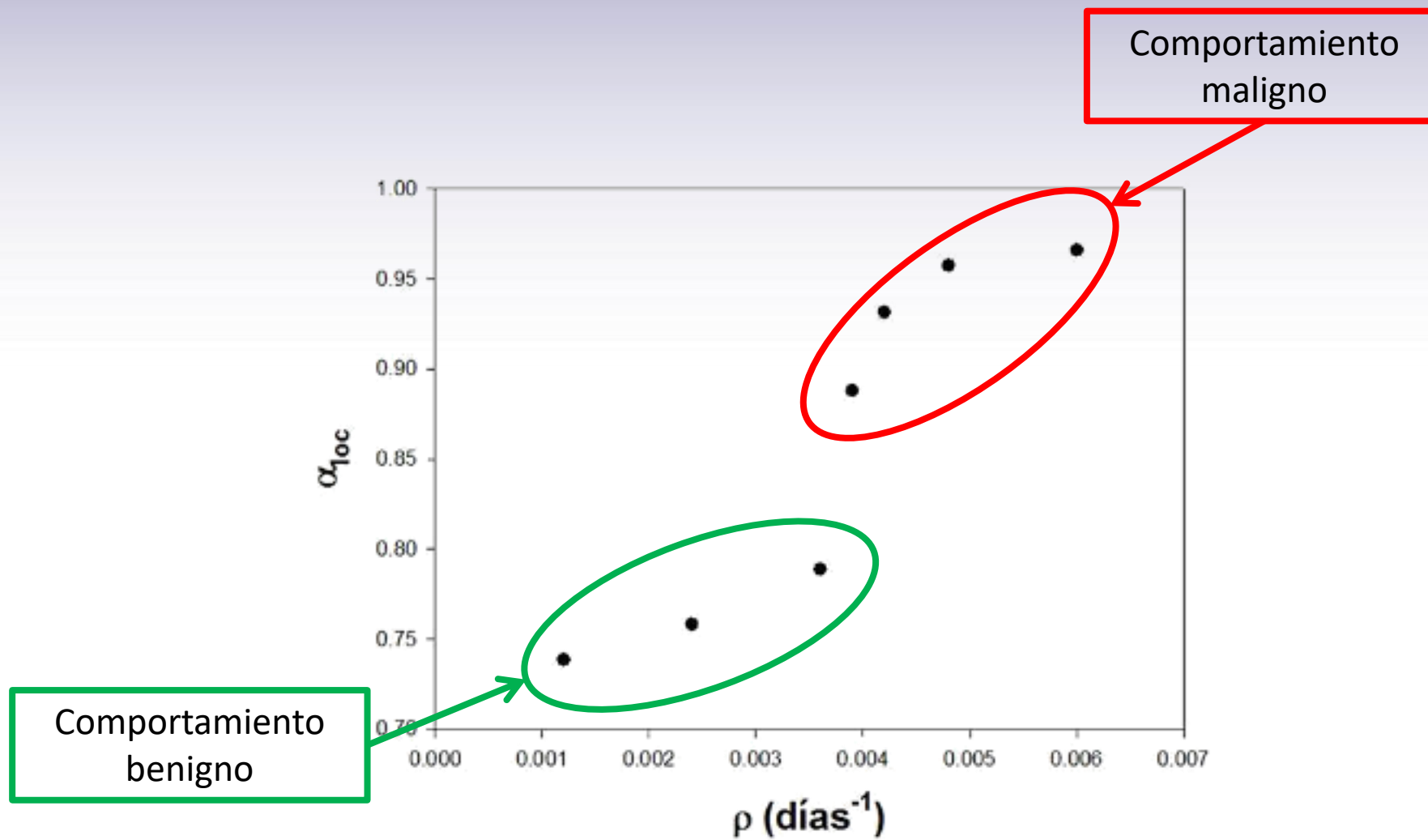


Crecimiento tumoral. Simulación.





Crecimiento tumoral. Simulación.





La probabilidad escala con el tamaño de la caja cómo

$$p_i(l) \propto l^{\alpha_i}$$

donde α_i es la fuerza de singularidad (“singularity strength”). El número de elementos en un rango pequeño α y $\alpha + d\alpha$, escala cómo

$$N_l(\alpha) \sim l^{-f(\alpha)}$$

El espectro de singularidad se define cómo

$$f(\alpha) = \lim_{\epsilon \rightarrow 0} \lim_{l \rightarrow 0} \frac{\ln[N_l(\alpha + \epsilon) - N_l(\alpha - \epsilon)]}{\ln\left(\frac{1}{l}\right)}$$



$$Z_q(\epsilon) = \sum_j \left[\left(\mu(C_j(\epsilon)) \right) \right]^q : \textit{Función de Partición}$$

$$\lim_{\epsilon \rightarrow 0}, \quad Z_q(\epsilon) \sim \epsilon^{\tau(q)}$$

$$D_q = \frac{\tau(q)}{(q-1)} : \textit{Exponente de escalamiento para el momento } q$$



Dimensiones generalizadas de Rényi, D_q

$$D_q = \lim_{\epsilon \rightarrow 0} \frac{1}{1-q} \frac{\ln \left\{ \sum_j \left[\mu(C_j) \right]^q \right\}}{\ln \left(\frac{1}{\epsilon} \right)}$$

D_0 : *Dimensión de Capacidad*

$$D_1 = -\lim_{\epsilon \rightarrow 0} \frac{\sum_j \mu(C_j) \ln[\mu(C_j)]}{\ln \left(\frac{1}{\epsilon} \right)} : \textit{Dimensión de Información}$$

$$D_2 = \lim_{\epsilon \rightarrow 0} \frac{\ln(S(\epsilon))}{\ln \epsilon} = \lim_{\epsilon \rightarrow 0} \frac{\ln(\sum_{i \neq j} u(\epsilon - |x_i - x_j|))}{\ln \epsilon} : \textit{Dimensión de Correlación}$$



Dimensiones generalizadas de Rényi, D_q

Suponiendo que la distribución de α viene dada por $\rho(\alpha)\epsilon^{-f(\alpha)}$

$$Z_q(\epsilon) \cong \int \rho(\alpha) \epsilon^{q\alpha - f(\alpha)} d\alpha$$

$$\lim_{\epsilon \rightarrow 0}, \quad Z_q(\epsilon) \sim \epsilon^{\min(q\alpha - f(\alpha))}$$

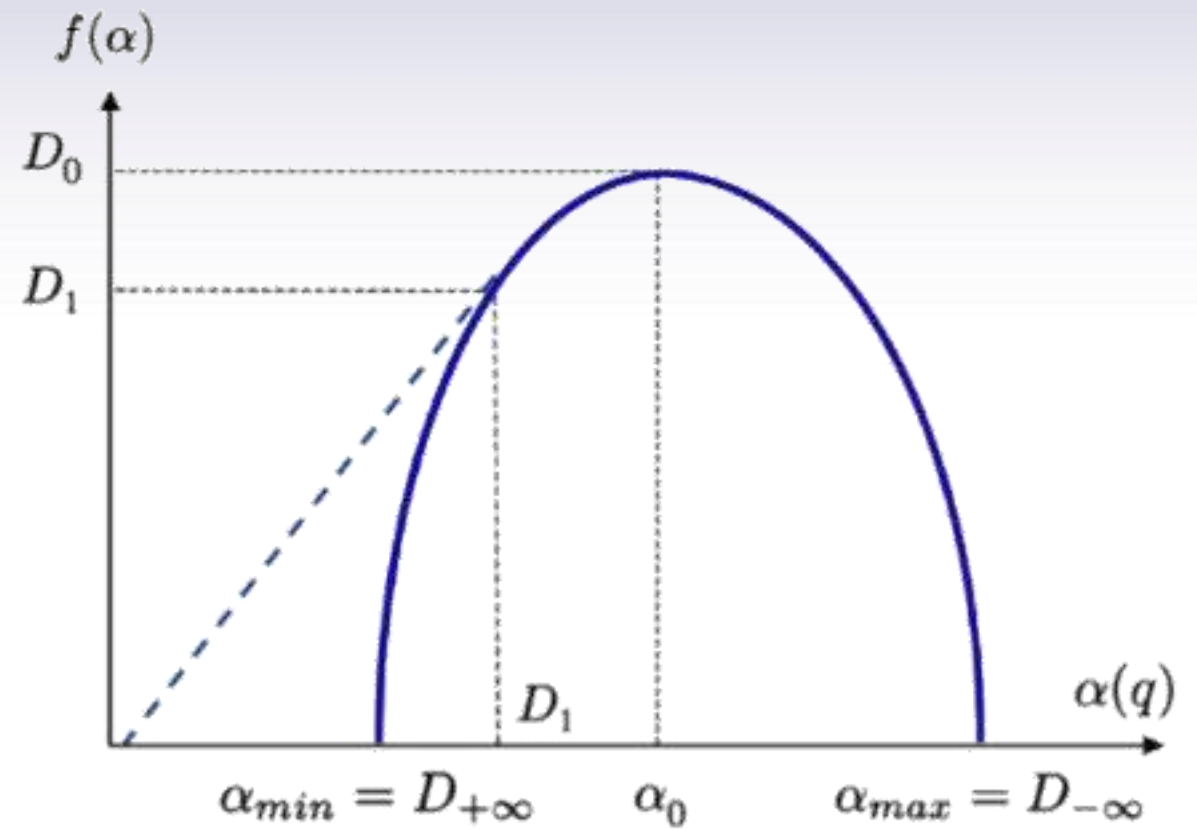
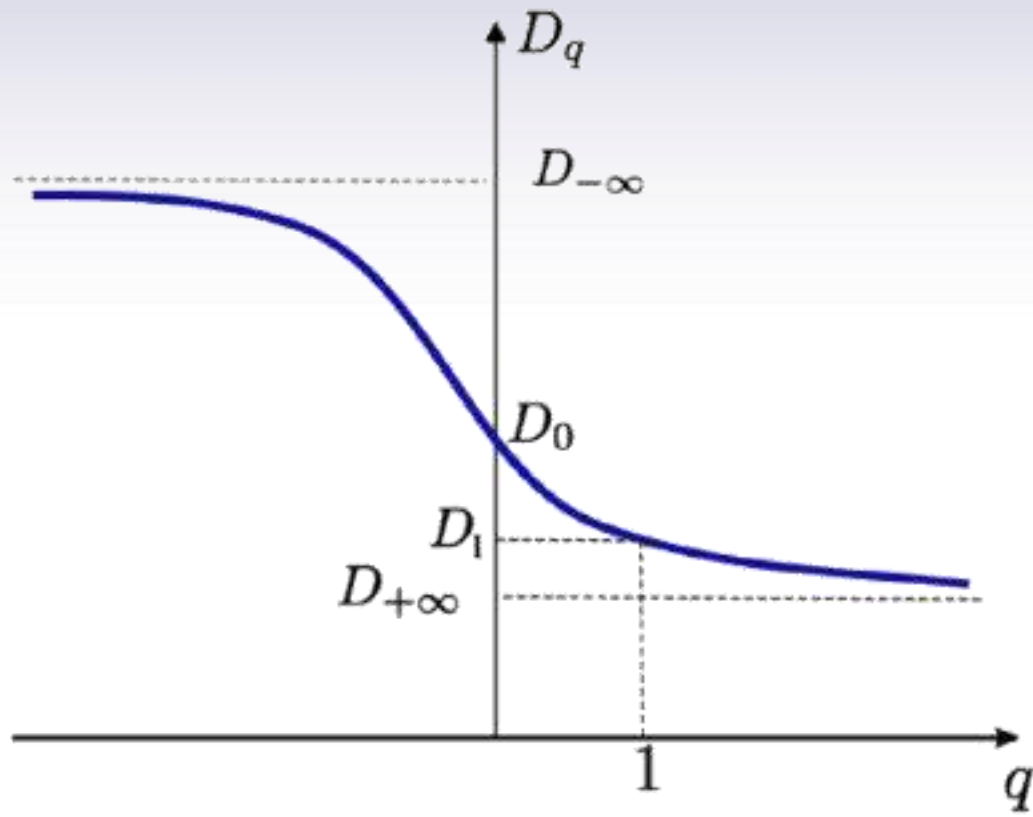
$$\tau(q) = \min_{\alpha} (q\alpha - f(\alpha)) \Rightarrow$$

$$\left. \frac{d}{d\alpha} [q\alpha - f(\alpha)] \right|_{\alpha=\alpha(q)} = 0, \quad \left. \frac{d^2}{d\alpha^2} [q\alpha - f(\alpha)] \right|_{\alpha=\alpha(q)} > 0$$

$$\tau(q) = q\alpha - f(\alpha), \quad \frac{df}{d\alpha} = q, \quad \frac{d^2 f}{d\alpha^2} < 0$$



Dimensiones generalizadas de Rényi, D_q





Dimensiones generalizadas de Rényi, D_q

Dado que

$$\tau(q) = \min_{\alpha} (q\alpha - f(\alpha))$$

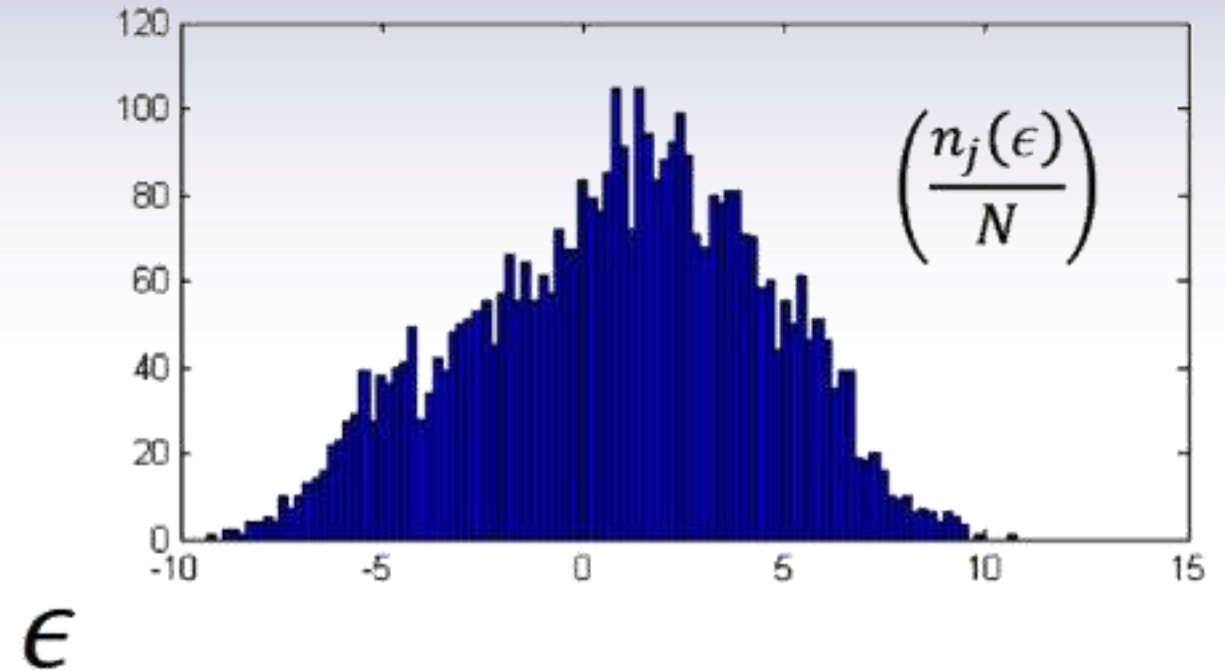
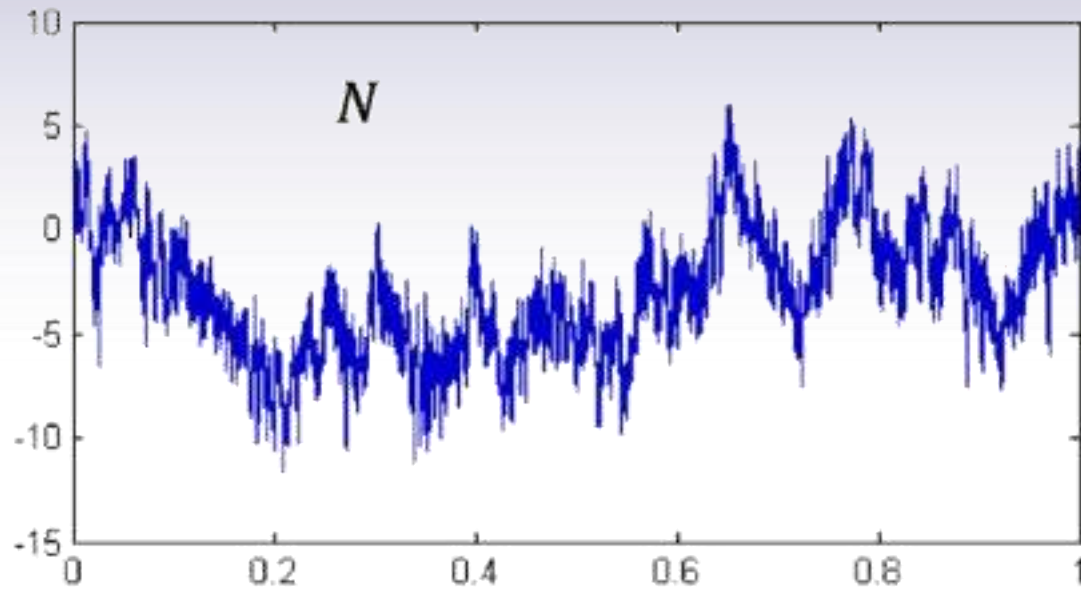
Es decir, $\tau(q)$ es la Transformada de Legendre de $f(\alpha)$, entonces

$$f(\alpha) = \min_q (q\alpha - \tau(q))$$

De manera que podemos explotar esta propiedad para obtener tanto la distribución de $\tau(q)$, como la distribución de los exponentes de singularidad $f(\alpha)$



Método de los momentos. Series temporales.



$$Z_q(\epsilon) = \sum_j \left[\left(\frac{n_j(\epsilon)}{N} \right) \right]^q \quad \tau(q) = \lim_{\epsilon \rightarrow 0} \frac{\ln(Z_q(\epsilon))}{\ln(\epsilon)} \quad f(\alpha) = \min_q (q\alpha - \tau(q))$$



1

$$Y(i) = \sum_{k=1}^i |x_k - \langle x \rangle| \quad i = 1, \dots, N$$

2

$$N_s \equiv \text{int} \left(\frac{N}{s} \right)$$

3

$$F^2(s, v) \equiv \frac{1}{s} \sum_{i=1}^s \{Y[(v-1)s + i] - y_v(i)\}^2 \quad v = 1, \dots, N_s$$

$$F^2(s, v) \equiv \frac{1}{s} \sum_{i=1}^s \{Y[N - (v - N_s)s + i] - y_v(i)\}^2 \quad v = N_s + 1, \dots, 2N_s$$

4

$$F_q(s) \equiv \left\{ \frac{1}{2N_s} \sum_{v=1}^{2N_s} [F^2(s, v)]^{\frac{q}{2}} \right\}^{\frac{1}{q}} \quad \text{para } s \text{ grande,} \quad F_q(s) \sim s^{h(q)}$$



Análisis Multifractal (MFA)

1

$$Y(i) = \sum_{k=1}^i |x_k - \langle x \rangle| \quad i = 1, \dots, N$$

2

$$N_s \equiv \text{int} \left(\frac{N}{s} \right)$$

3

$$F_{FA}^2 \equiv [Y(vs) - Y((v-1)s)]^2$$

4

$$\left\{ \frac{1}{2N_s} \sum_{v=1}^{2N_s} |Y(vs) - Y((v-1)s)|^q \right\}^{\frac{1}{q}} \sim S^{h(q)}$$

$$\sum_{v=1}^{N/s} |Y(vs) - Y((v-1)s)|^q \sim S^{qh(q)-1}$$



5

$$p_s(v) = \sum_{k=(v-1)s+1}^{vs} x_k = Y(vs) - Y((v-1)s)$$

6

$$Z_q(s) = \sum_{v=1}^{N_s} |p_s(v)|^q \sim s^{\tau(q)} \text{ para } s \text{ grande}$$

7

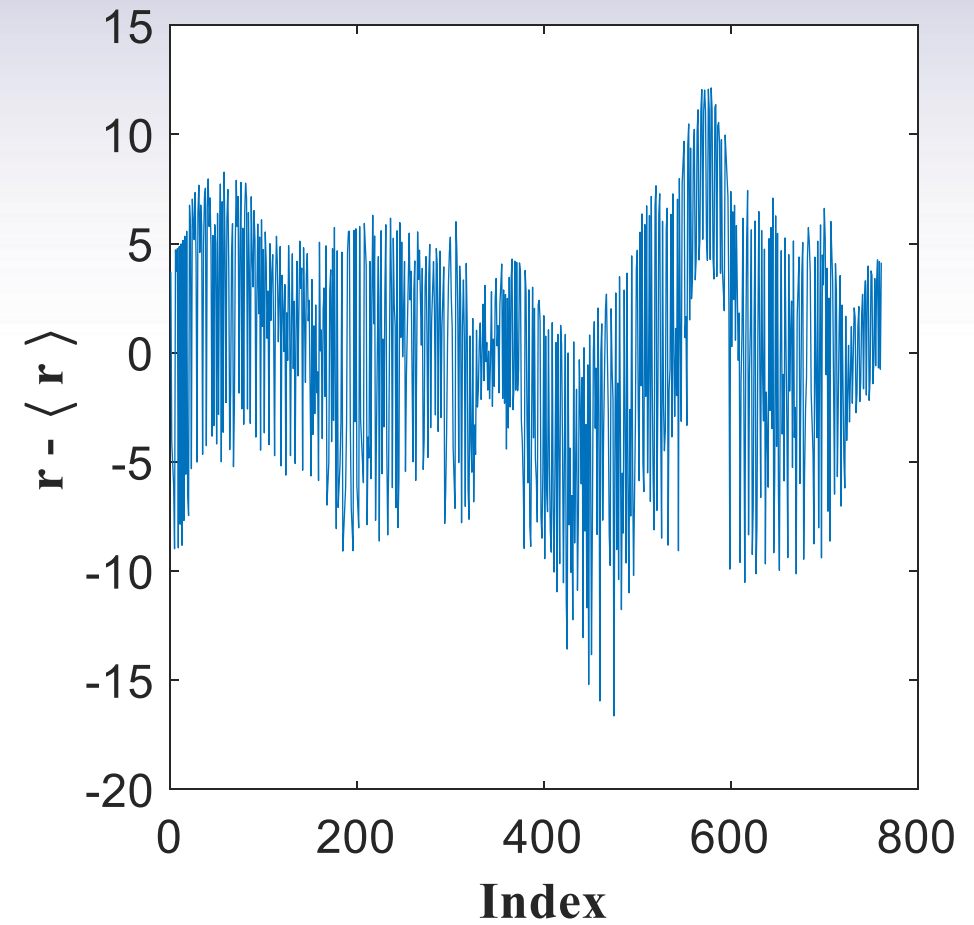
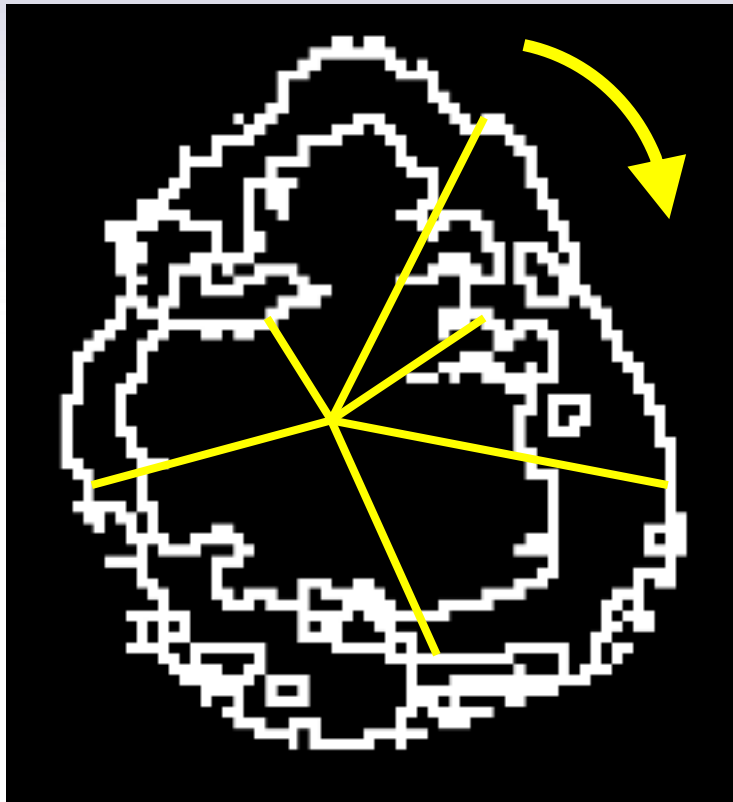
$$\tau(q) = qh(q) - 1$$

8

$$D(q) \equiv \frac{\tau(q)}{q-1} = \frac{qh(q) - 1}{q-1}$$

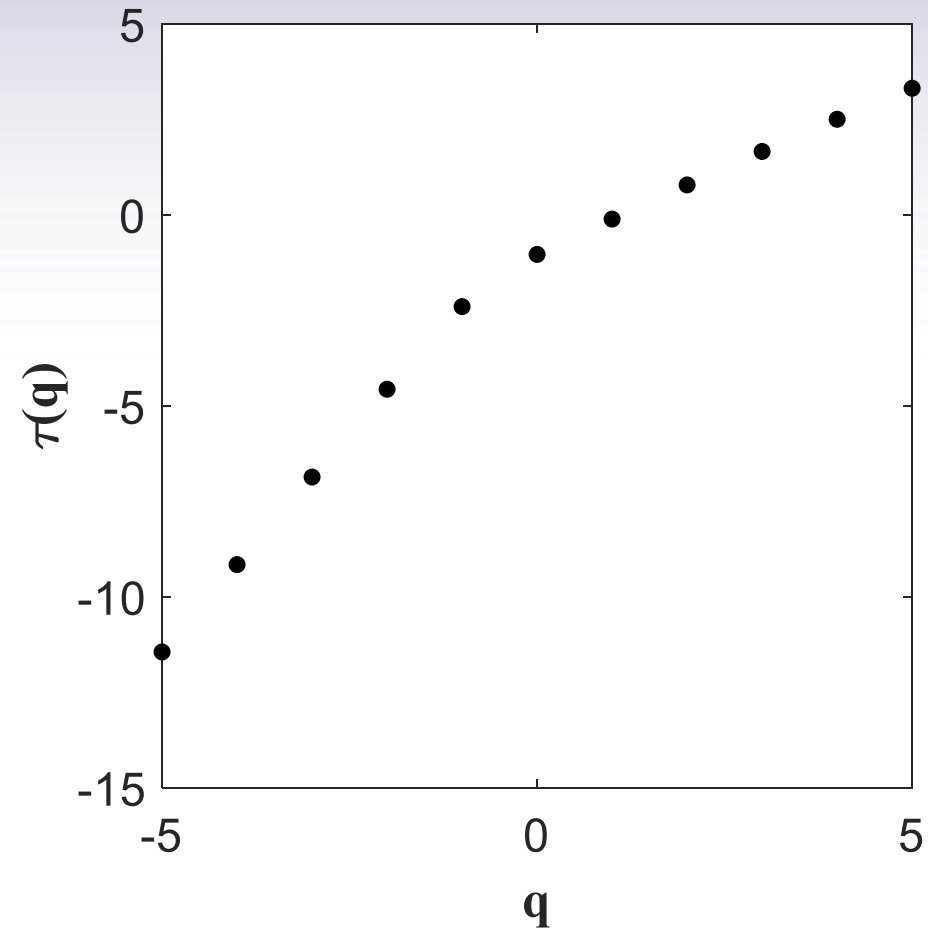
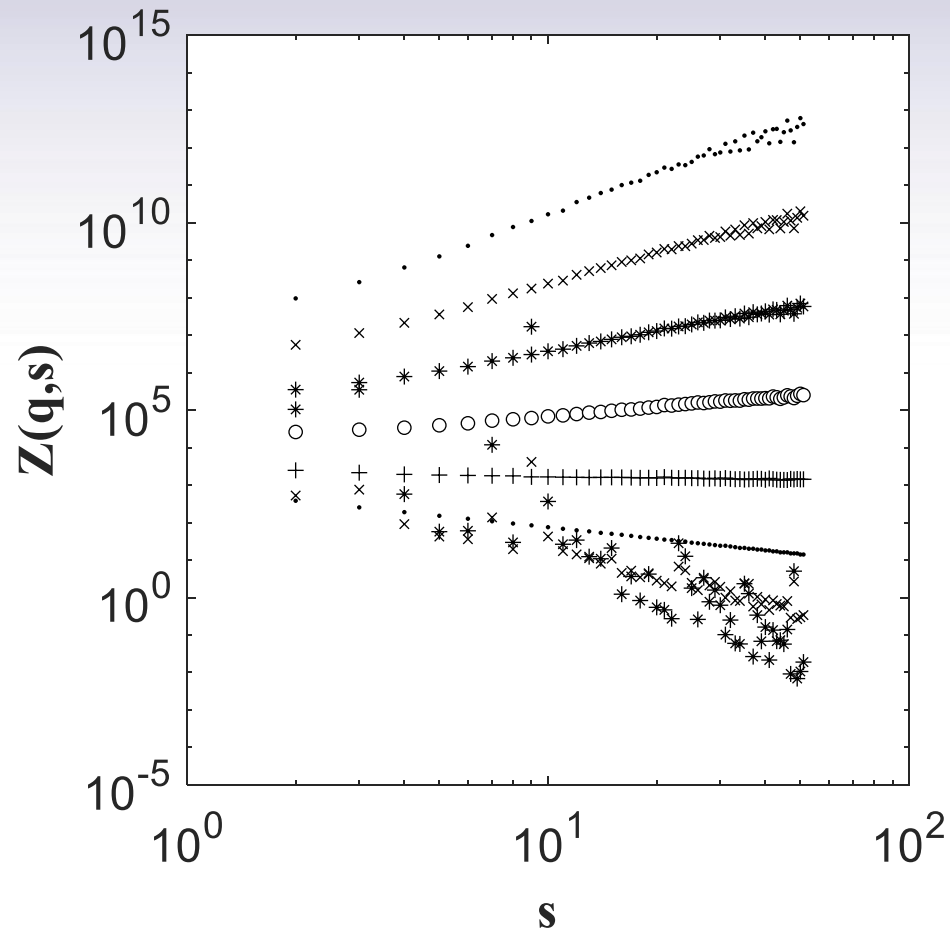


Análisis Multifractal (MFA)



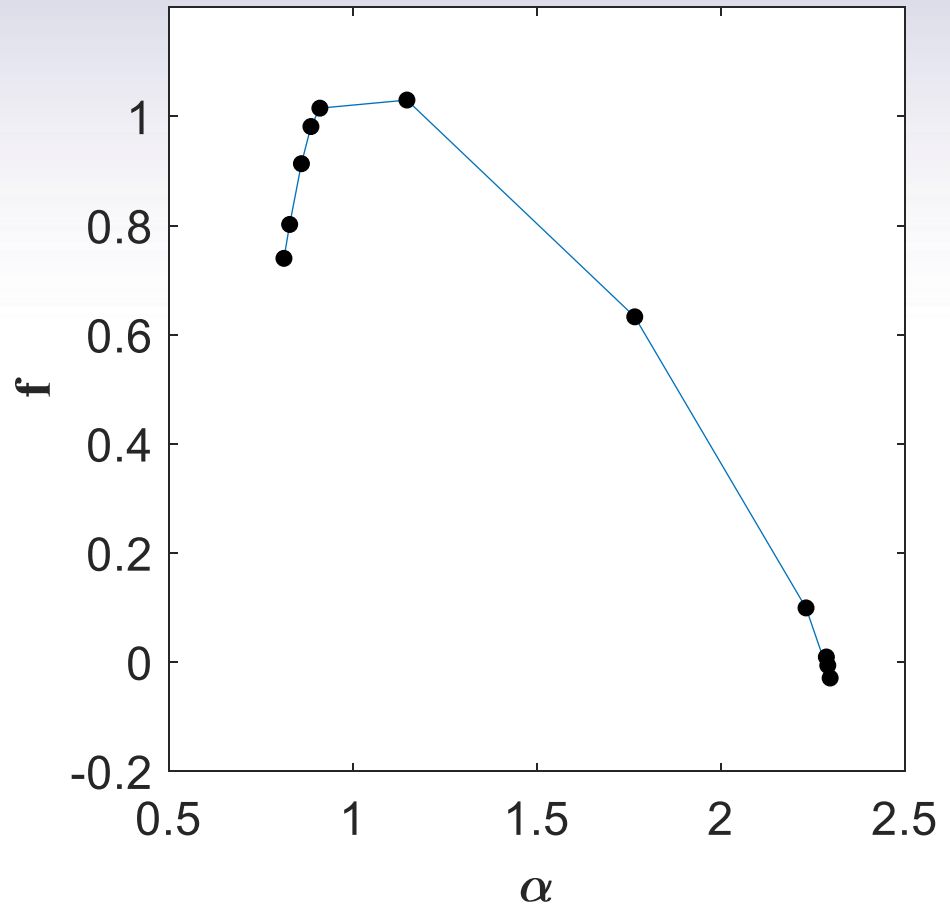
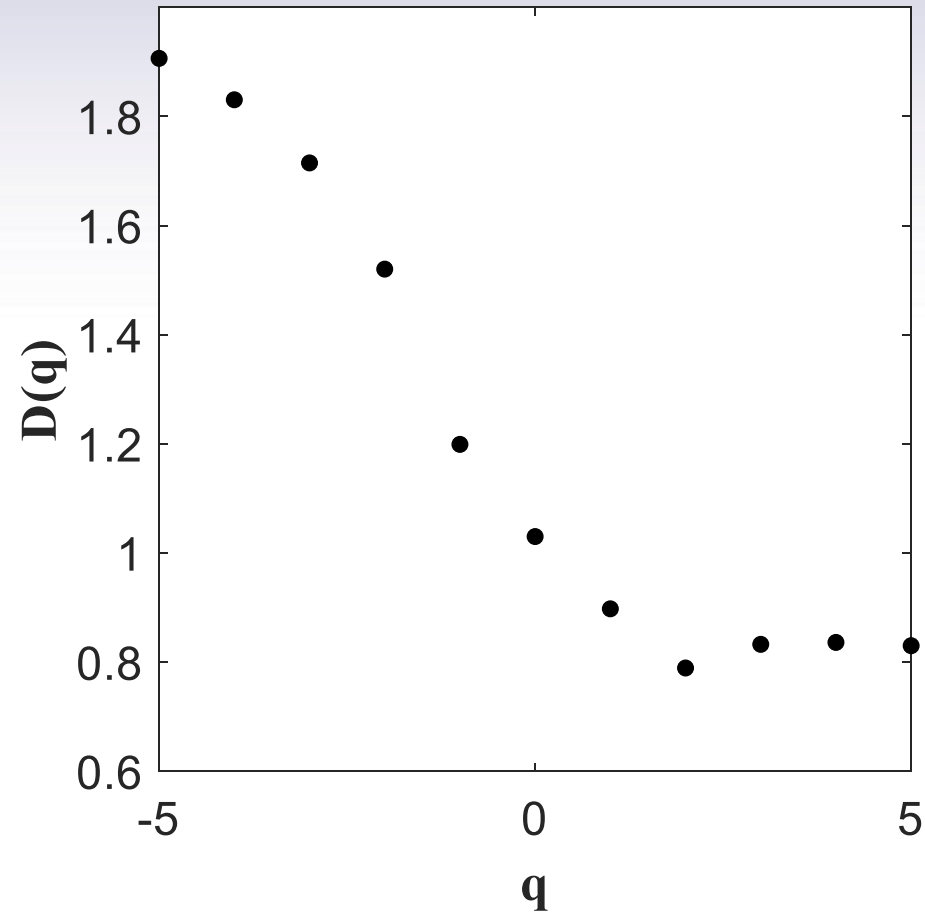


Análisis Multifractal (MFA)



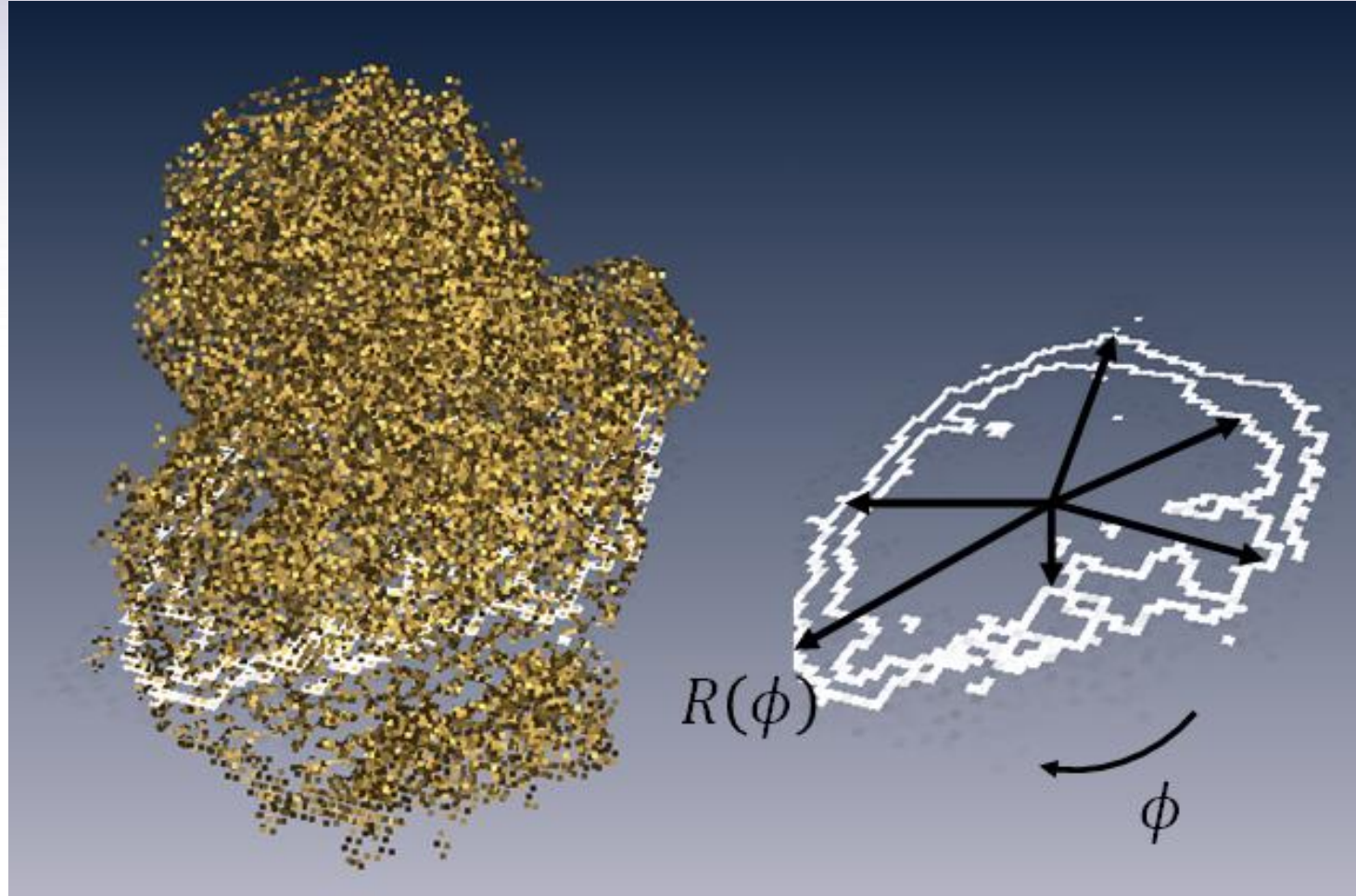


Análisis Multifractal (MFA)



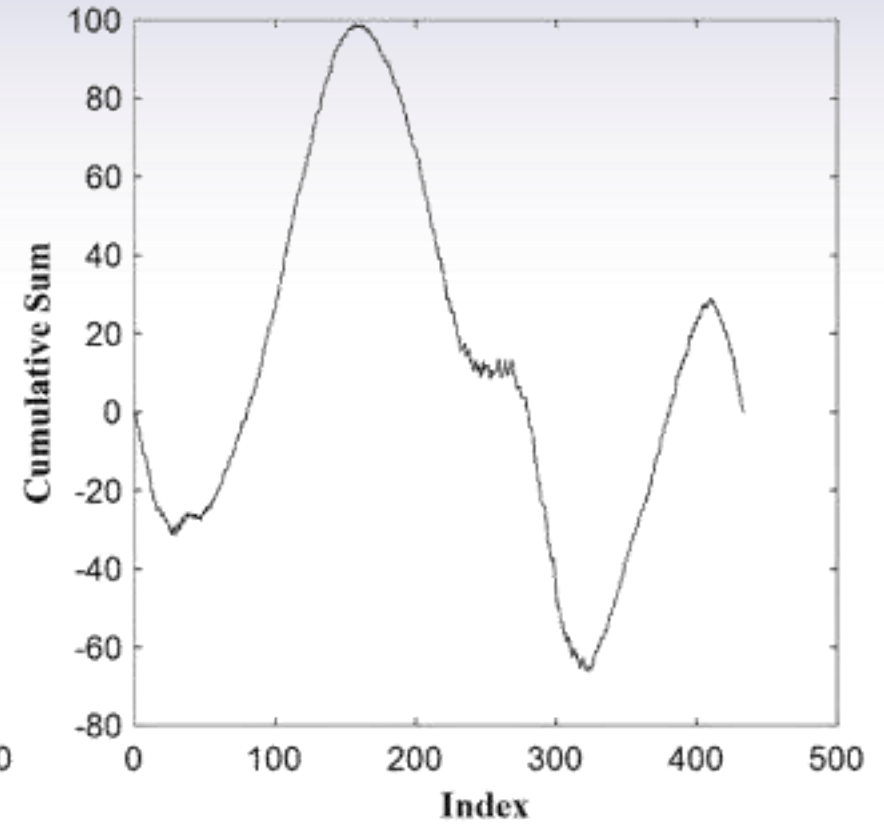
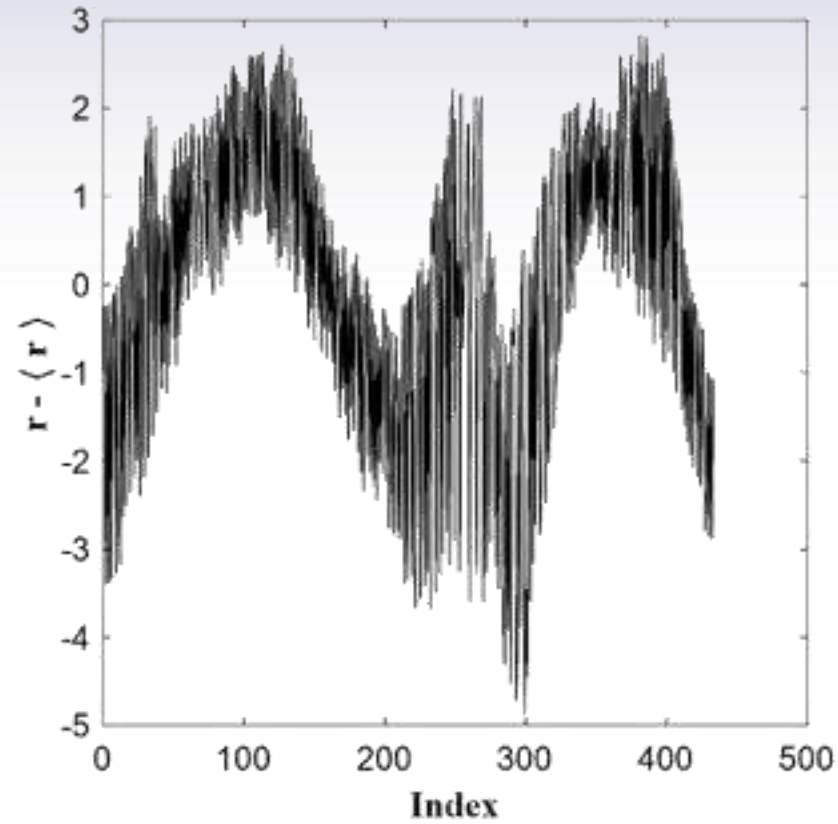
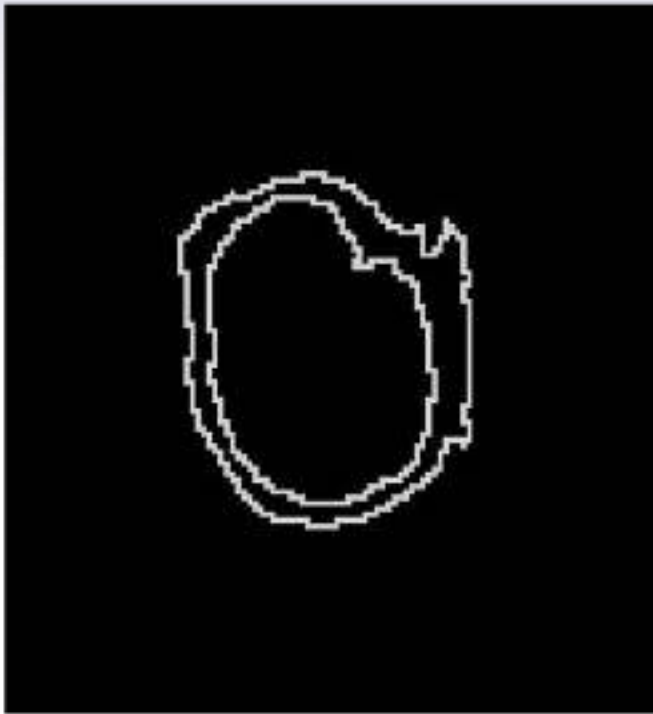


Series ordenadas



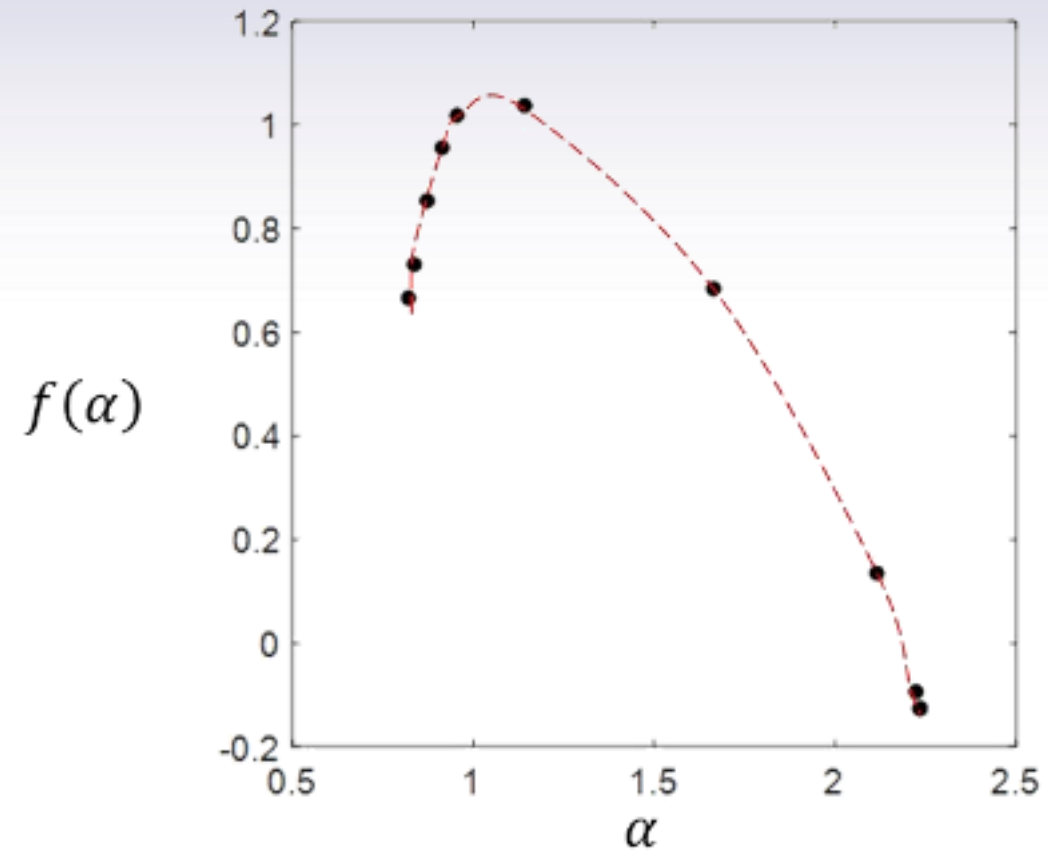
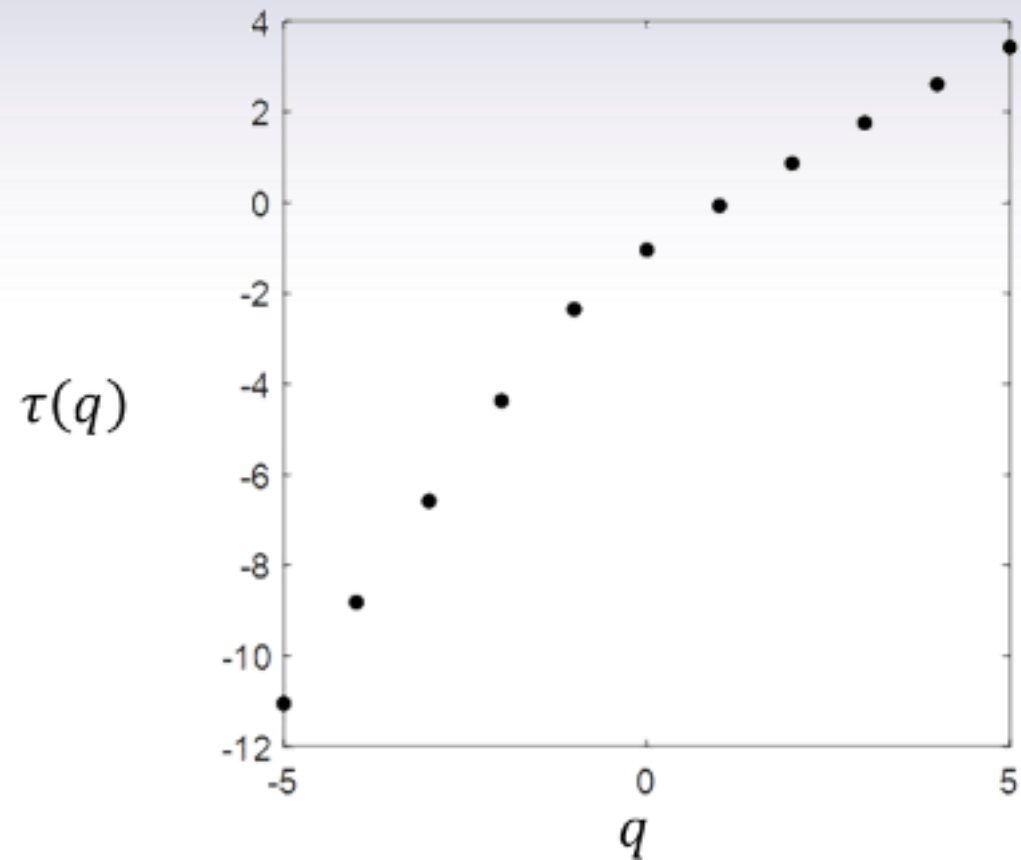


Análisis de la interfaz tumoral. Series ordenadas 1D





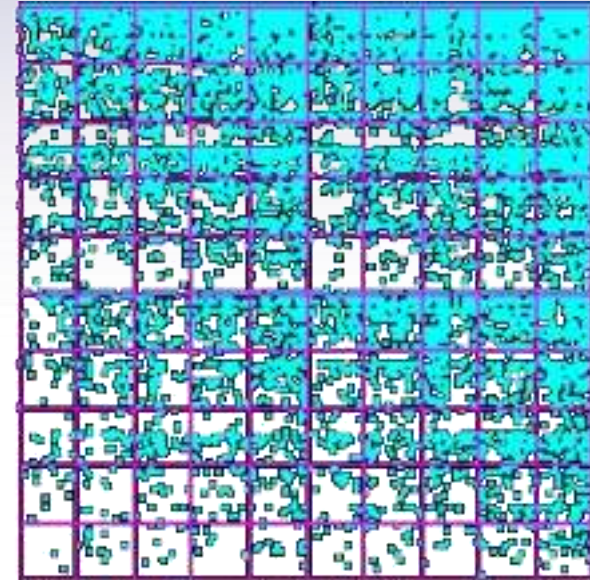
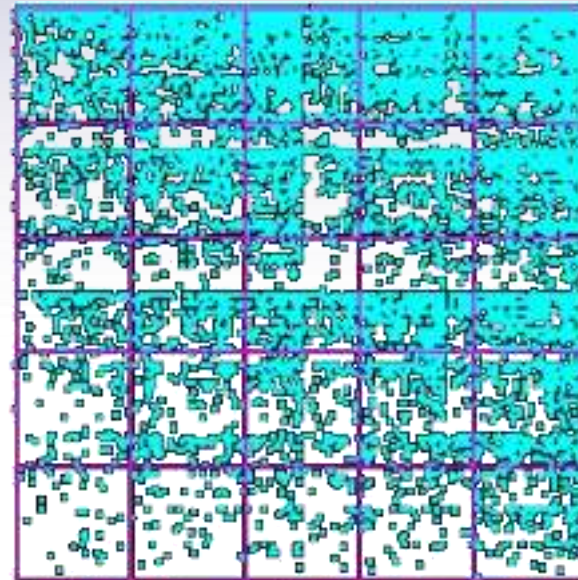
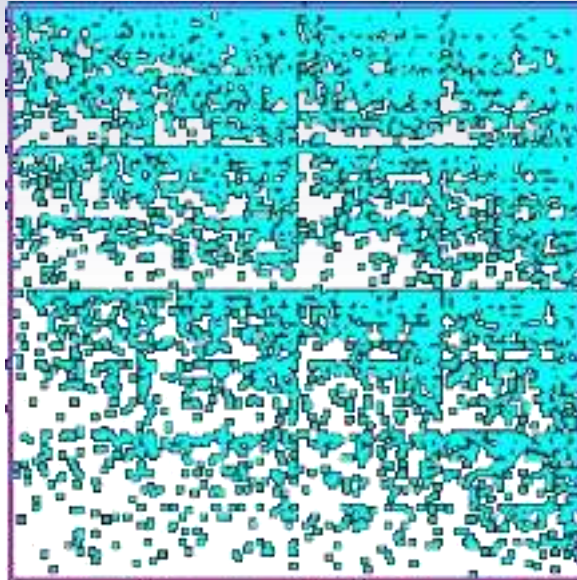
Análisis de la interfaz tumoral. Series ordenadas 1D





Método de los momentos. Varias dimensiones.

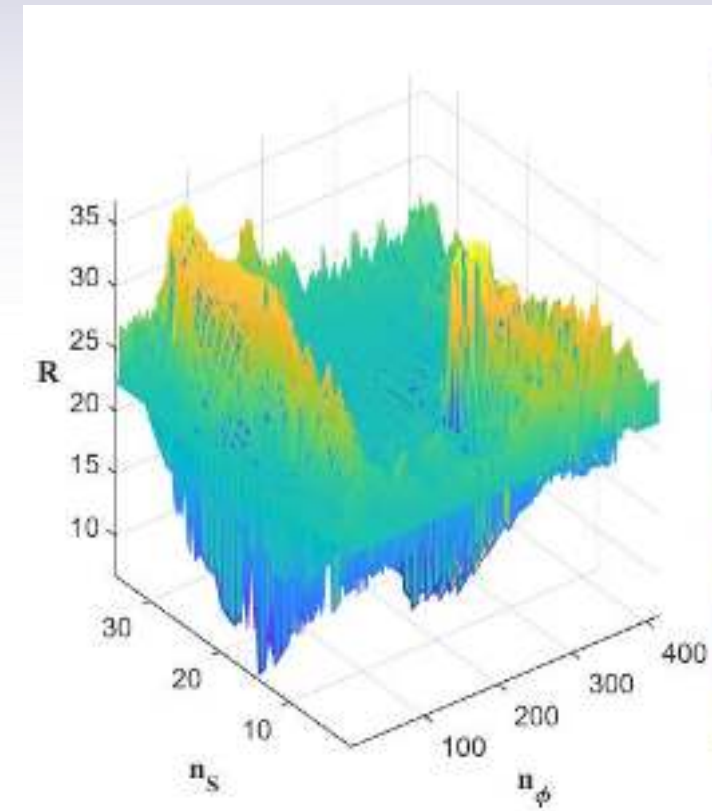
ϵ



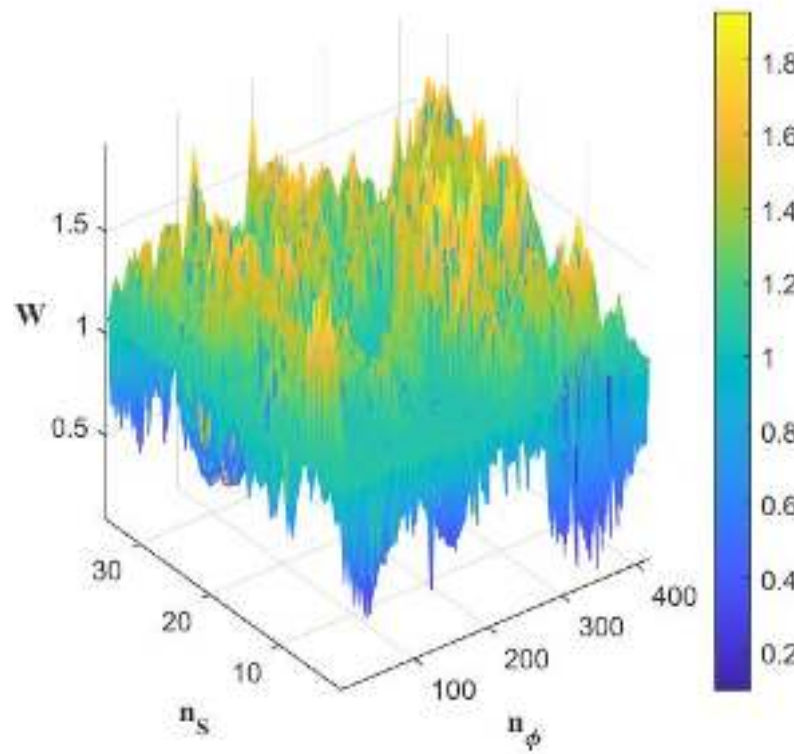
$$Z_q(\epsilon) = \sum_j \left[\left(\frac{n_j(\epsilon)}{N} \right) \right]^q$$

$$\tau(q) = \lim_{\epsilon \rightarrow 0} \frac{\ln(Z_q(\epsilon))}{\ln(\epsilon)}$$

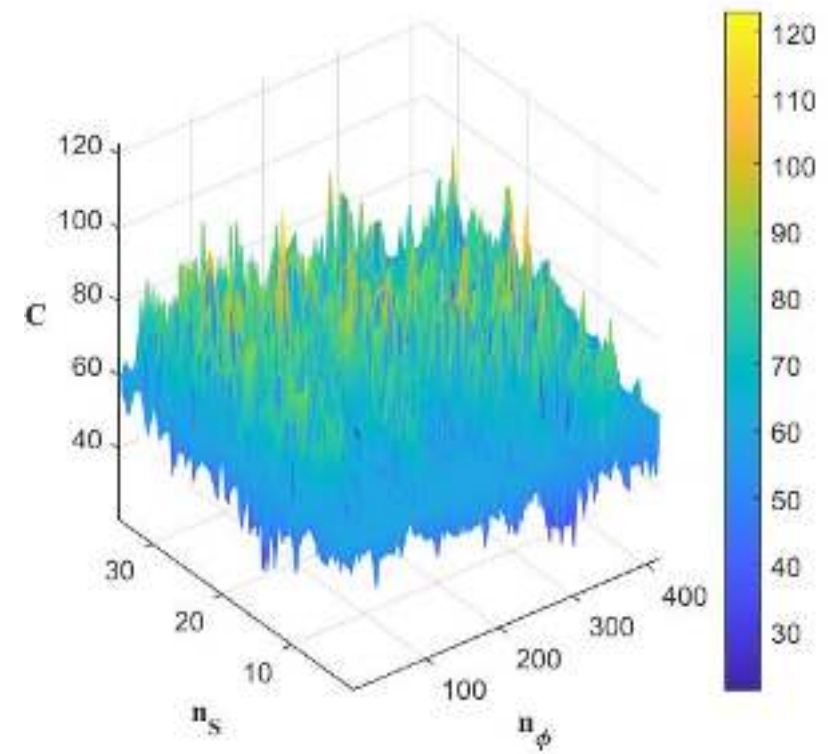
$$f(\alpha) = \min_q (q\alpha - \tau(q))$$



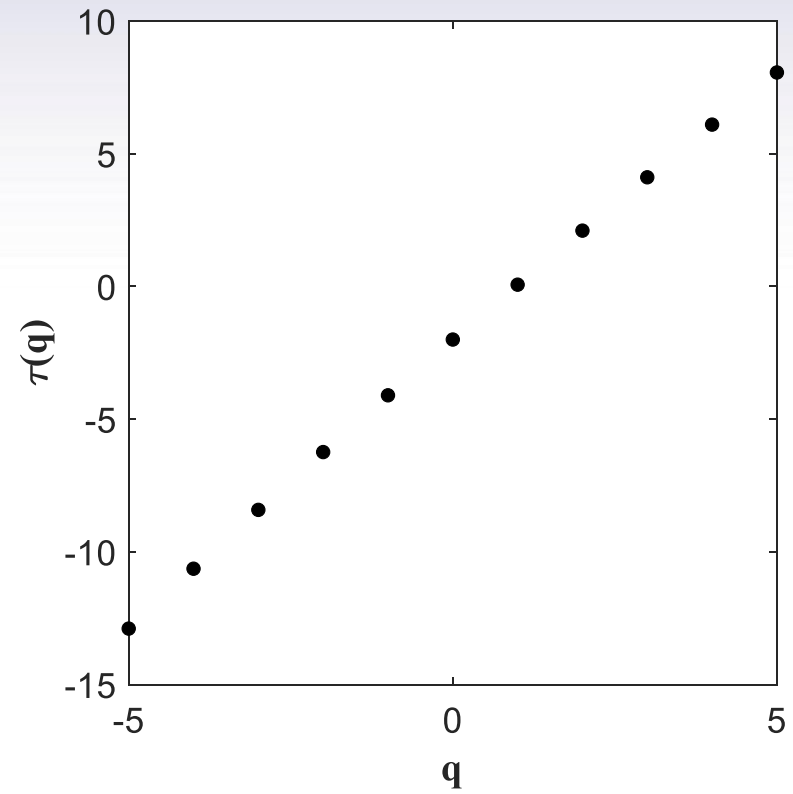
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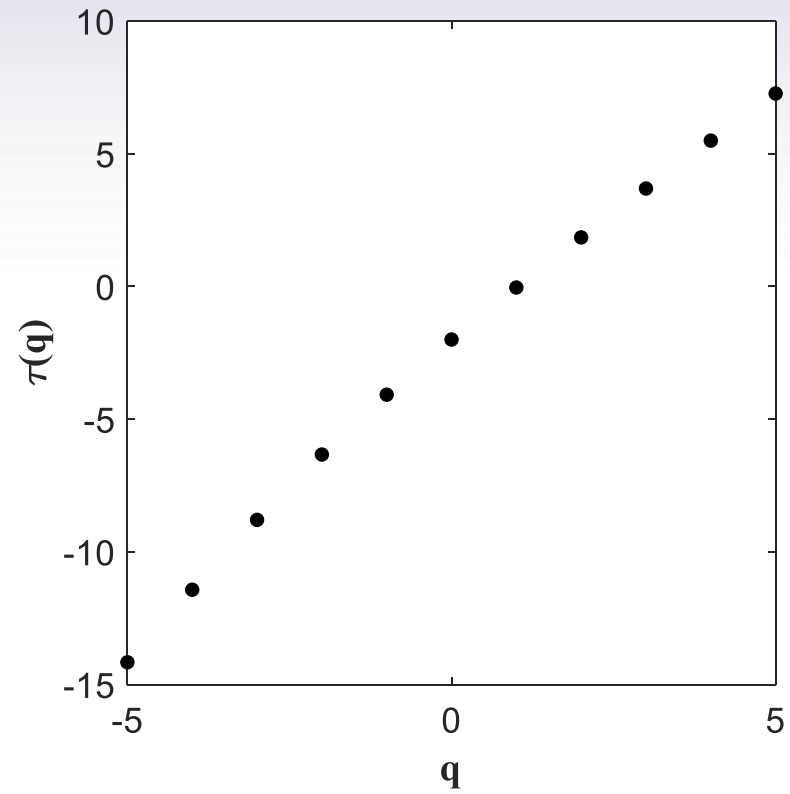
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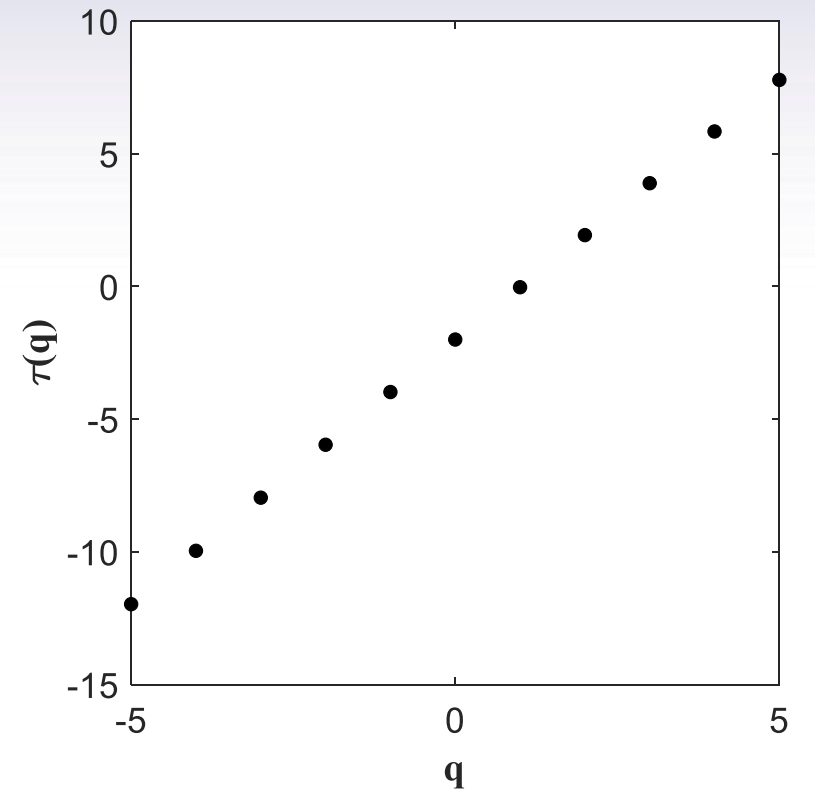
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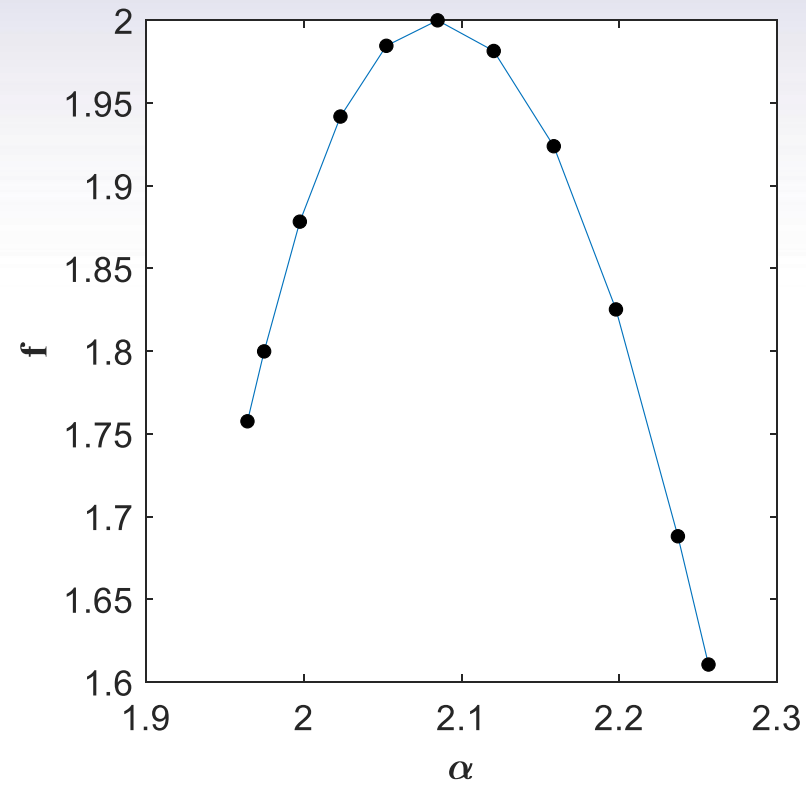
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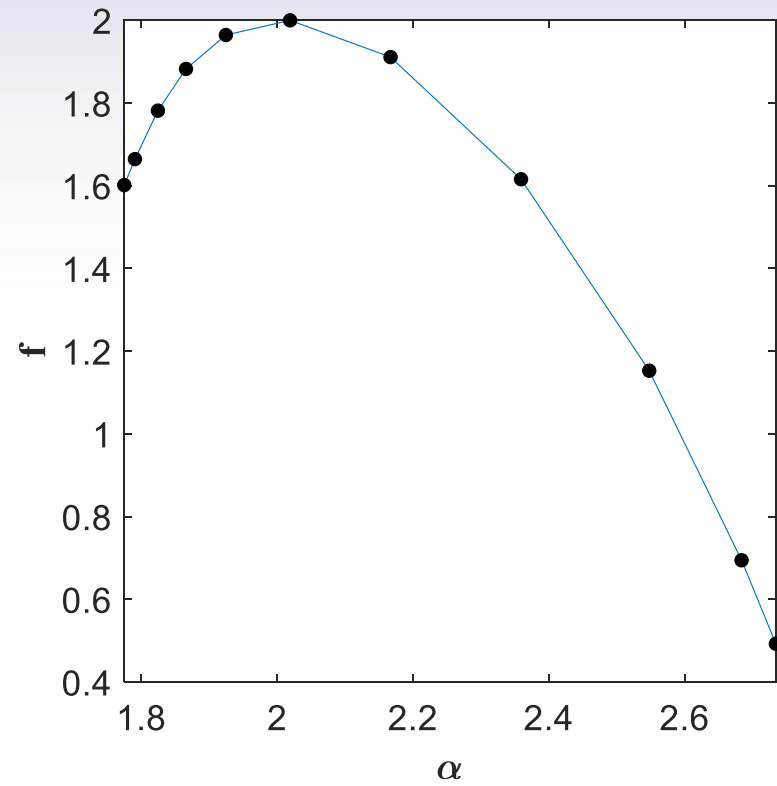
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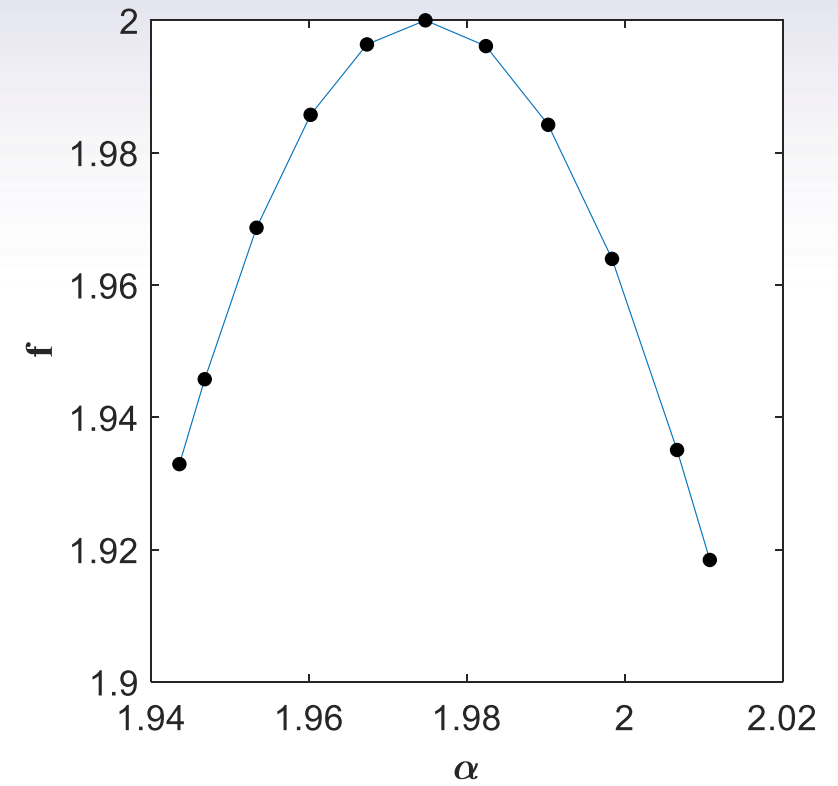
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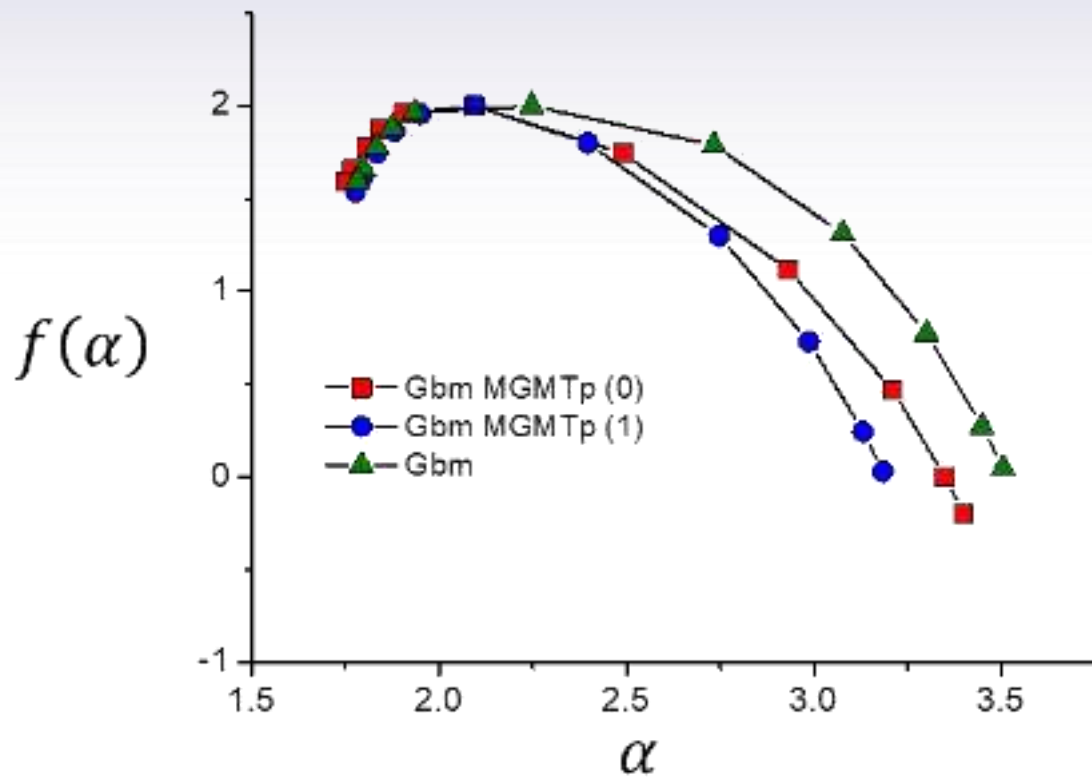
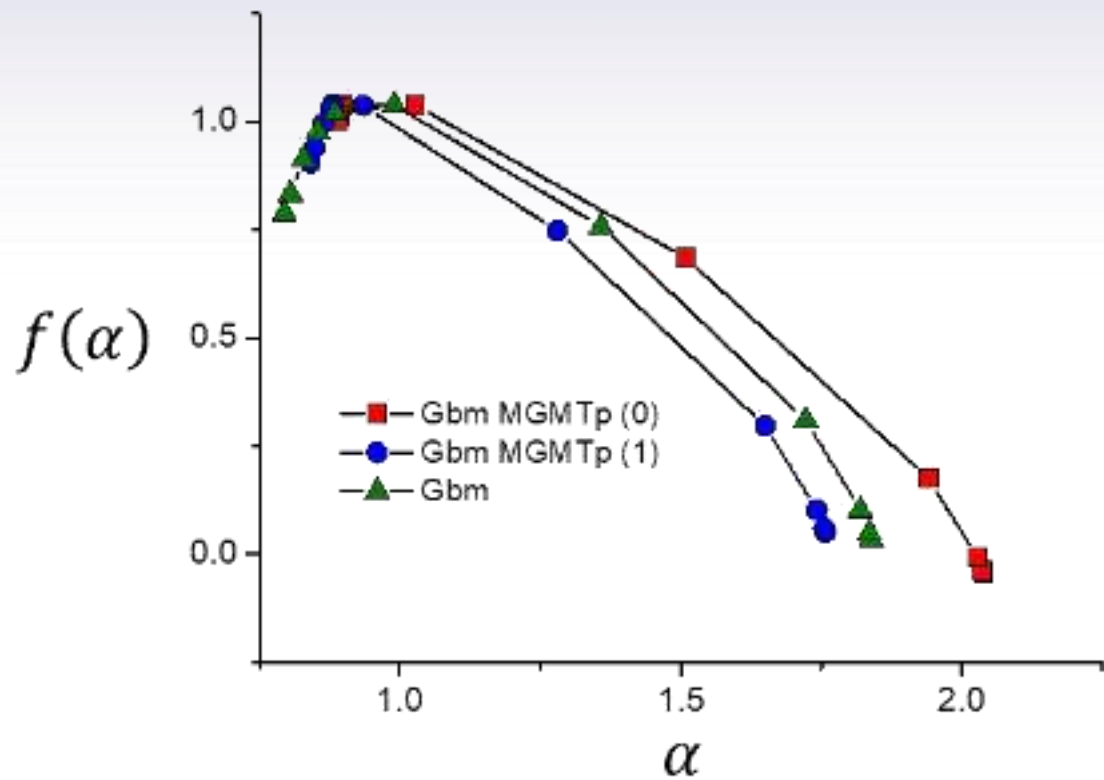
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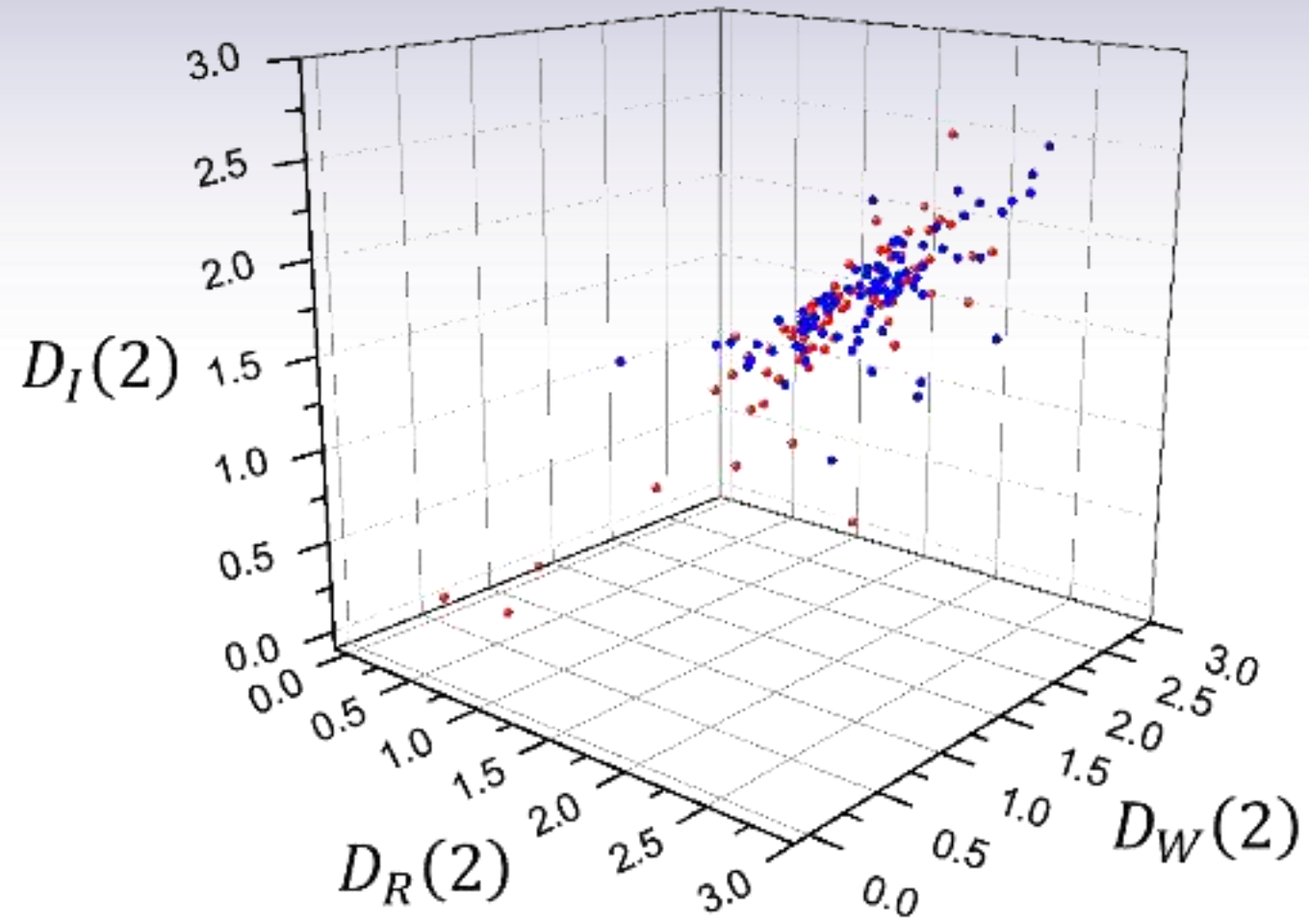


W



C







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SUBJECT AREAS:
NONLINEAR
PHENOMENA
COMPLEX NETWORKS

Received
14 July 2014

Accepted
1 December 2014

Published
18 December 2014

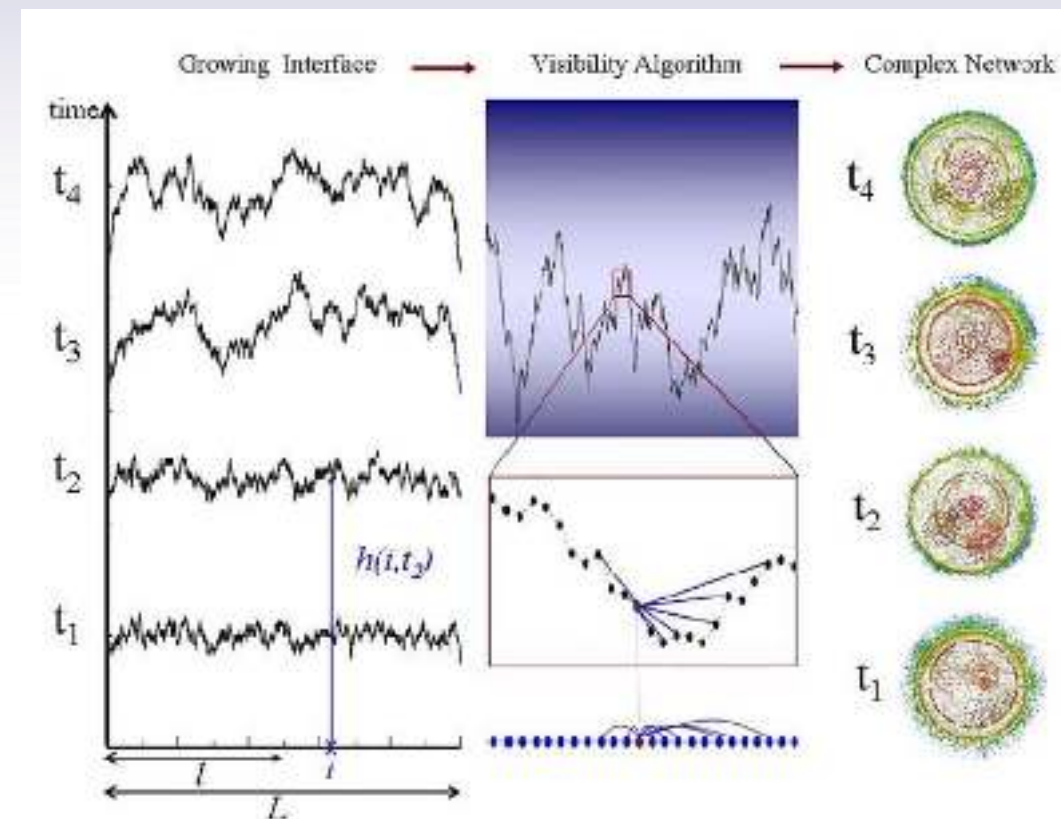
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Scaling in complex systems: a link between the dynamics of networks and growing interfaces

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We consider growing interfaces as dynamical networks whose nodes are the discrete points of the interface and the edges the physical interactions among them. We map the points of the interface formed at each time into a graph by means of a visibility algorithm. As the corresponding interfaces grow, their visibility graphs change over time. We show that the visibility graphs are all scale free for each time. We use the variance of the node degrees as a measure of the dynamical properties of these graphs. This magnitude reveals an unexpected scaling behaviour of these graphs in both the number of nodes and time. This enables to define three robust exponents that characterize any type of dynamics with more detail than the classical scaling analysis applied directly to the physical interfaces. To check the feasibility of this approach we study and classify six different dynamical processes and estimate their critical exponents. We conclude that the dynamics of physical systems far from equilibrium can be determined by its corresponding visibility network. Indeed, this methodology is able to discern among dynamical processes that hitherto have been classified in the same universality class according to the scaling analysis of their interfaces.



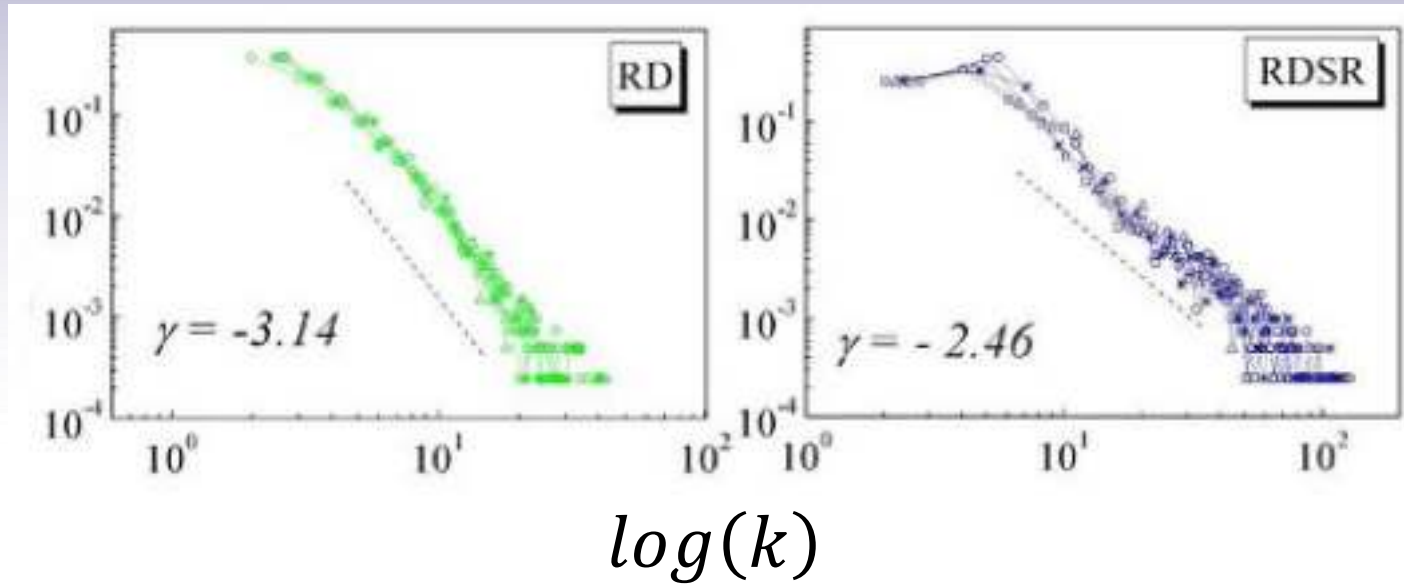


- RD: Random Deposition
- RDSR: Random Deposition with Surface Relaxation
- EW: Edwards-Wilkinson
- KPZ: Kardar-Parisi-Zang
- Eden
- MBE: Molecular Beam Epitaxy

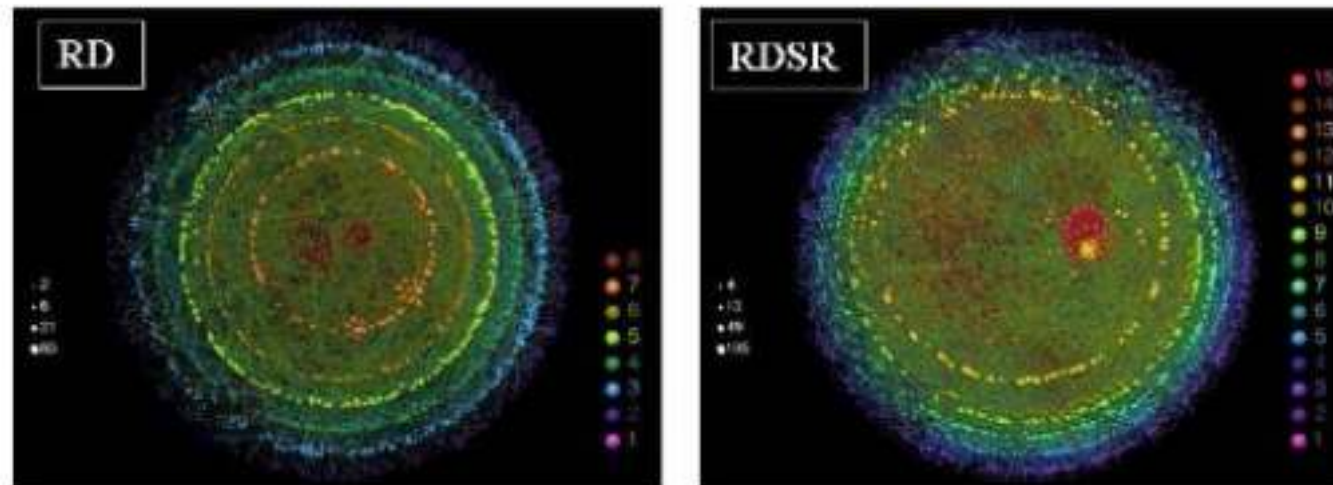


Redes Complejas. Redes de visibilidad.

$$\log(P(k))$$



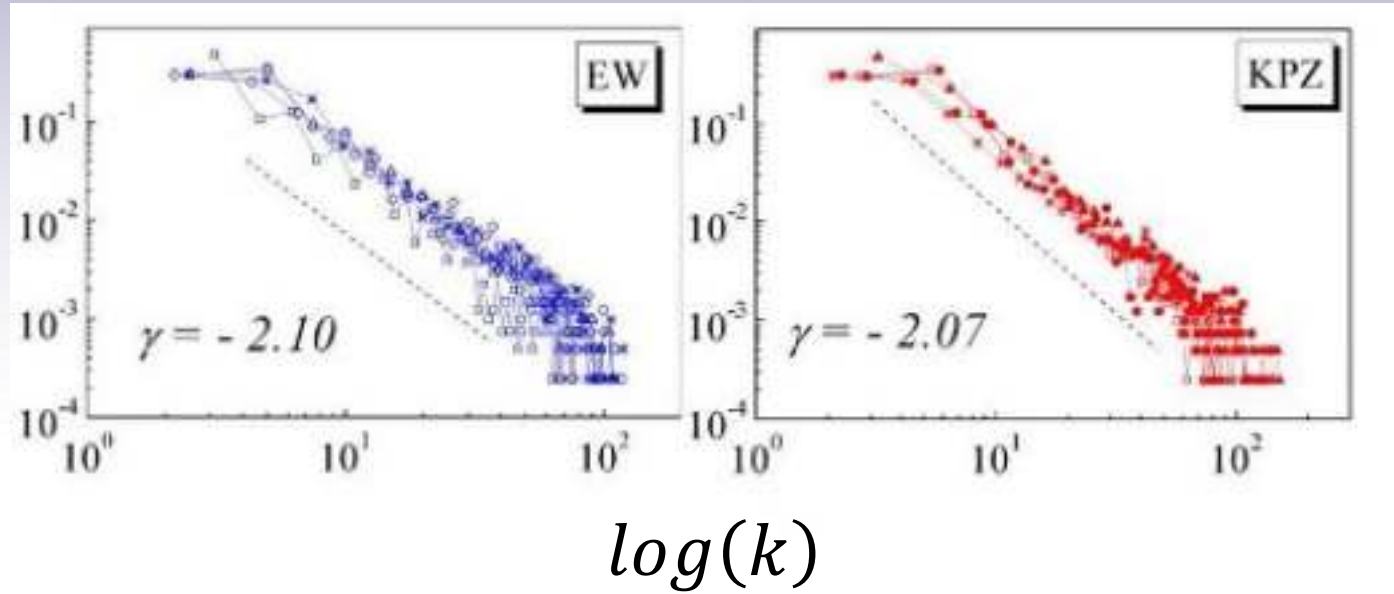
- 2000
- 4000
- △ 6000
- ◇ 8000
- * 10000



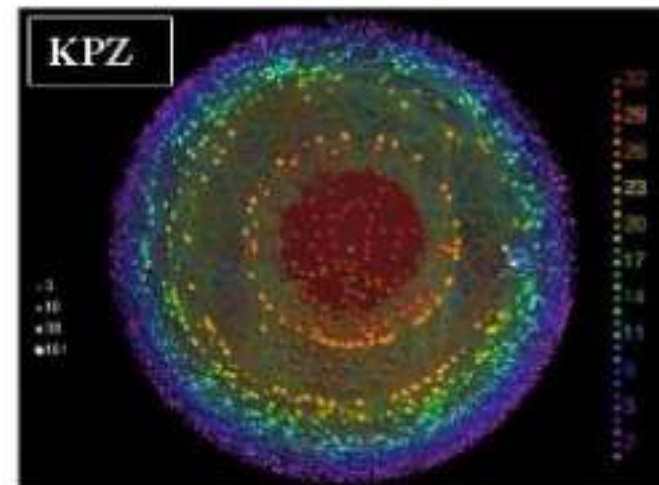
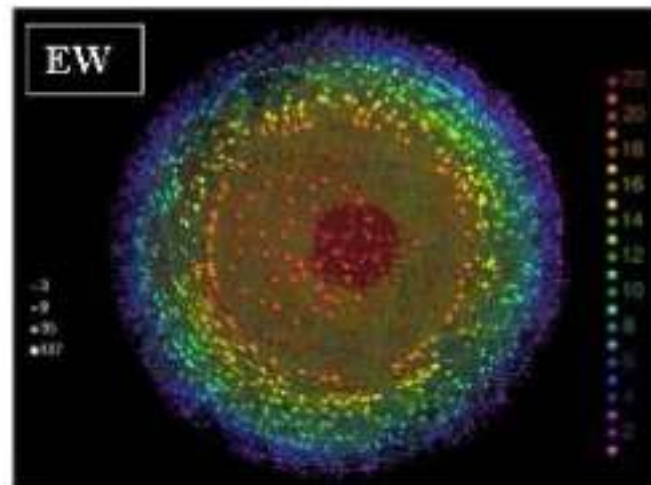


Redes Complejas. Redes de visibilidad.

$\log(P(k))$



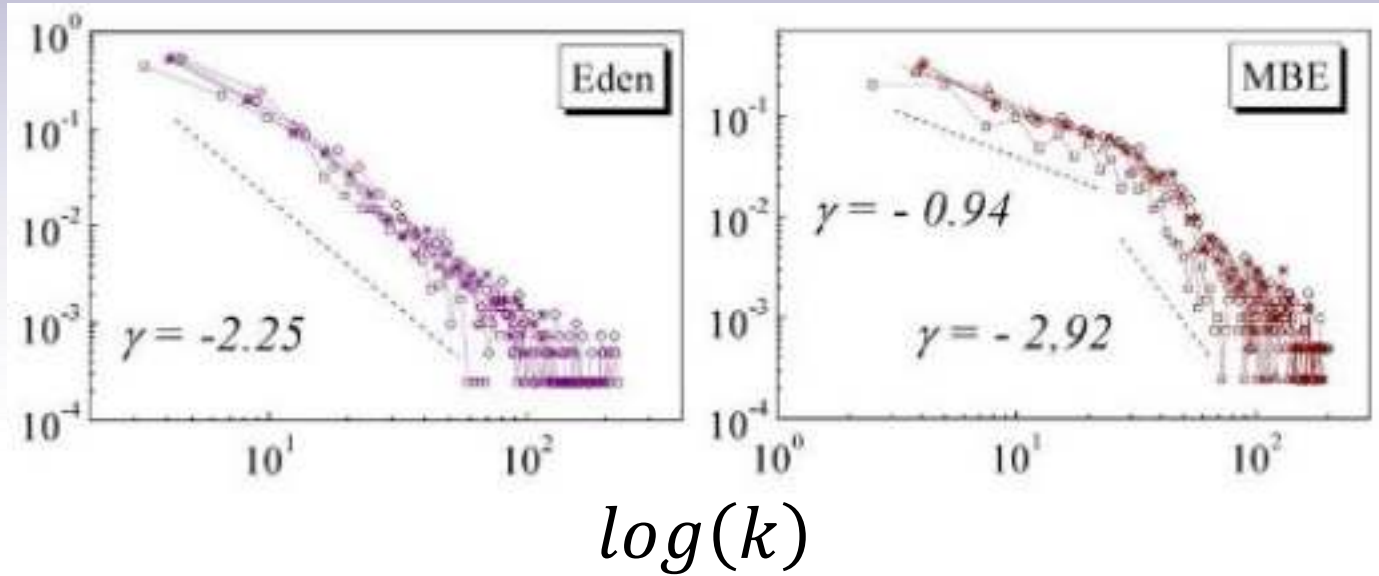
- 2000
- 4000
- △ 6000
- ◇ 8000
- * 10000



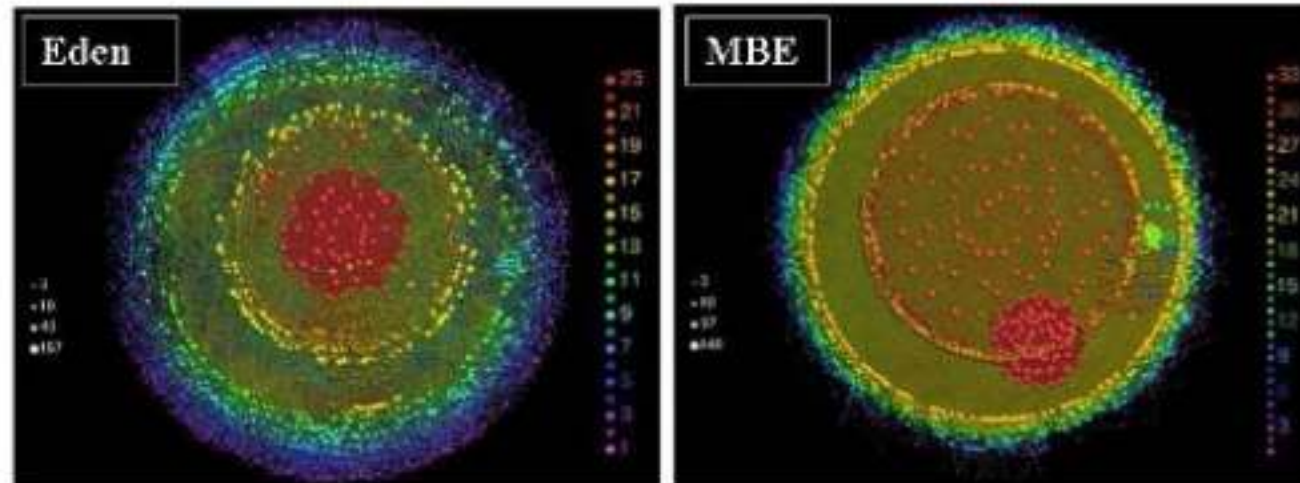


Redes Complejas. Redes de visibilidad.

$$\log(P(k))$$



- 2000
- 4000
- △ 6000
- ◇ 8000
- * 10000

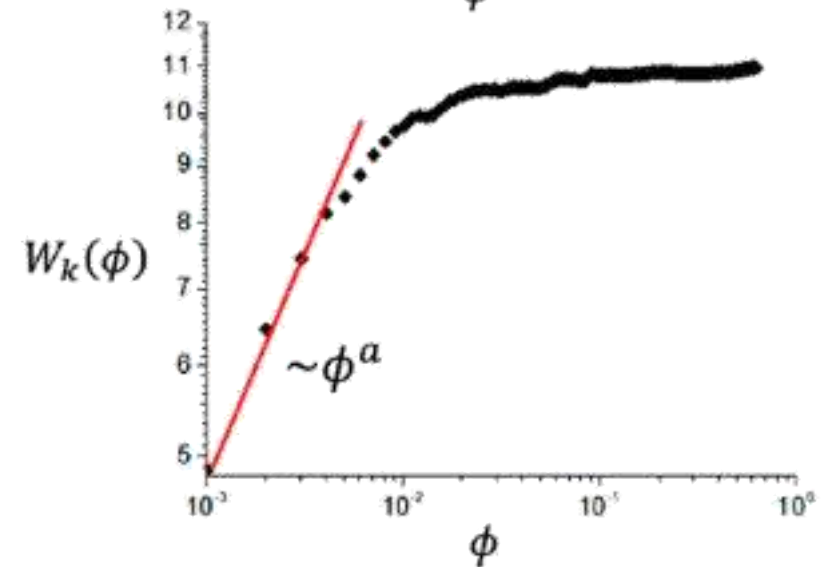
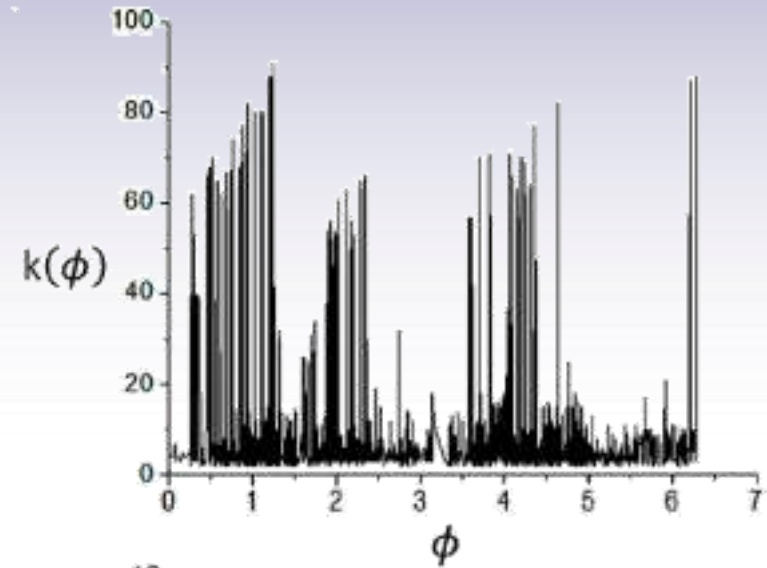




Redes Complejas. Redes de visibilidad.

$$W_k(\phi) = \left\{ \left\langle \frac{1}{\phi} \sum_{k_i \in \phi} (k_i - \langle k_i \rangle)^2 \right\rangle^{\frac{1}{2}} \right\}_{\Phi}$$

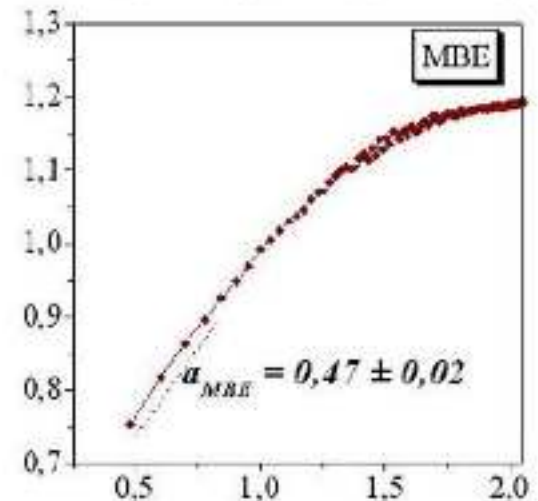
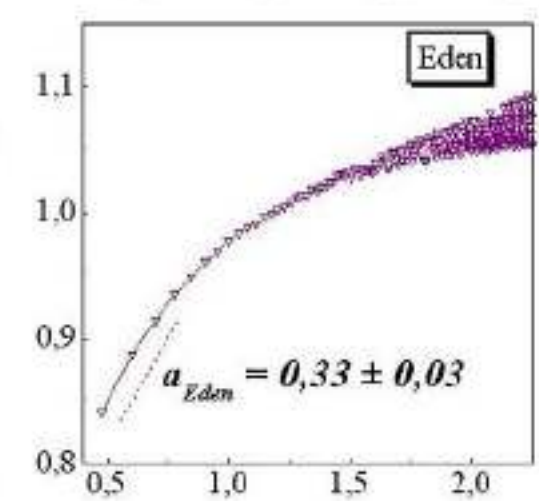
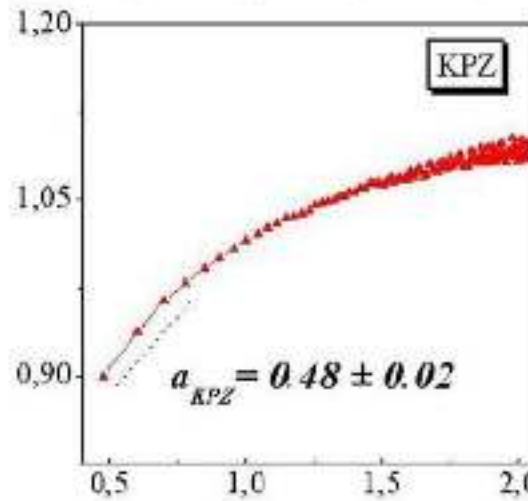
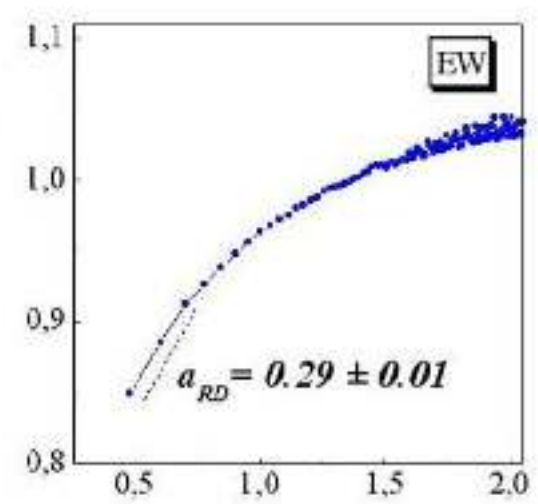
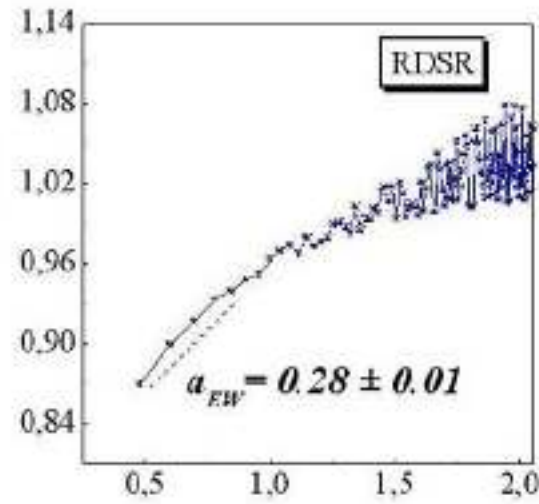
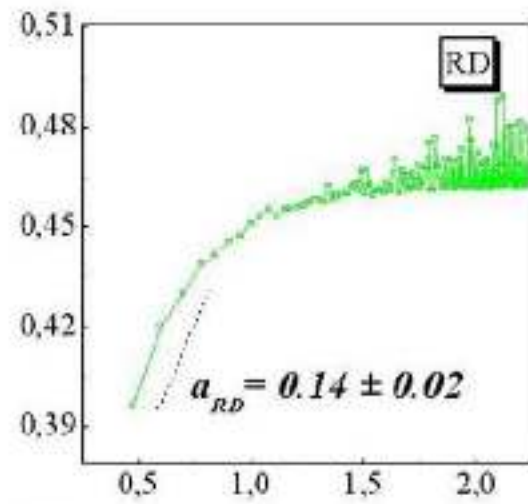
$$W_k \sim \phi^a$$





Redes Complejas. Redes de visibilidad.

$\log(W_k(\phi))$

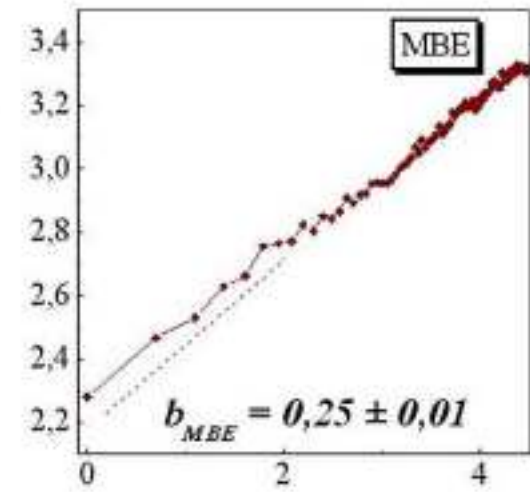
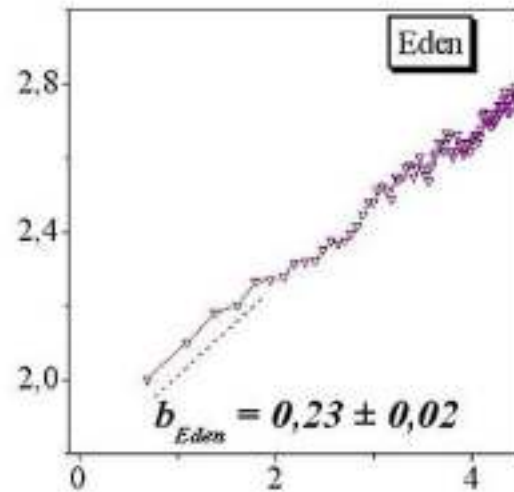
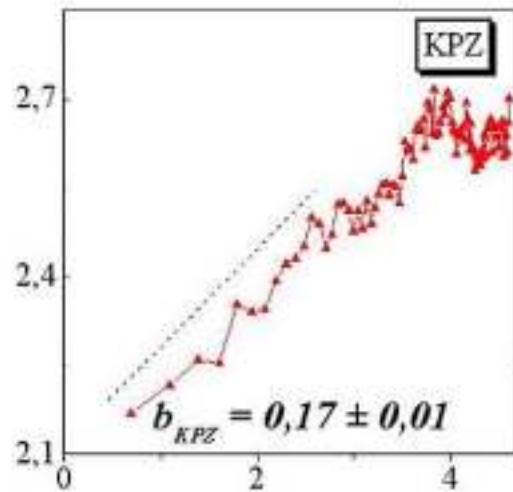
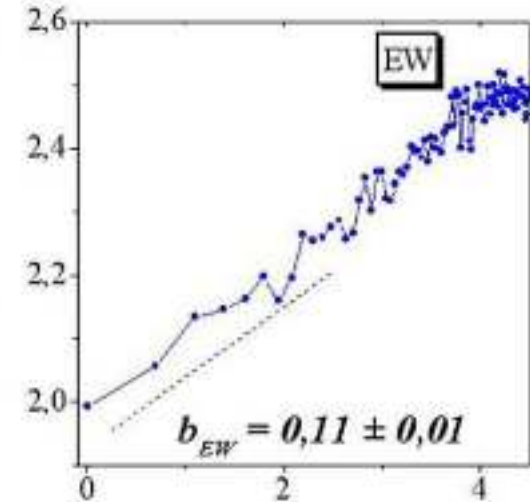
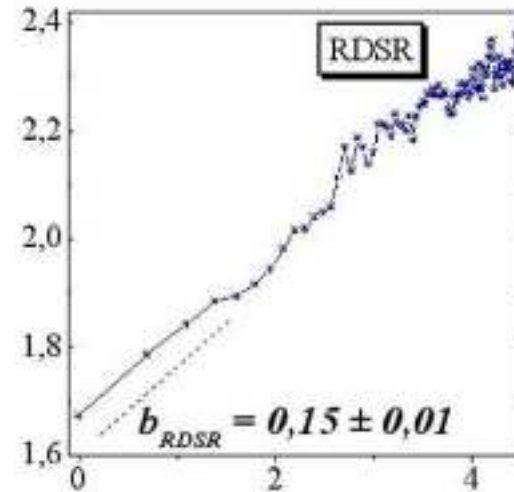
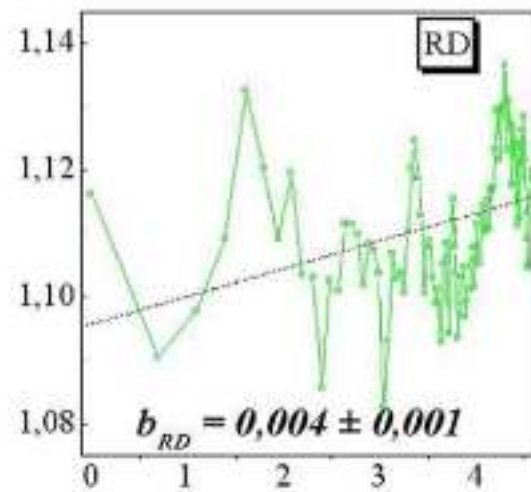


$\log(\phi)$



Redes Complejas. Redes de visibilidad.

$\log(W_k(t))$

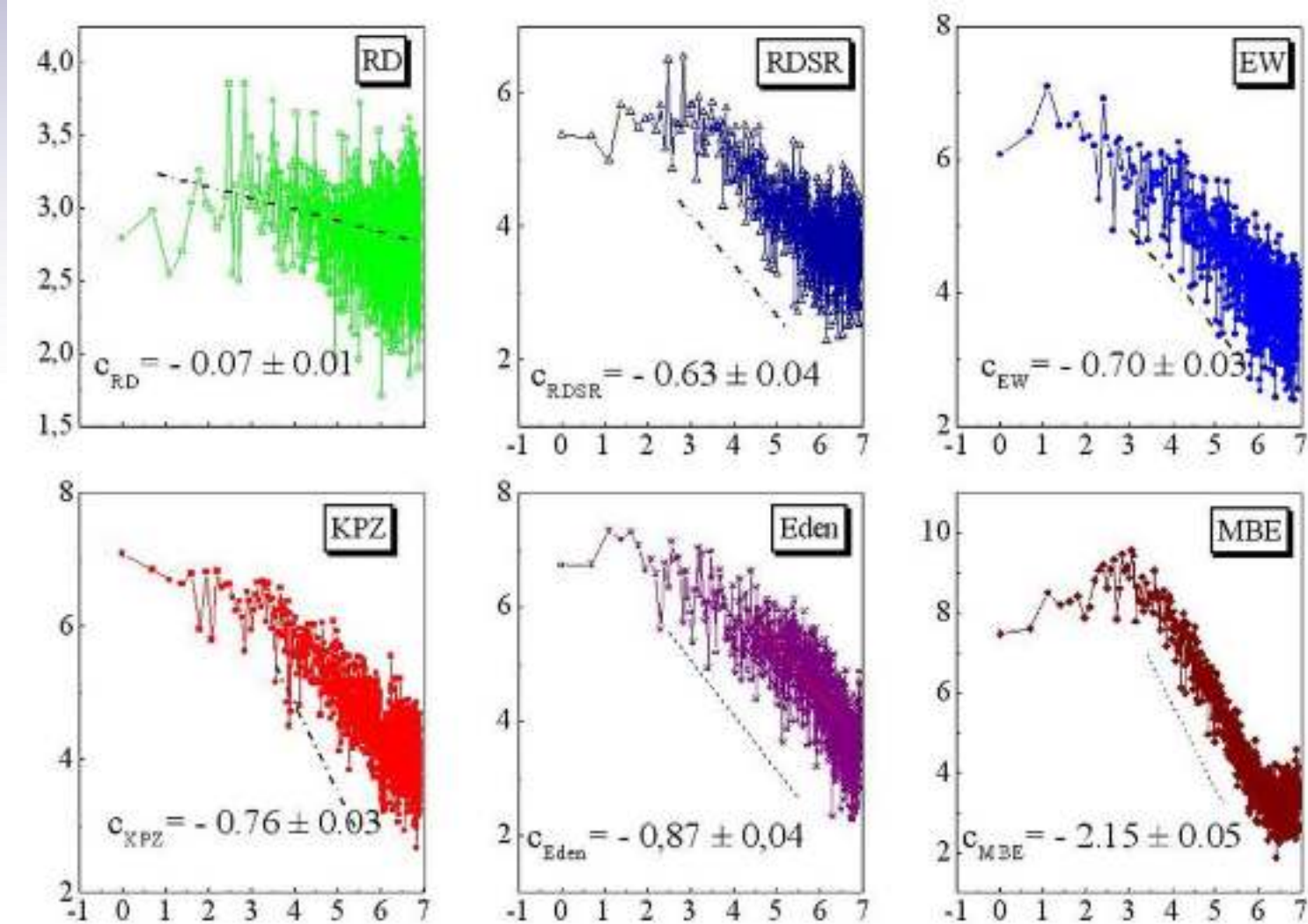


$\log(t)$



Redes Complejas. Redes de visibilidad.

$\log(S(q))$



$\log(q)$

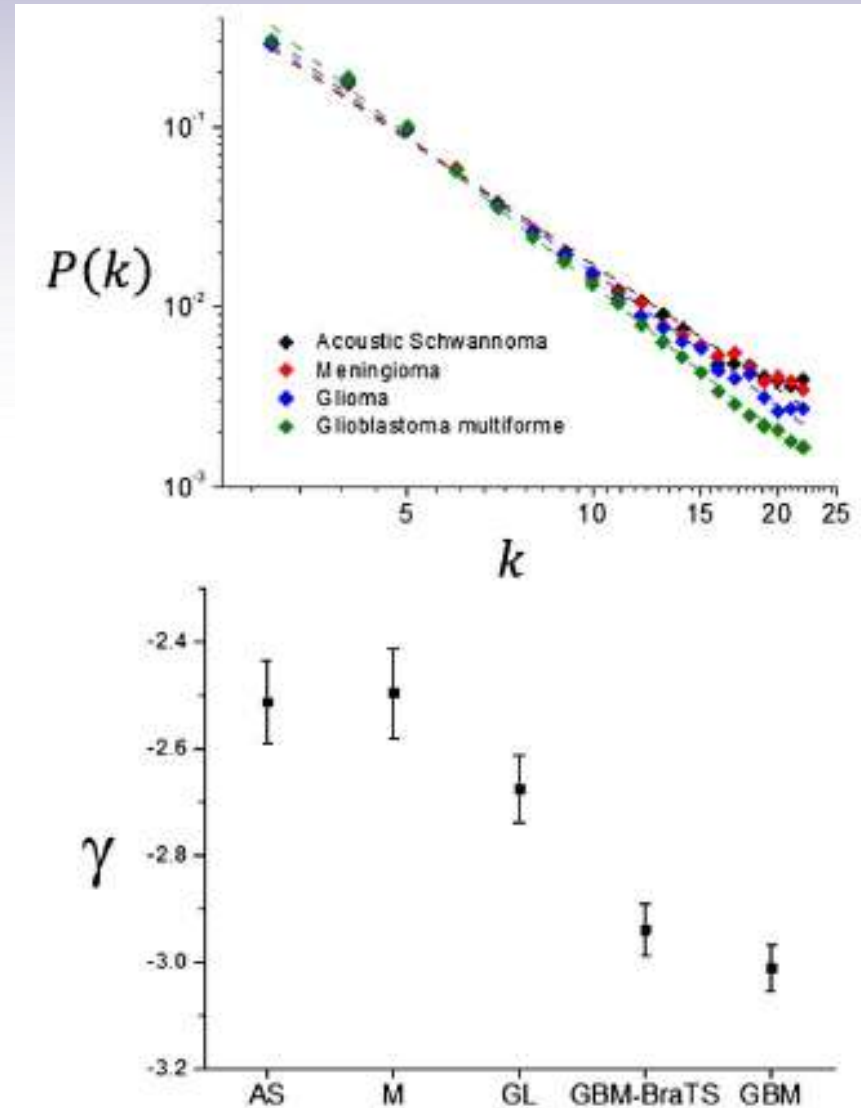
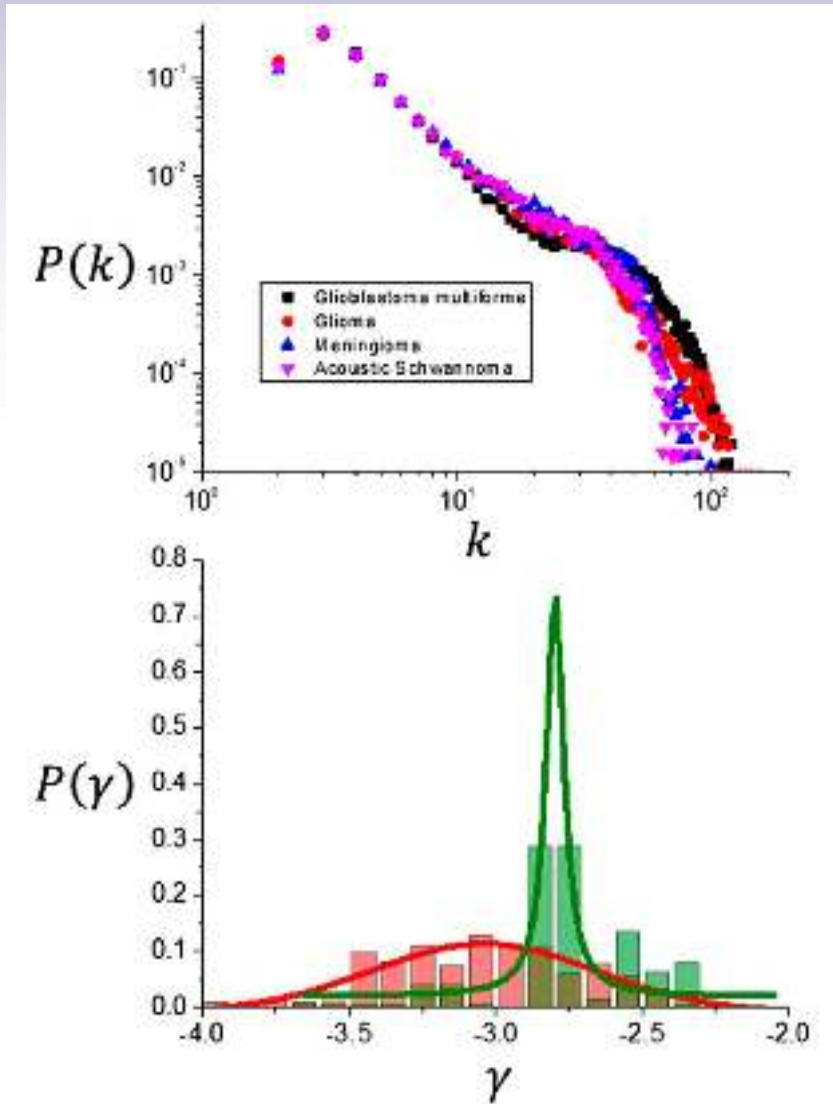


Redes Complejas. Redes de visibilidad.

dynamical Process	Network exponents	Classical exponents
RD	$a = 0.14, b = 0.004, c = 0.07$	α not defined $\beta = \frac{1}{2}$
EW	$a = 0.12, b = 0.28, c = 0.79$	$\alpha = \frac{1}{2} \beta = \frac{1}{4}$
KPZ	$a = 0.29, b = 0.14, c = 0.76$	$\alpha = \frac{1}{2} \beta = \frac{1}{3}$
MBE	$a = 0.48, b = 0.25, c = 2.12$	$\alpha_s = \frac{3}{2}, \alpha = 1 \beta = \frac{3}{8} \beta^* = \beta - \frac{\alpha_{loc}}{z} = \frac{1}{8}$
RDSR	$a = 0.28, b = 0.15, c = 0.63$	$\alpha = \frac{1}{2} \beta = \frac{1}{4}$
Eden	$a = 0.33, b = 0.23, c = 0.87$	$\alpha = \frac{1}{2} \beta = \frac{1}{3}$



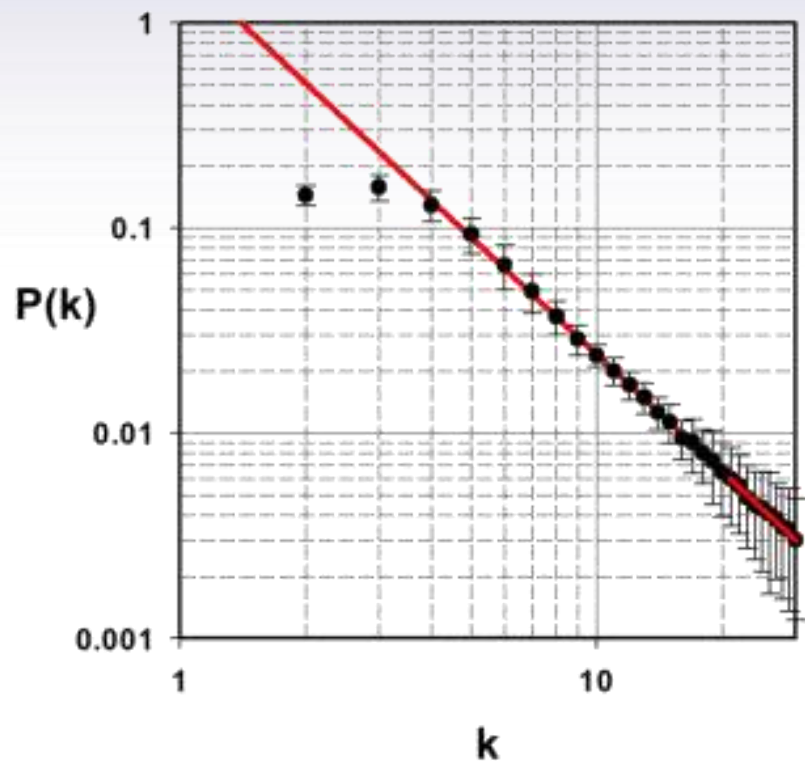
Redes Complejas. Tumores en cerebro.





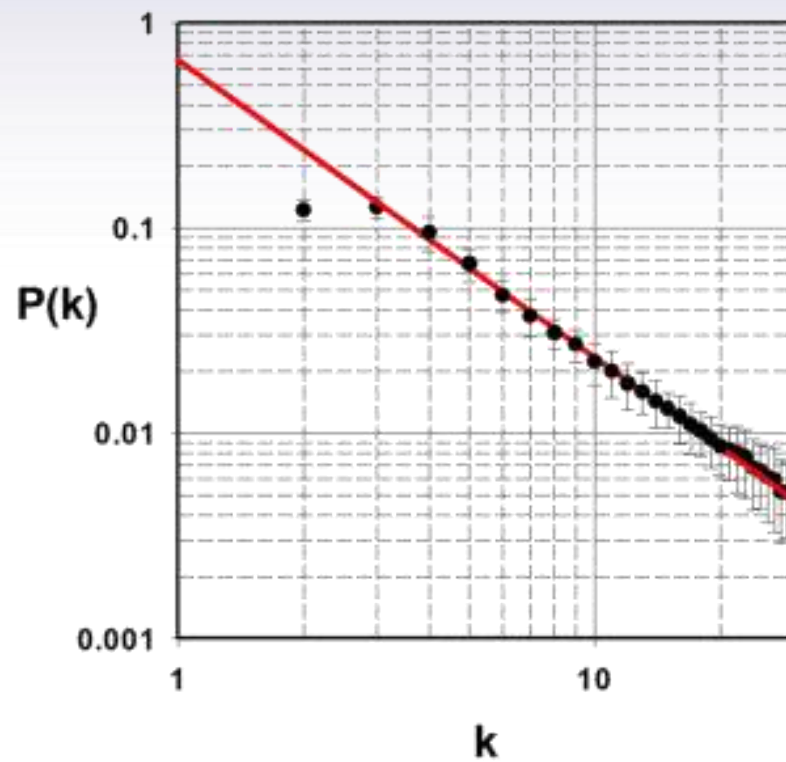
Redes Complejas. Tumores en piel.

-1.893

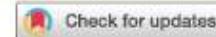


Melanoma

-1.450



Nevus



Universal scaling laws rule explosive growth in human cancers

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Most physical and other natural systems are complex entities that are composed of a large number of interacting individual elements. It is a surprising fact that they often obey the so-called scaling laws that relate an observable quantity to a measure of the size of the system. Here, we describe the discovery of universal superlinear metabolic scaling laws in human cancers. This dependence underpins increasing tumour aggressiveness, owing to evolutionary dynamics, that leads to an explosive growth as the disease progresses. We validated this dynamic using longitudinal volumetric data of different histologies from large cohorts of patients with cancer. To explain our observations we tested complex, biologically inspired mathematical models that describe the key processes that govern tumour growth. Our models predict that the emergence of superlinear allometric scaling laws is an inherently three-dimensional phenomenon. Moreover, the scaling laws that we identified allowed us to define a set of metabolic metrics with prognostic value, which adds clinical utility to our findings.

$$Z = \alpha V^\beta$$

Ley de Kleiber →

$$\beta = 3/4$$

Efecto Warburg

$$\beta > 1 ?$$



Leyes universales de escalamiento

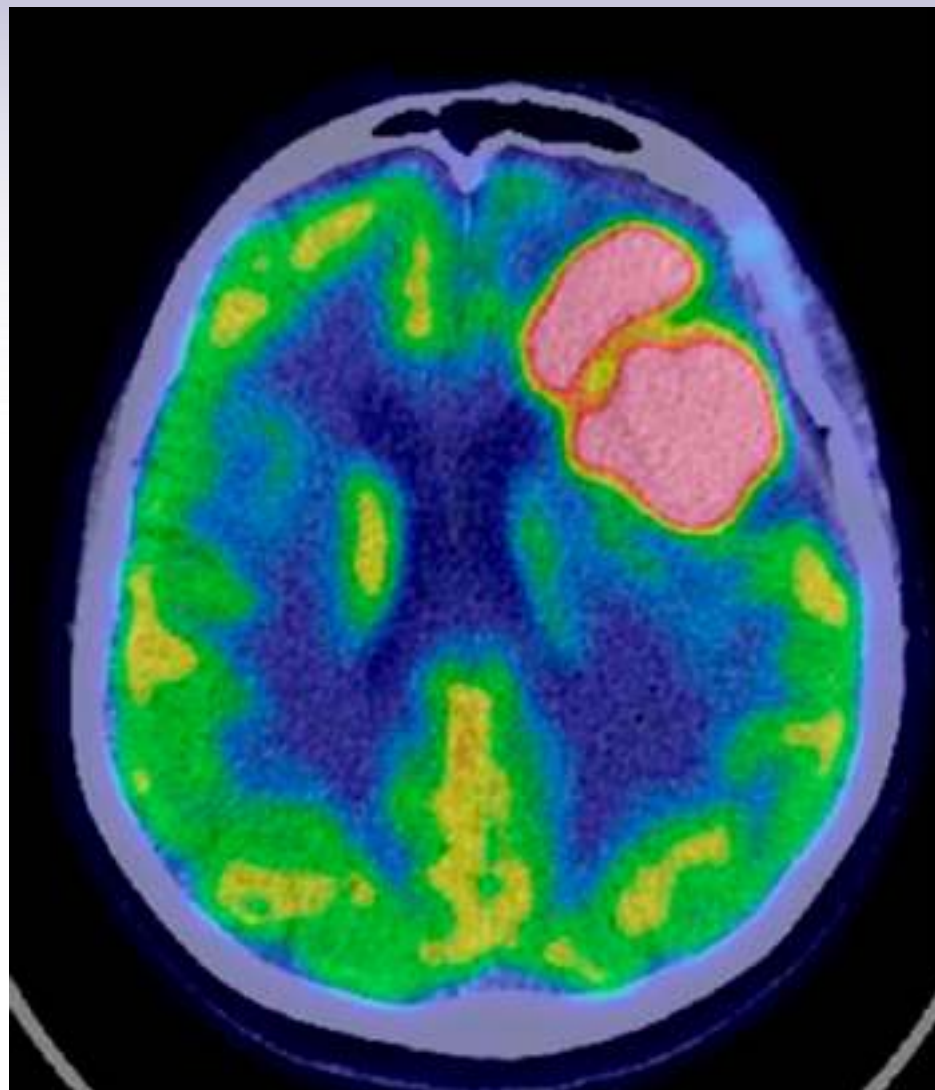
^{18}F -FDG





Leyes universales de escalamiento

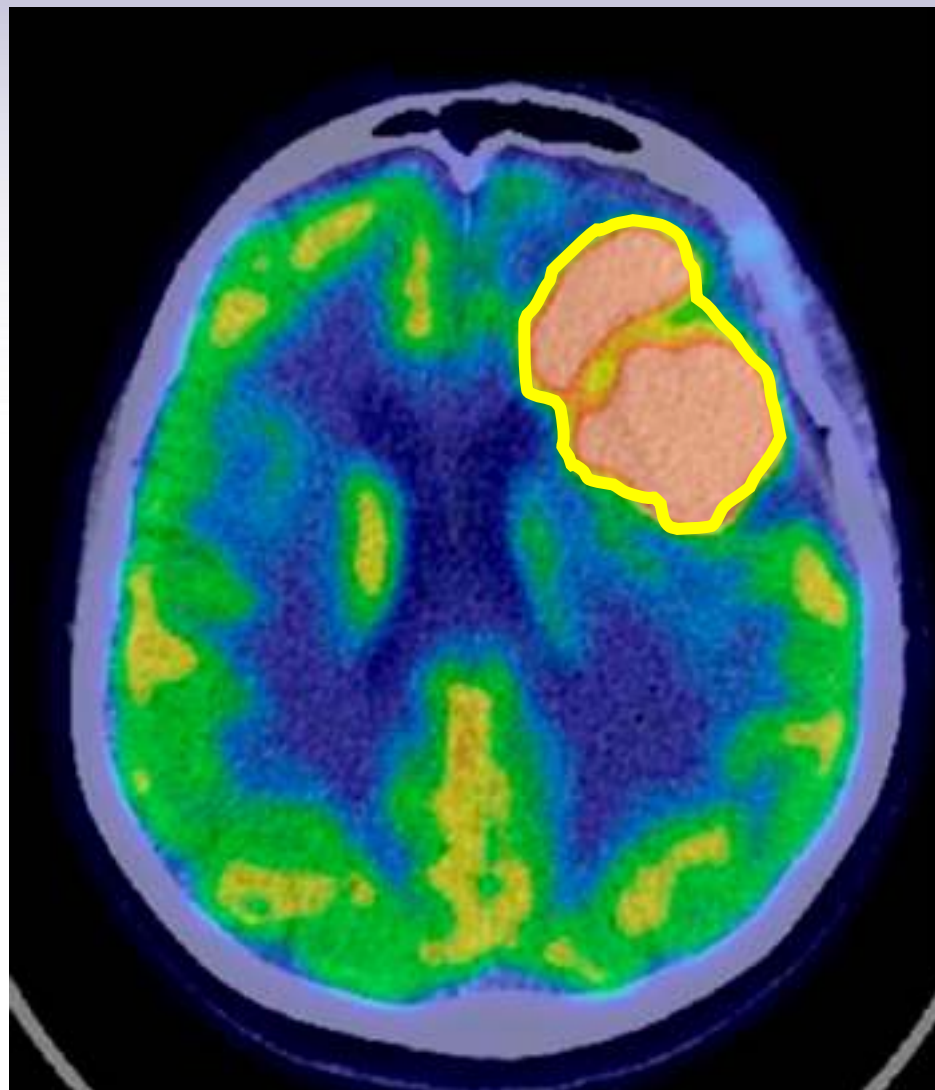
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Leyes universales de escalamiento

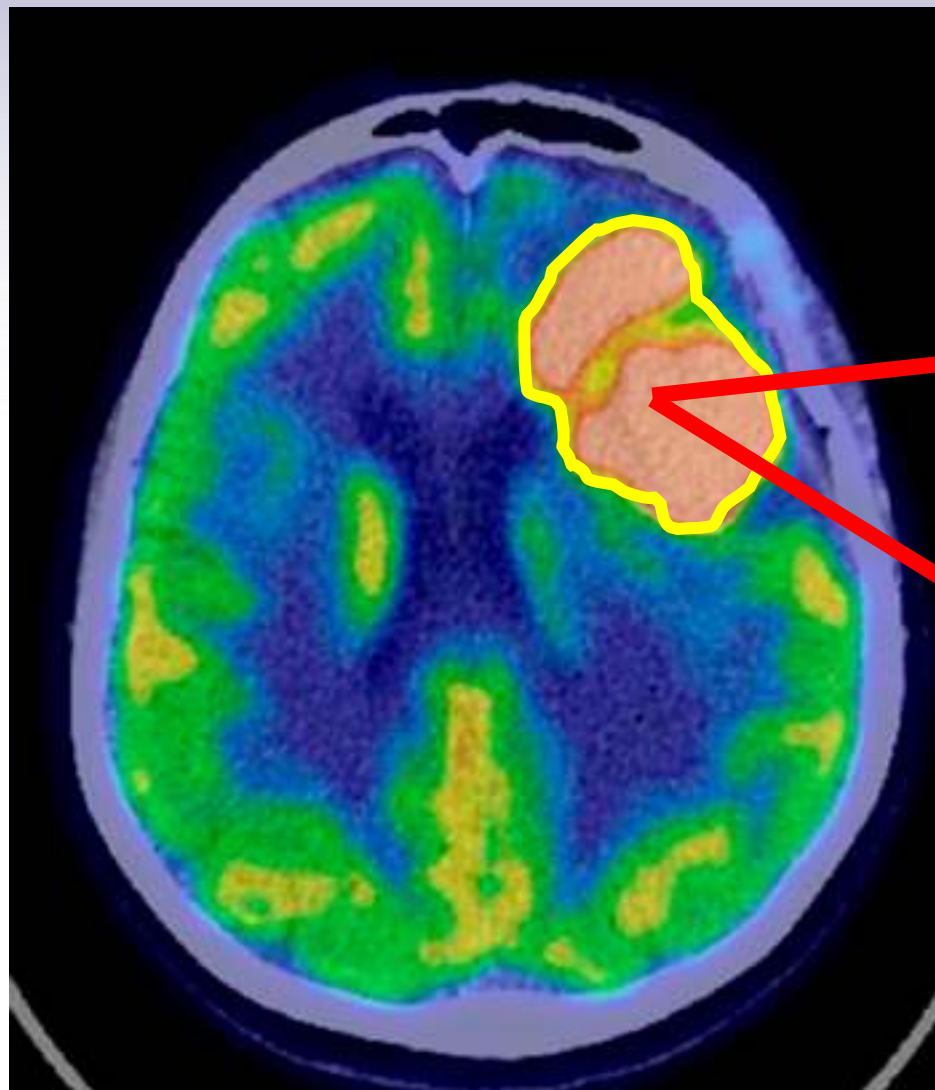
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Leyes universales de escalamiento

^{18}F -FDG

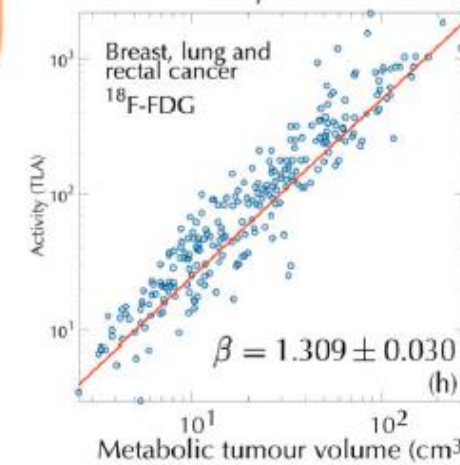
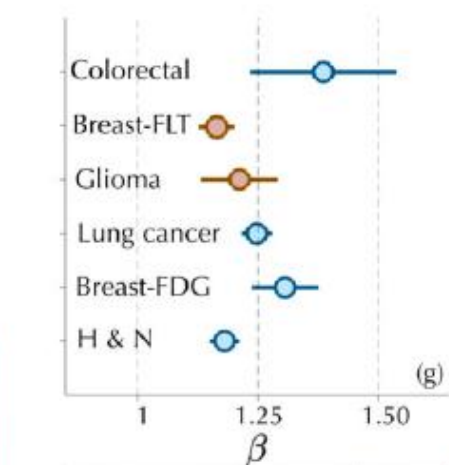
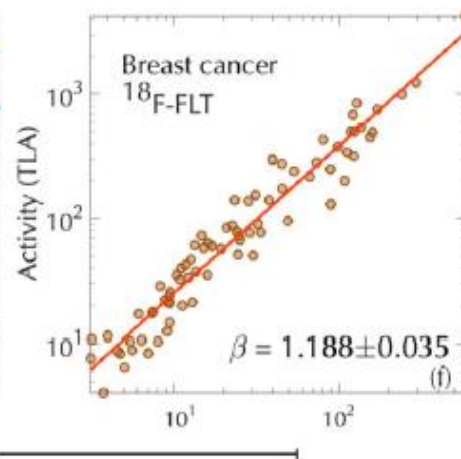
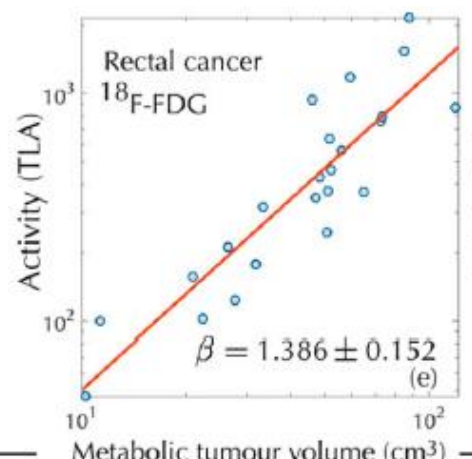
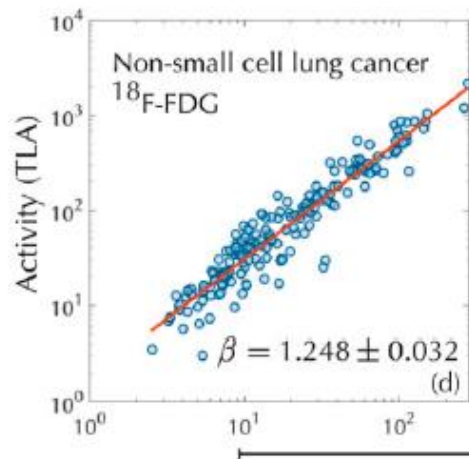
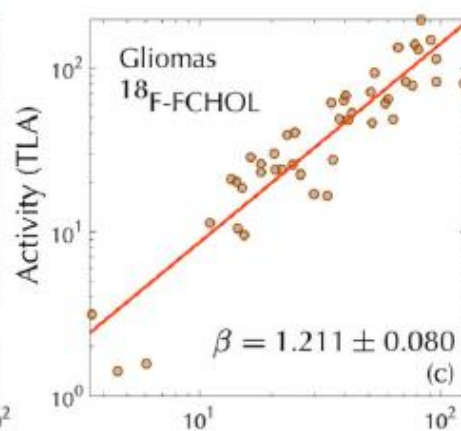
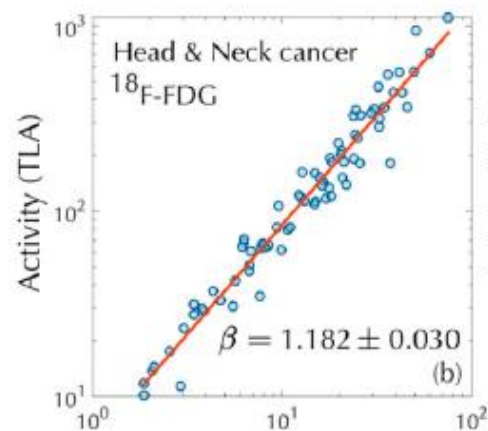
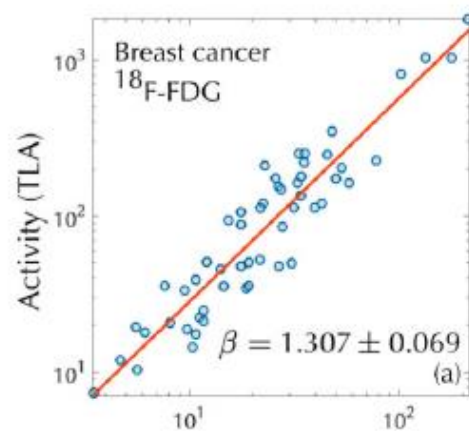


$$TLA = \sum_{v_i \in V} v_i \times SUV_i$$

$$MTV = \sum_{v_i \in V} v_i$$

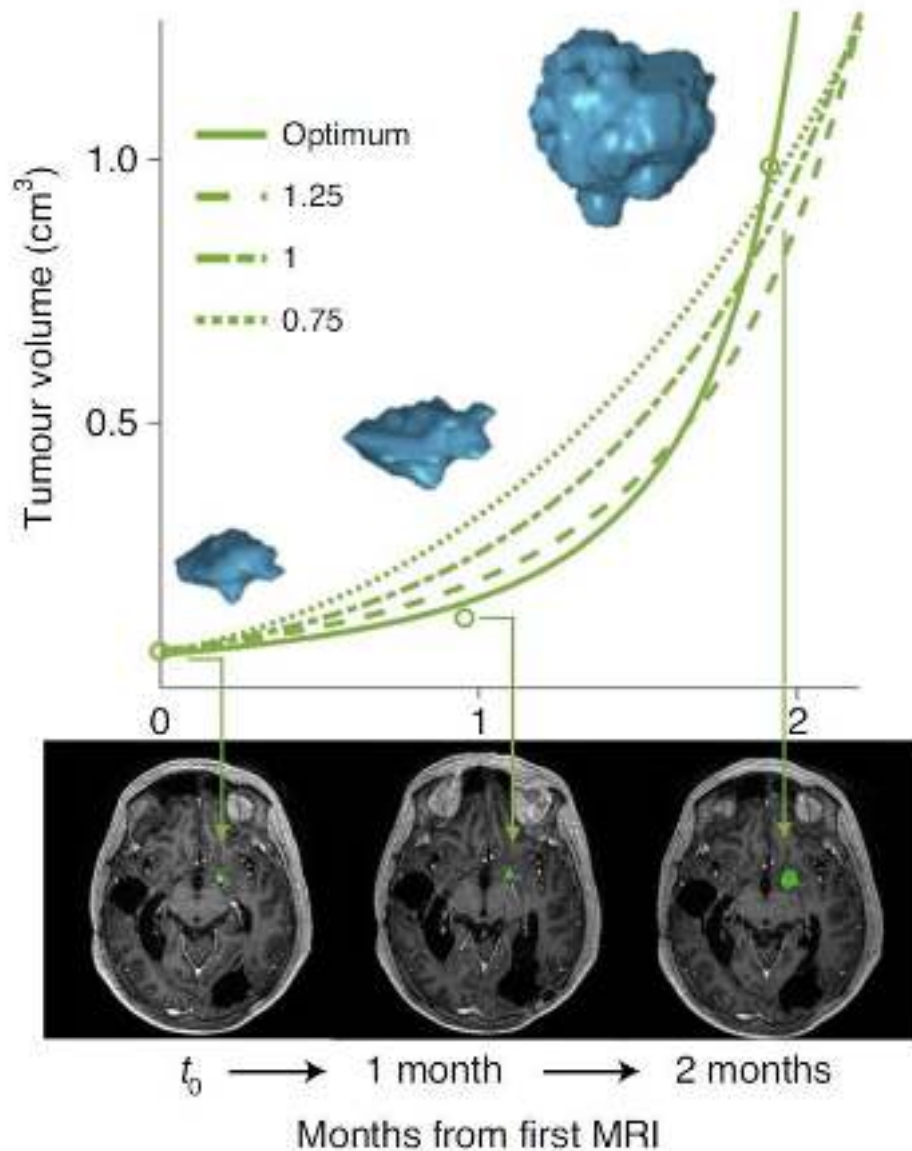


Leyes universales de escalamiento





“Explosión del volumen”



$$B = aV + b \frac{dV}{dt}$$

$$\frac{dV}{dt} \approx \alpha V^\beta$$

$$\beta > 1$$

$$t_{crit} = t_0 + \frac{V_0^{1-\beta}}{\alpha(\beta - 1)}$$

West, G. B., Brown, J. H. & Enquist, B. J. A general model for ontogenetic growth. *Nature* 413, 628–631 (2001).



“Explosión del volumen”. Caso general.

$$z(t) = V^{1-\beta}$$

$$\frac{dV}{dt} = -\gamma V + \alpha V^\beta \quad \rightarrow \quad \frac{dz}{dt} = (1-\beta)(\alpha - \gamma z)$$

$$V(t) = \left[\frac{\alpha - \left(\alpha - \gamma V_0^{1-\beta} \right) e^{\gamma(\beta-1)(t-t_0)}}{\gamma} \right]^{\frac{1}{1-\beta}}$$

$$t_{crit} = t_0 + \frac{1}{(\beta-1)\gamma} \log \left(\frac{\alpha}{\alpha - \gamma V_0^{1-\beta}} \right)$$



$$\psi_{a,b}(t) = \frac{1}{\sqrt{a}} \psi \left(\frac{t-b}{a} \right)$$

$$x_a(t) = \int_{\mathbb{R}} WT_{\psi} \{x\}(a, b) \cdot \psi_{a,b}(t) db$$

$$WT_{\psi} \{x\}(a, b) = \langle x, \psi_{a,b} \rangle = \int_{\mathbb{R}} x(t) \psi_{a,b}(t) dt = \frac{1}{\sqrt{a}} \int_{\mathbb{R}} x(t) \psi \left(\frac{t-b}{a} \right) dt$$

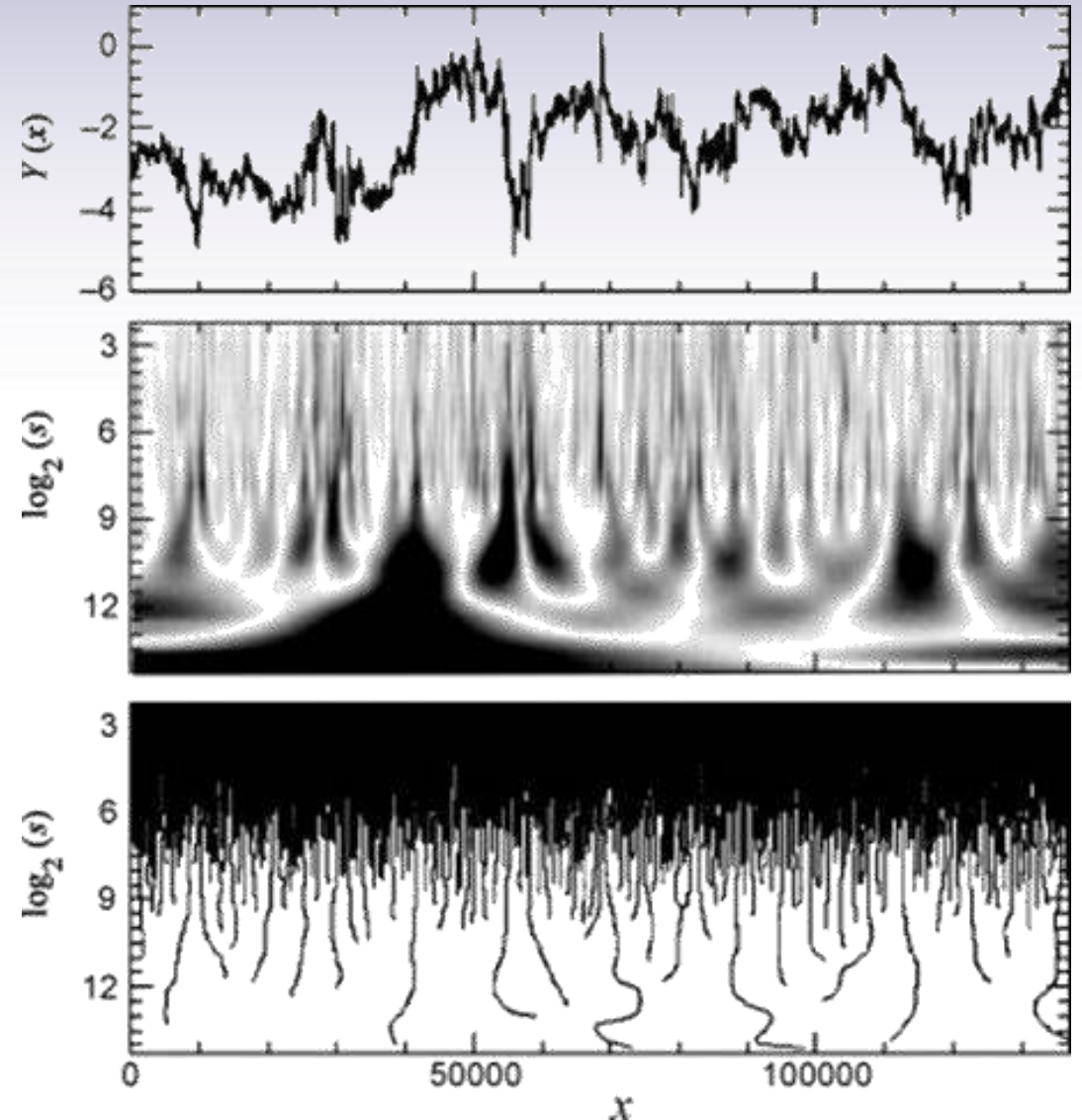


Método de los módulos máximos de la transformada de ondícula (wavelet).

$$Z_q(a) = \int |WT_\psi\{x\}(a, x)|^q dx$$

$$Z_q(a) = \sum_{l \in L(a)} \left(\sup_{(x, \hat{a}) \in l} |WT_\psi\{x\}(\hat{a}, x)|^q \right)$$

$$Z_q(a) \sim a^{\tau(q)}$$





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