A RANDOM NETWORK MODEL FOR LIVING CELL PLASTICITY

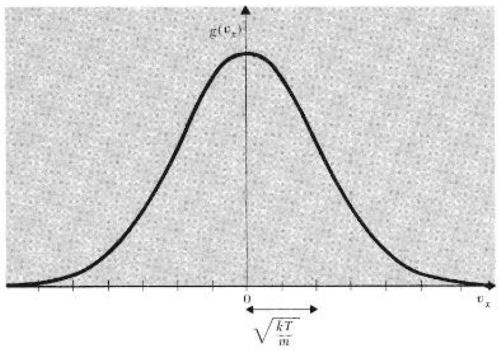
Stefano Polizzi

PhD student, University of Bordeaux

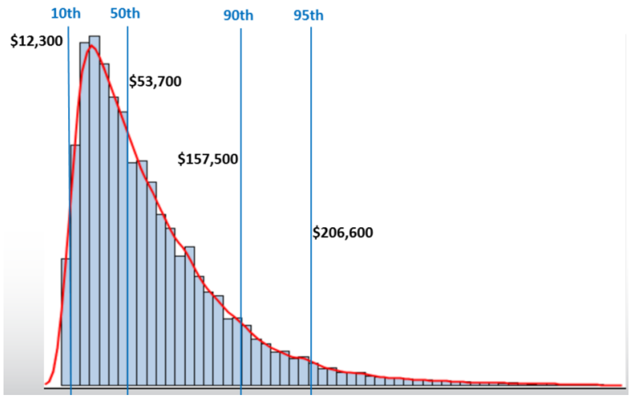
Supervisors A. Arneodo & F. Argoul

ISINP, Lake Como, 29/07/2019

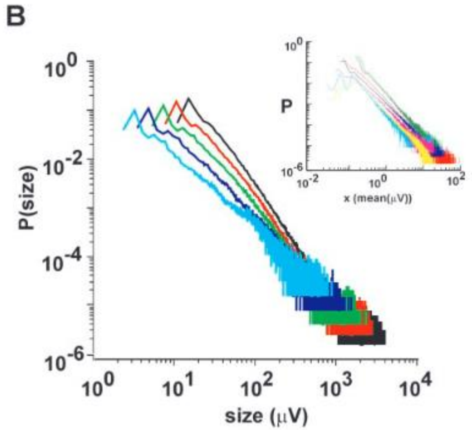
Introduction



F. Reif, 2009, *Fundamentals of Statistical and Thermal Physics*



Source U.S. Bureau, Current Population Survey, 2015



From Beggs, J. M., & Plenz, D. (2003). Neuronal avalanches in neocortical circuits. Journal of neuroscience, 23(35), 11167-11177.

- Criticality ⇨ power laws (*e.g.* Ising model)
- Self-organized criticality
- Scale free network and propagation of catastrophic events (Barabàsi)
- Spread of epidemics in a population
- Avalanches in solid and amorphous materials, avalanches in brain, energy released during an earthquake, forest fires

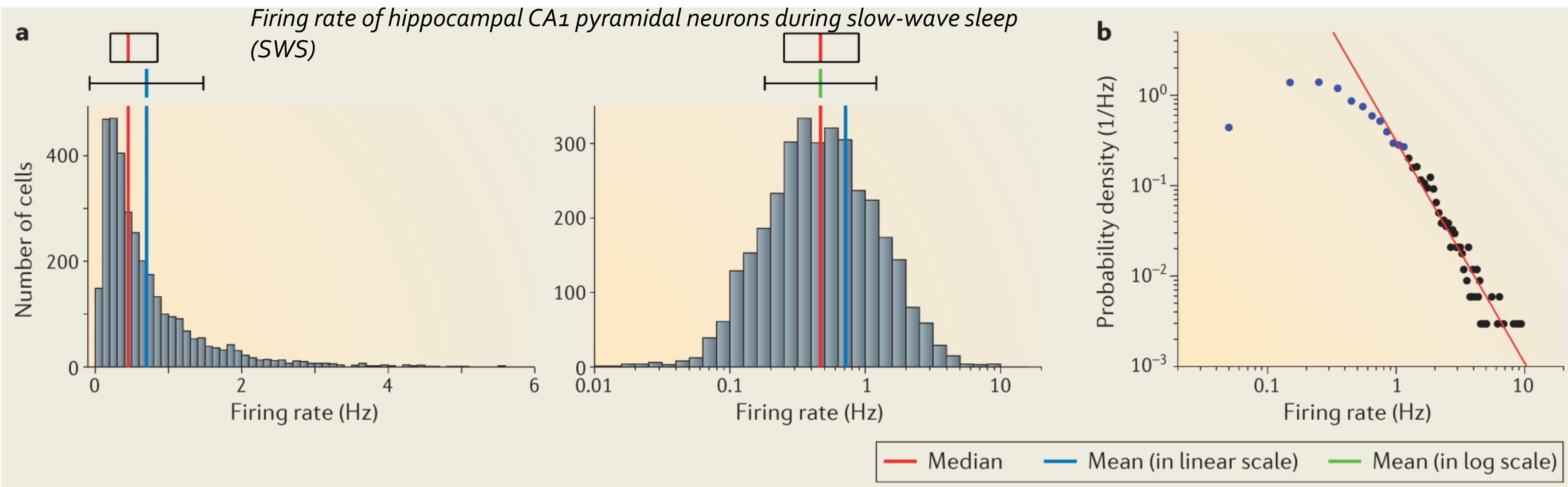
The «networked» world

NEUROSCIENCE OBSERVATIONS

Skewed distributions of anatomical and physiological features permeate nearly every level of brain logical organization:

* 10% of neurons are sufficient to deal with most situations
* the other 90% seem secondary

POWER LAW AVALANCHES ??



Buzsacki, **The log-dynamic brain: how skewed distributions affect network operations,** *Nat. Neurosci. 2014*

Ongoing Debate

In real data log-normal distributions are more common!

Broido, A. D., & Clauset, A. (2019). **Scale-free networks are rare**. *Nature communications*, *10*(1), 1017.

nature
COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-019-08746-5 OPEN

Scale-free networks are rare

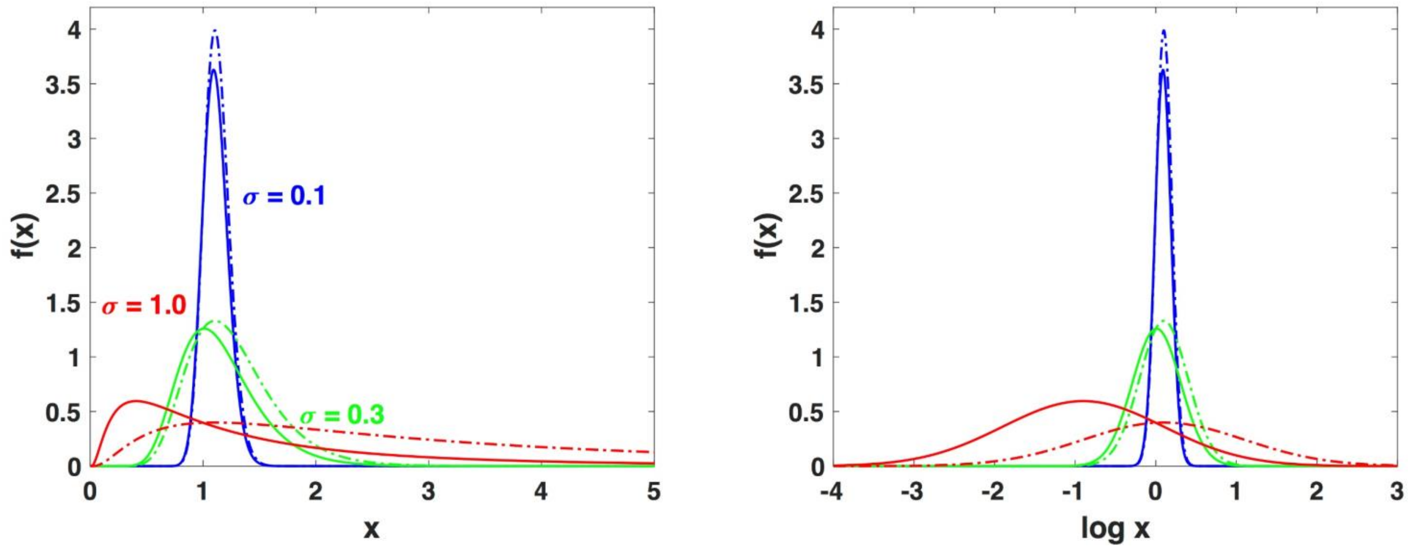
Anna D. Broido[1] & Aaron Clauset[2,3,4]

Real-world networks are often claimed to be scale free, meaning that the fraction of nodes with degree k follows a power law $k^{-\alpha}$, a pattern with broad implications for the structure and dynamics of complex systems. However, the universality of scale-free networks remains controversial. Here, we organize different definitions of scale-free networks and construct a severe test of their empirical prevalence using state-of-the-art statistical tools applied to nearly 1000 social, biological, technological, transportation, and information networks. Across these networks, we find robust evidence that strongly scale-free structure is empirically rare, while for most networks, log-normal distributions fit the data as well or better than power laws. Furthermore, social networks are at best weakly scale free, while a handful of technological and biological networks appear strongly scale free. These findings highlight the structural diversity of real-world networks and the need for new theoretical explanations of these non-scale-free patterns.

Focus on the log-normal distribution

f(x): probability density function
of a log-normally distributed random variable

$$f(x) = \begin{cases} \dfrac{1}{\sqrt{2\pi}\sigma x} \exp\left\{-\dfrac{(\ln x - \mu)^2}{2\sigma^2}\right\} & x > 0 \\ 0 & x \leq 0 \end{cases}$$



The log-normal distributions are skewed to larger x values
These distributions have been first explained by:

- *The law of proportionate effect (Gibrat 1930-31)*

Modelling fat tail distributions

POWER-LAW

- Pareto (1896) distribution
- Density function

$$P[X \geq x] = \left(\frac{x}{k}\right)^{-\alpha}$$

$$\rho(x) = \alpha k^{\alpha} x^{-\alpha-1}$$

$0 < \alpha \leq 2$ Infinite variance

$\alpha \leq 1$ Infinite mean

Self-Organized Criticality (P. Bak, 1996)
Scale-Free Networks (A. Barabasi, 1999)

LOG-NORMAL

- Density function

$$\rho(x) = \frac{1}{\sqrt{2\pi}\sigma x} e^{-(\ln x - \mu)^2/2\sigma^2}$$

$$\begin{aligned} \text{mean} &= e^{\mu + 1/2\sigma^2} \\ \text{median} &= e^{\mu} \\ \text{variance} &= e^{2\mu+\sigma^2}(e^{\sigma^2} - 1) \end{aligned}$$

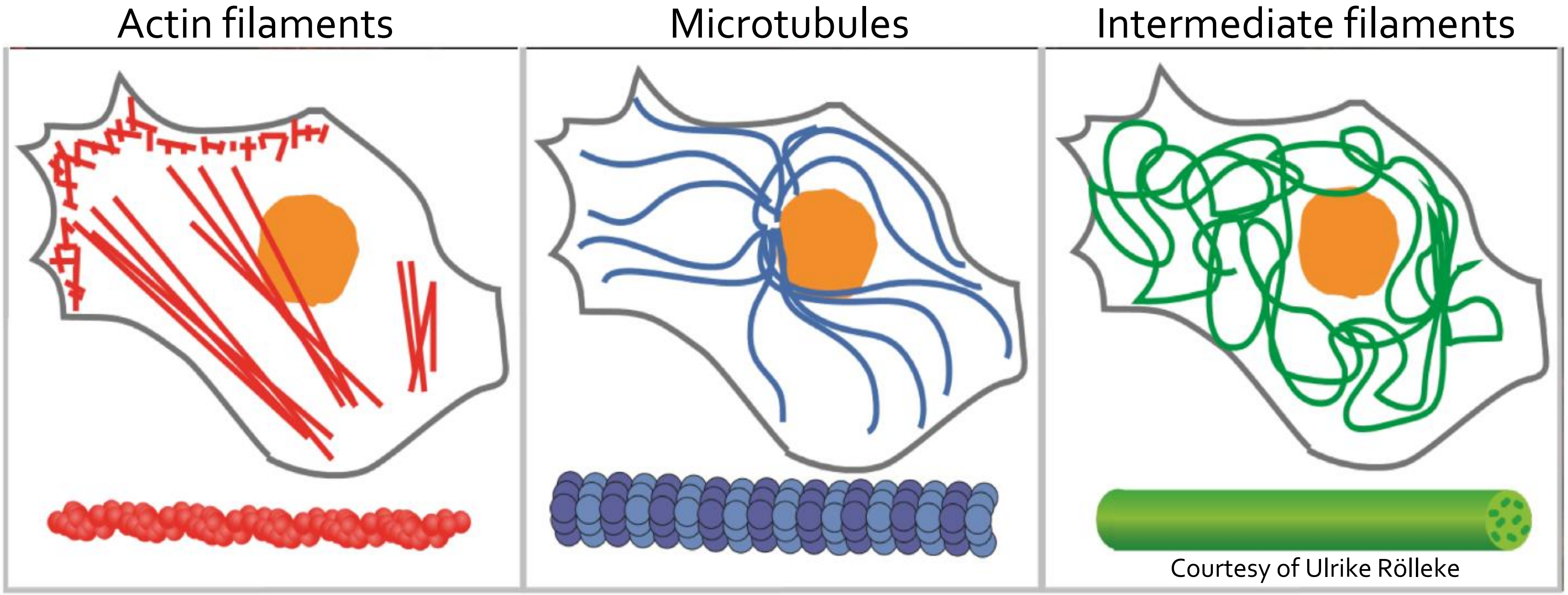
Fully Developed Turbulence
(Kolmogorov & Obukov, 1962)
Economics (F. Black & M. Scholes, 1973)

FROM GIBRAT (1931) to KESTEN (1973)

$$X_t = a_t X_{t-1} + b_t$$

Random growth process (a_t, b_t positive random variables)	Conditions for stationary distribution
• Branching process: $a_t = a$	$\lvert a \rvert < 1$
• Multiplicative process: $b_t = 0$	Non stationary distribution
• Kesten process: a_t (multiplicative) + b_t (additive)	$E[\ln a_t] < 0$ $\quad E[a^{\alpha}] = 1$ $\rho(x)$ has a a power law tail α

The cell and the cytoskeleton



$l_p > 10\mu m$

Cell shape
Cell mechanics
Migration

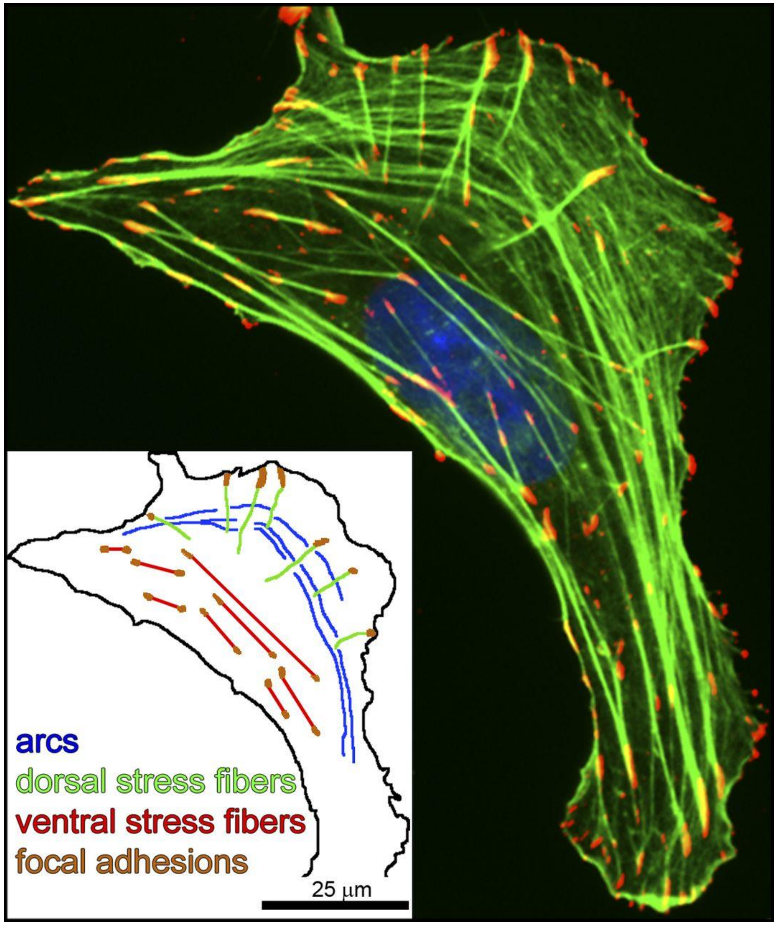
$l_p > 1mm$

Mitosis
Transport

$l_p > 1\mu m$

Very soft
Cell-type specific

Actin cytoskeleton is crucial

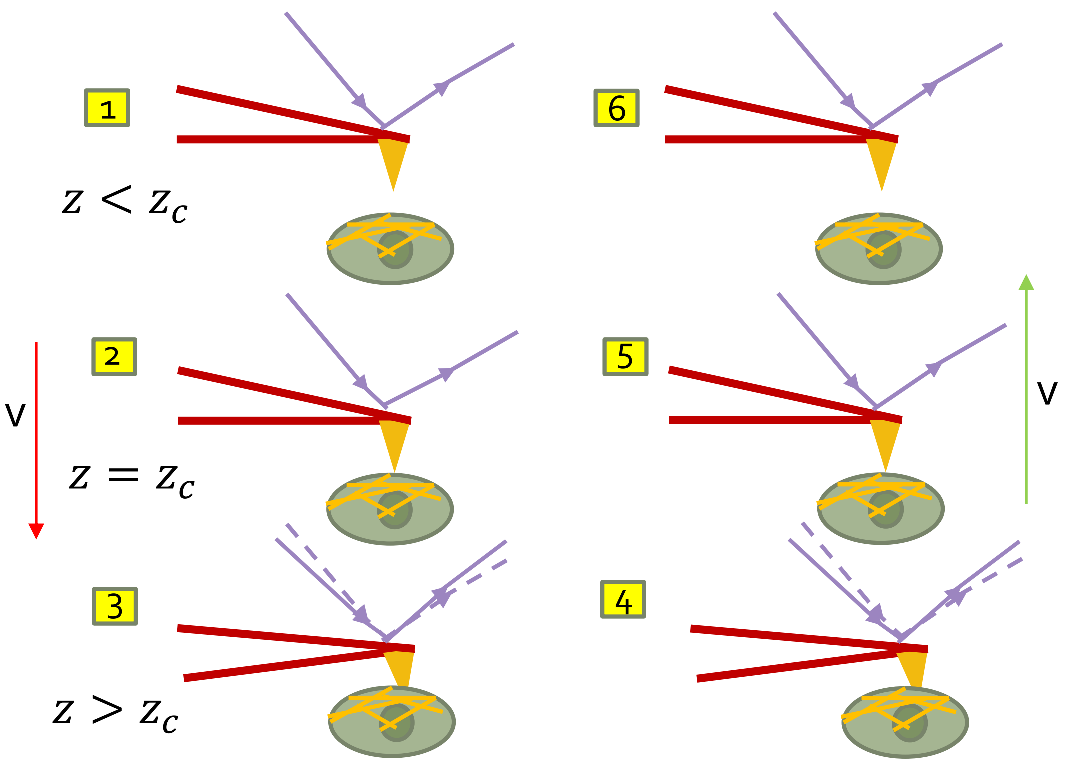


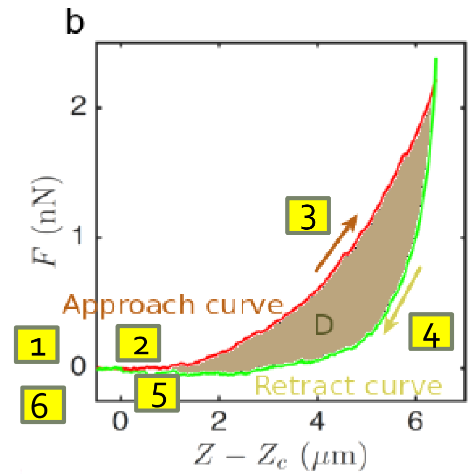
Burridge, K., & Wittchen, E. S. (2013). The tension mounts: stress fibers as force-generating mechanotransducers. *J Cell Biol*, *200*(1), 9-19.

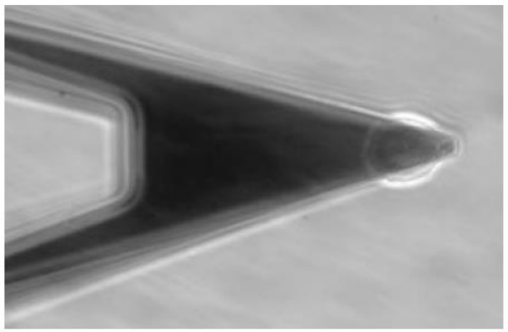
- a parallel arrangement of long ($10\ \mu$m) fibers
- a tightly connected meshwork of short ($<1\ \mu$m) filaments. The latter presented a 100 nm average mesh size
- Thickness actin filaments $\simeq 7\ nm$

Rheology experiments on cells

Atomic Force Microscope (AFM) working principle

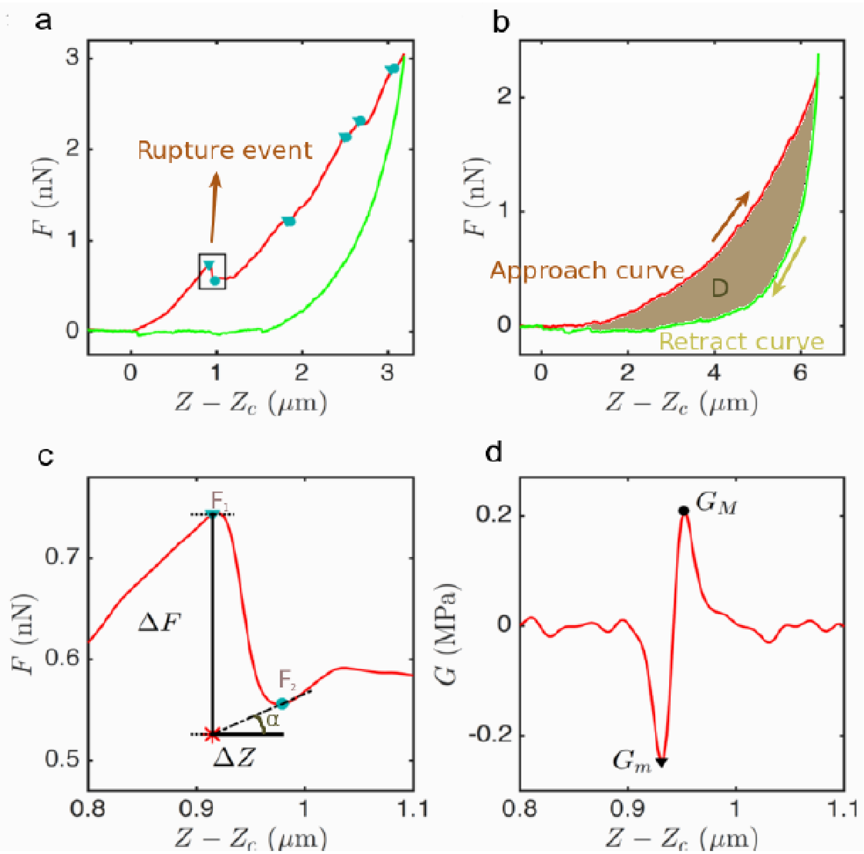






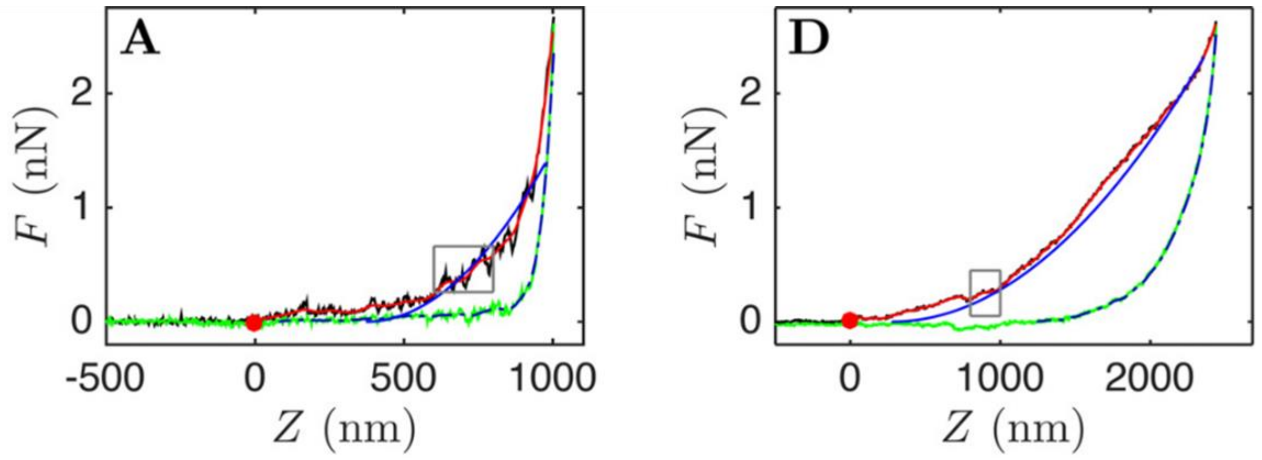
A sharp AFM tip indents a living immature hematopoietic cell (CD34+) and records the reaction to external constraints

Singular events in FICs



- Global Young modulus E:
  $$F(z) \propto E(Z - Z_c)^2$$
- Force drop:
  $$\Delta F = F_1 - F_2 + \Delta Z \tan(\alpha)$$
- Released energy:
  $$E = \Delta F \, \Delta Z$$

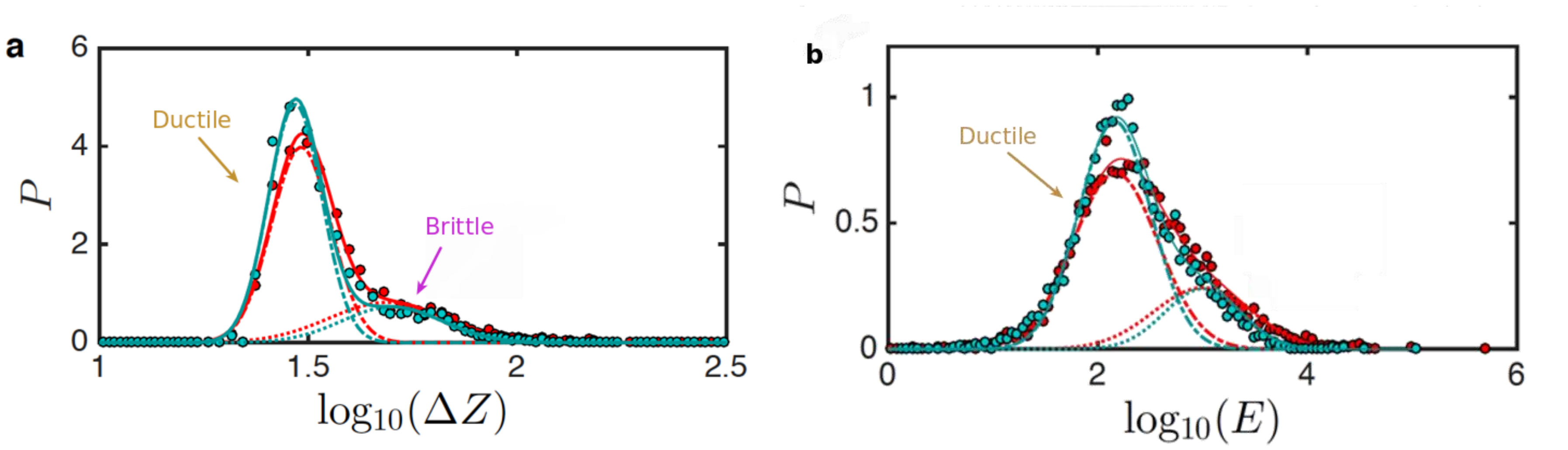
Cancer cells *vs* healthy cells



Local ruptures in FICs of CD34+ cells from patients with Chronic Myelogenous Leukemia compared to healthy ones

	Cancer (CML)	Healthy
Cells	$N_c = 49$	$N_h = 60$
FICs	$n_c = 1301$	$n_h = 1671$
Events	$\mathcal{N}_c = 6161$	$\mathcal{N}_h = 6765$
Event density	$\delta = 2.1\ \mu m^{-1}$	$\delta = 1.4\ \mu m^{-1}$

Probability distributions



Two separated populations both with **log-normal** statistics for ΔZ and E:

1. Ductile regime: reversible in experiment time scales → **fluid-like regime**
($\Delta Z_d \simeq 30\ nm$, $E_d \simeq 200\ k_B T$)
2. Brittle regime: non-reversible, loss of connectivity → **solid-like regime**
($\Delta Z_d \simeq 50\ nm$, $E_d \simeq 1300\ k_B T$)

S. Polizzi *et al*, The new journal of physics (2018)

Random network model

The model proposed is based on a random Erdős–Rényi network (cytoskeleton):

Nodes ⇨ actin filaments

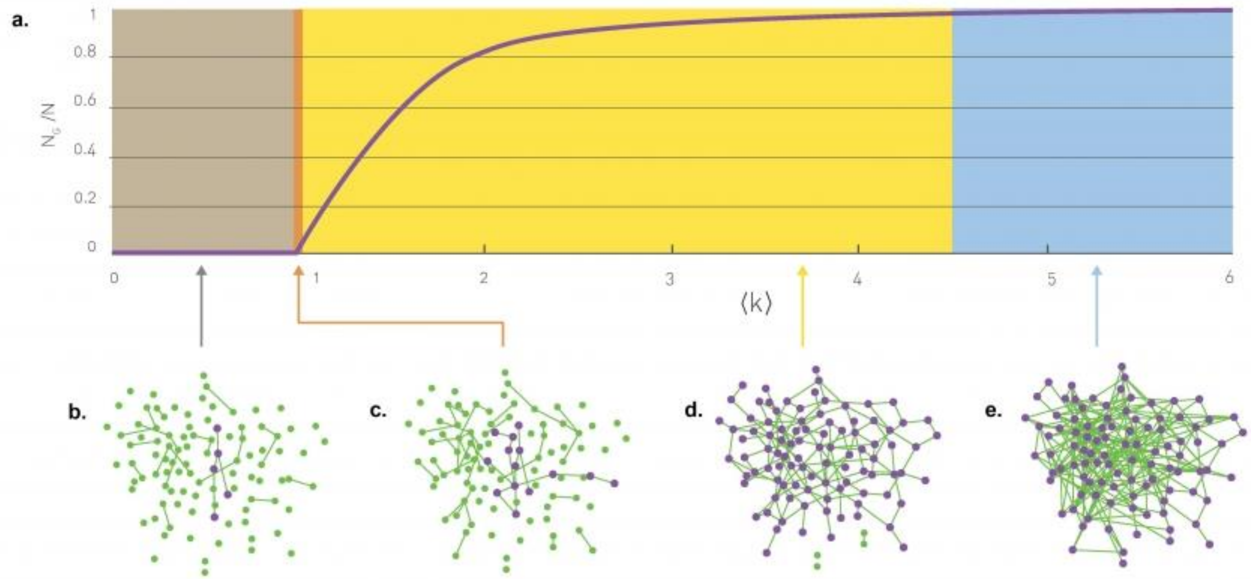
Links ⇨ crosslinkers

The network is defined by N number of nodes and p_l probability of connection

$$p_k = \binom{N}{k} {p_l}^k \, (1 - p_l)^{N-k} \qquad \langle k \rangle = p_l(N-1)$$

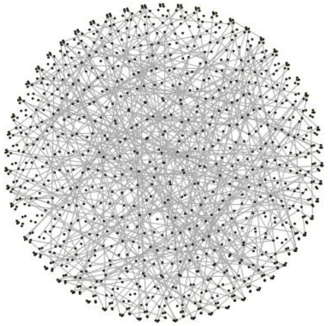
k degree of the network

Random network giant cluster

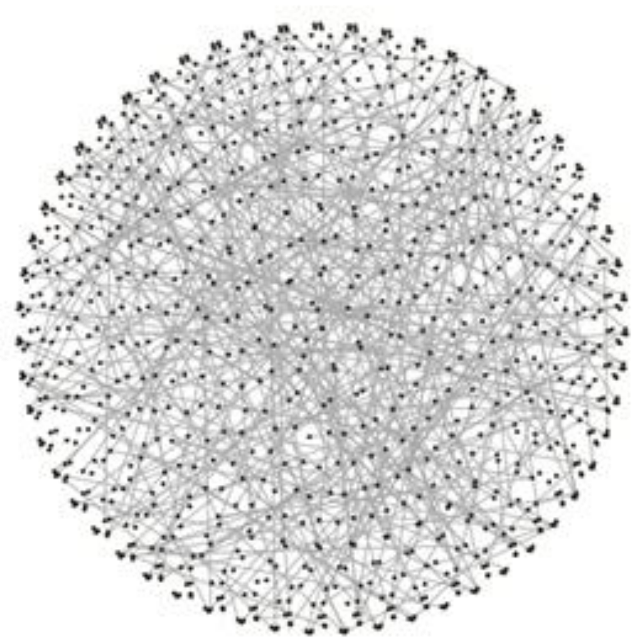


From The Network Science Book A. L. Barabási

For the cytoskeleton network $k \in [3,10]$



Cytoskeleton model

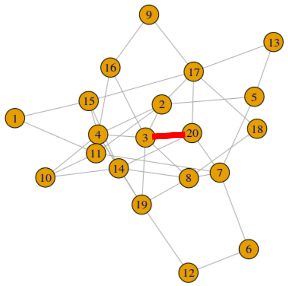


For the cytoskeleton network $k \in [3,10]$, $N = 10000$

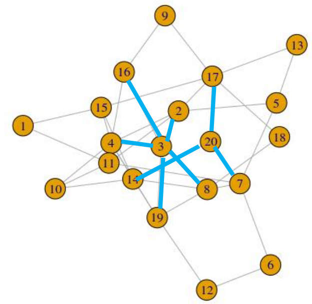
NO METRICS ⟹ ONLY INTERACTIONS MATTER

Over this network avalanches are driven with a certain rule

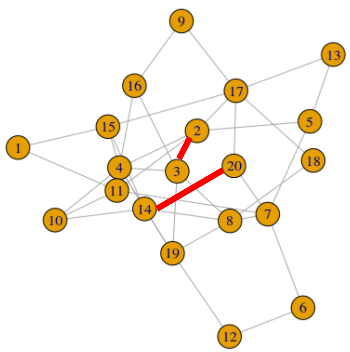
Rupture avalanche process



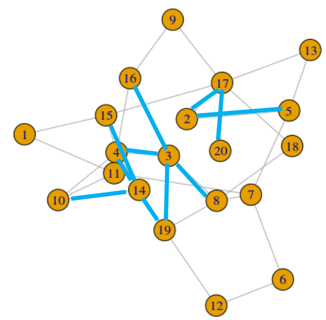
Break a randomly chosen link (here 3 ⟷ 20)



Look at all the neighbors



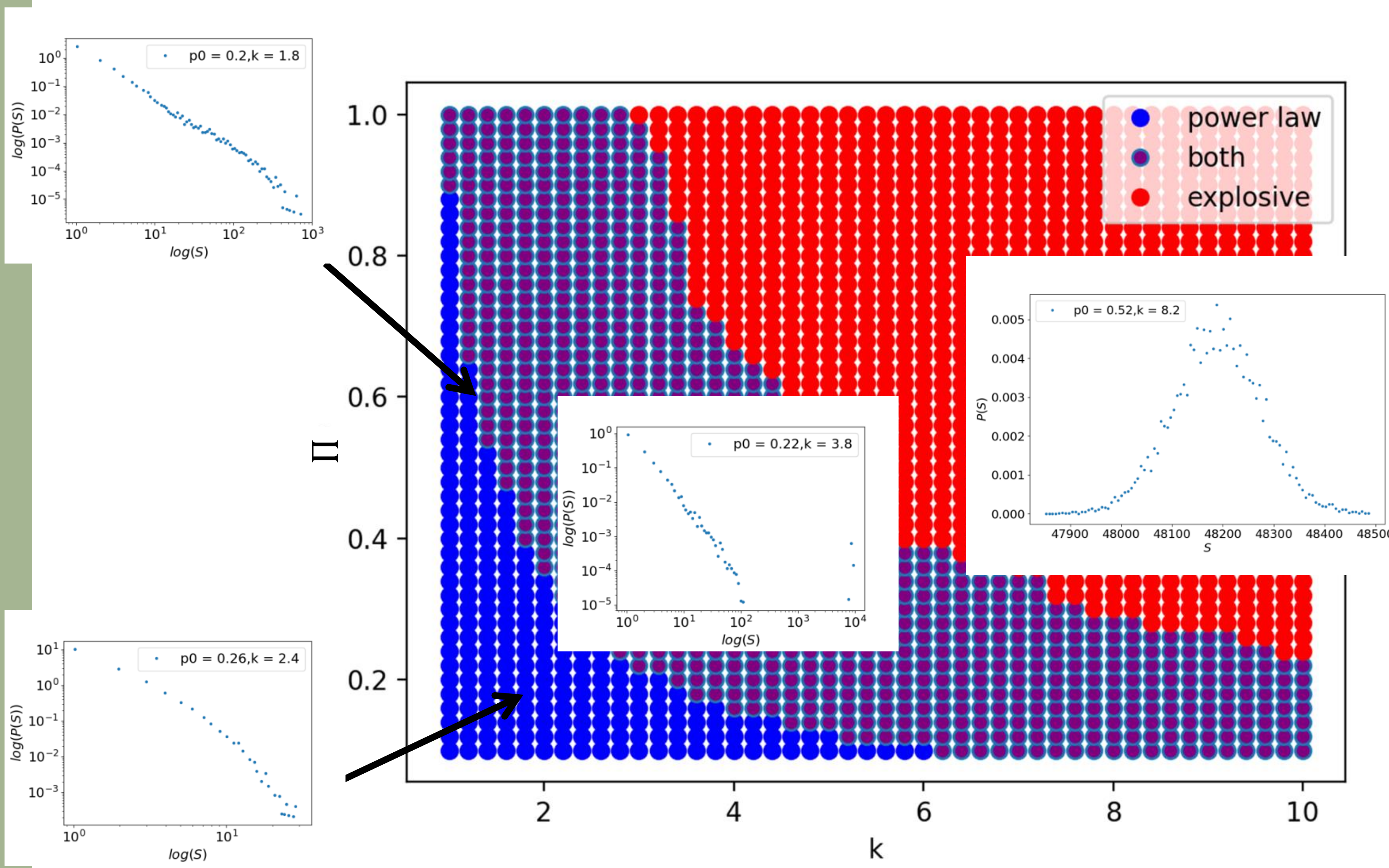
Break each of them with probability $\Pi_k(t=0)$: 14 2 break.



Take the broken links, look at all the neighbors from both sides and break with probability $\Pi_k(t+1)$

t: innovations times = times when rupture events induce other rupture events

First results (Π = constant)



Introducing fractional viscoelastisity

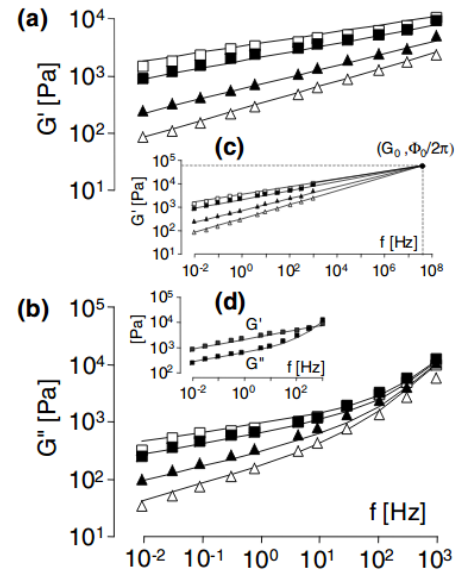
If we look at local perturbations of a system the complex shear relaxation modulus is

$$G_g^*(\omega) = G'(\omega) + iG''(\omega) \sim \omega^{\alpha}$$

- If material is purely elastic $\alpha = 0$ $\Rightarrow$ $G_g^*(\omega) = G_{const} = E/3$
- If material purely liquid $\alpha = 1$ $\Rightarrow$ $G_g^*(\omega) = iG''(\omega) \sim i\omega$

For cells α is fractional $\in [0{,}25 - 0{,}3]$

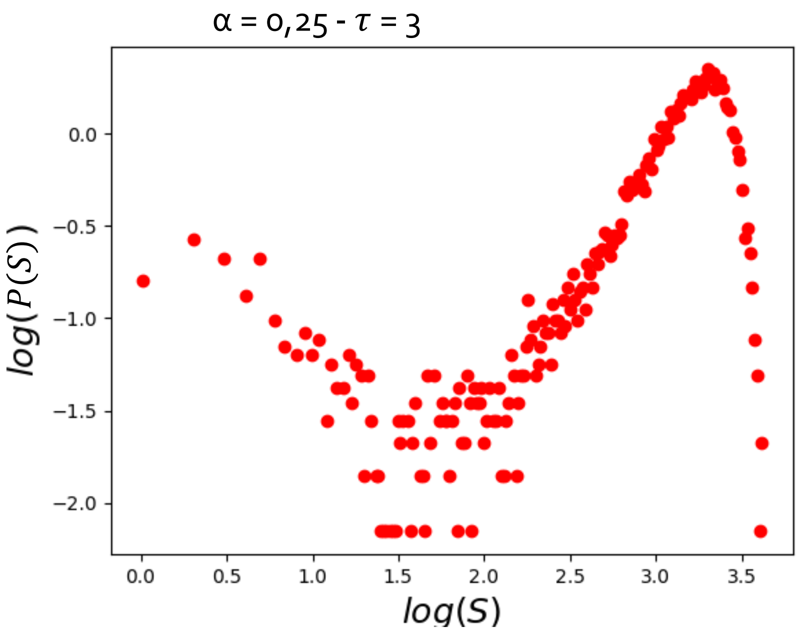
$$\Rightarrow \quad \Pi \longleftrightarrow G_g \propto e^{-\left(\frac{t}{\tau}\right)^{\alpha}/\Gamma(\alpha+1)}$$

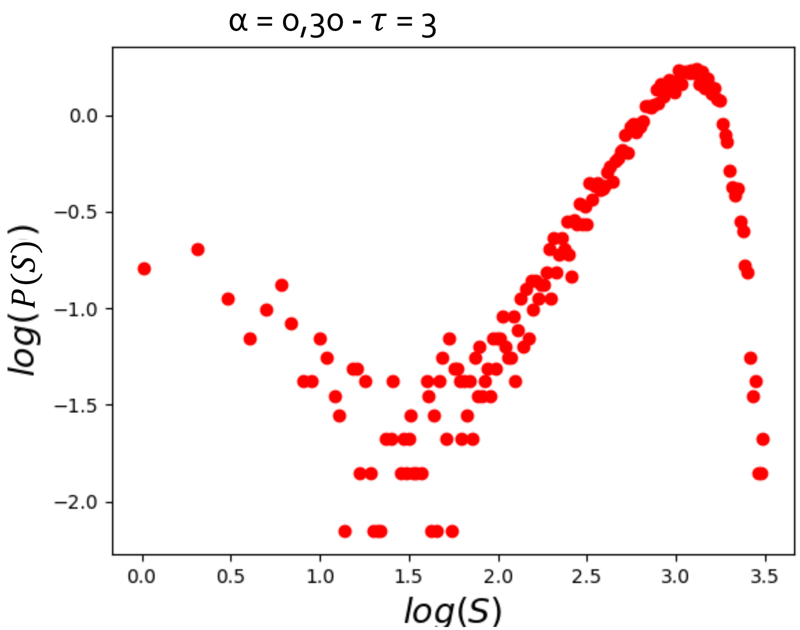


Fabry, Ben, *et al.* (2001). Scaling the microrheology of living cells. *Physical review letters*, *87*(14), 148102.

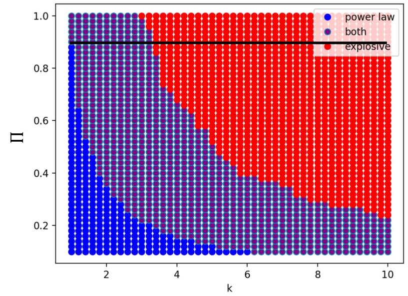
Size distribution

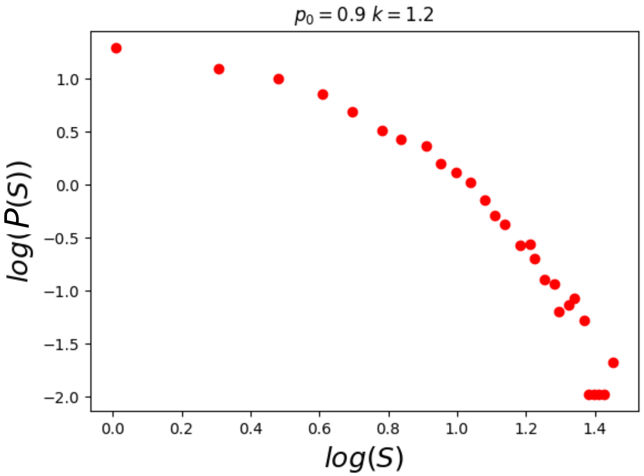
Streched exponential results for $\Pi = p_0 e^{-\left(\frac{t}{\tau}\right)^{\alpha}/\Gamma(\alpha+1)}$

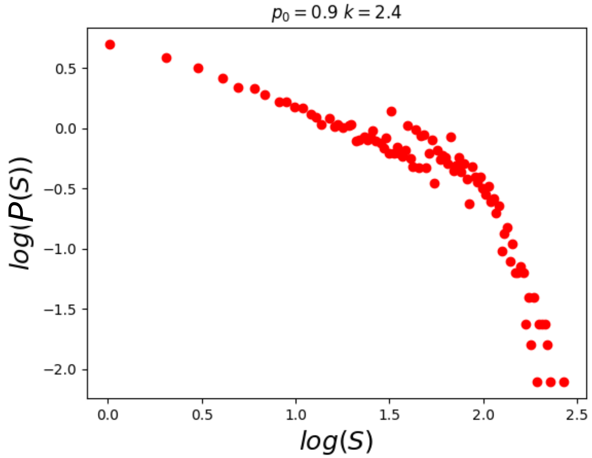


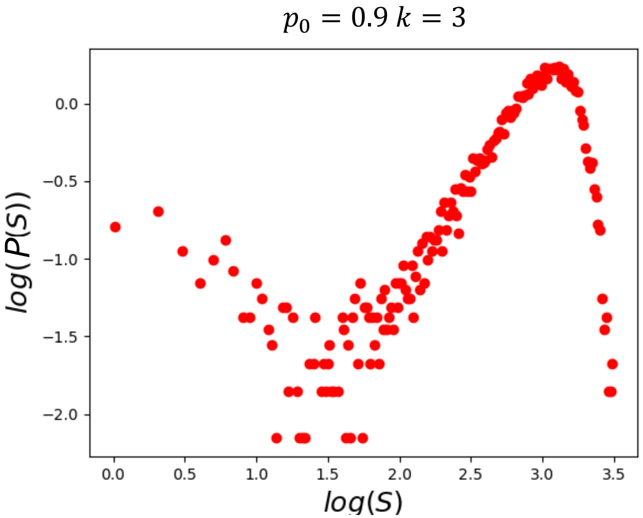


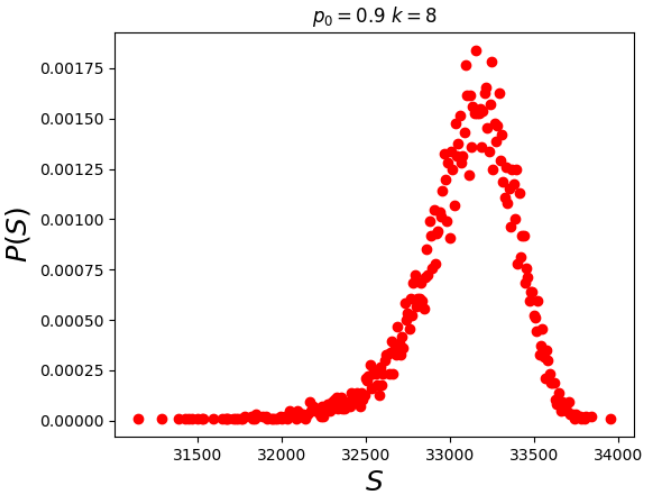
What about the rest of phase diagram?





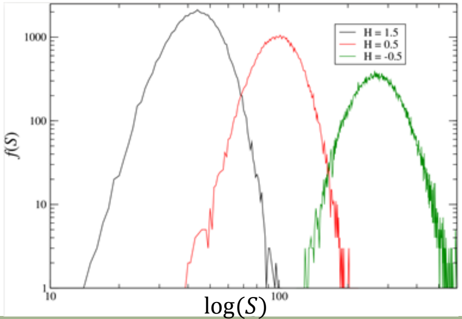






Conclusions and perspectives

- **Memories** and cooperative effects lead to **log-normal** distributions in the avalanche sizes, and this is crucial in cells and maybe for emergence of log-normal in **nature**
- We have models for log-normal kind avalanches on random networks but also on random regular graphs (RFIM)
- Type of phase transitions, analytical computation of the critical threshold…
- The same avalanches statistics is observed in other types of cells (myoblasts, yeast cells)
- Find this phase transition in hydrogel or cells avalanches (from power-law to log-normal), varying some experimental parameter (v, T, [$C_6H_{12}O_6$])



Acknowledgments

Oh putain, ça sent bon!

B. Laperrousaz

F. E. Nicolini

V. Maguer Satta A. Arneodo F. Argoul F. J. Perez-Reche

E. Harté A. Guillet

E-mail: stefano.polizzi@u-bordeaux.fr
francoise.argoul@u-bordeaux.fr

Questions?

Thank you!

On correlations

Beaulieu's theorem: with a particular structure of correlations the sum of log-normal variables is still log-normal in the limit $n \to \infty$

The covariance should be:

- $E\left[(Y_i - m_i)\left(Y_j - m_j\right)\right] = \lambda^2 \quad \forall\, i, j \; and \; \lambda \neq 0$

Surprisingly the covariance matrix is

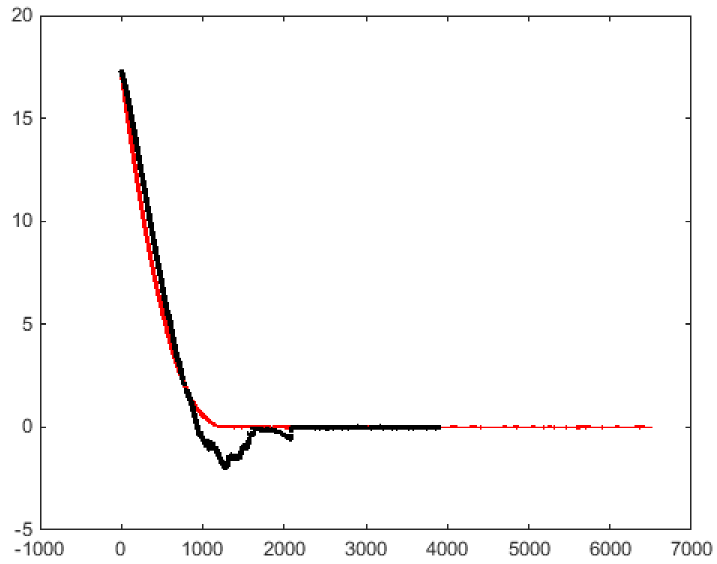
- $E\left[(Y_i - m_i)\left(Y_j - m_j\right)\right] = {\lambda_j}^2$ if $j < i$

where $Y_i = \ln(\Delta E_i)$ and λ_j function of distribution parameters but

ONLY DEPENDING ON j

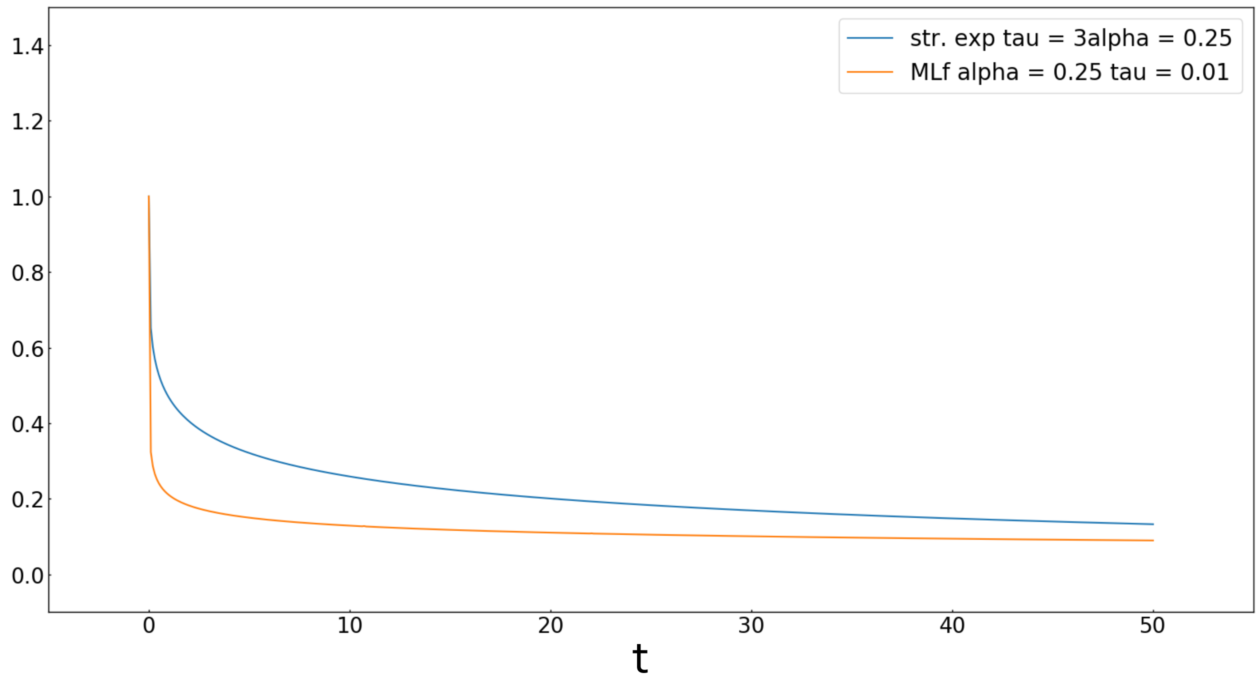
⇒ Generalization of Beaulieu's theorem to correlated data

No plastic rearrangement

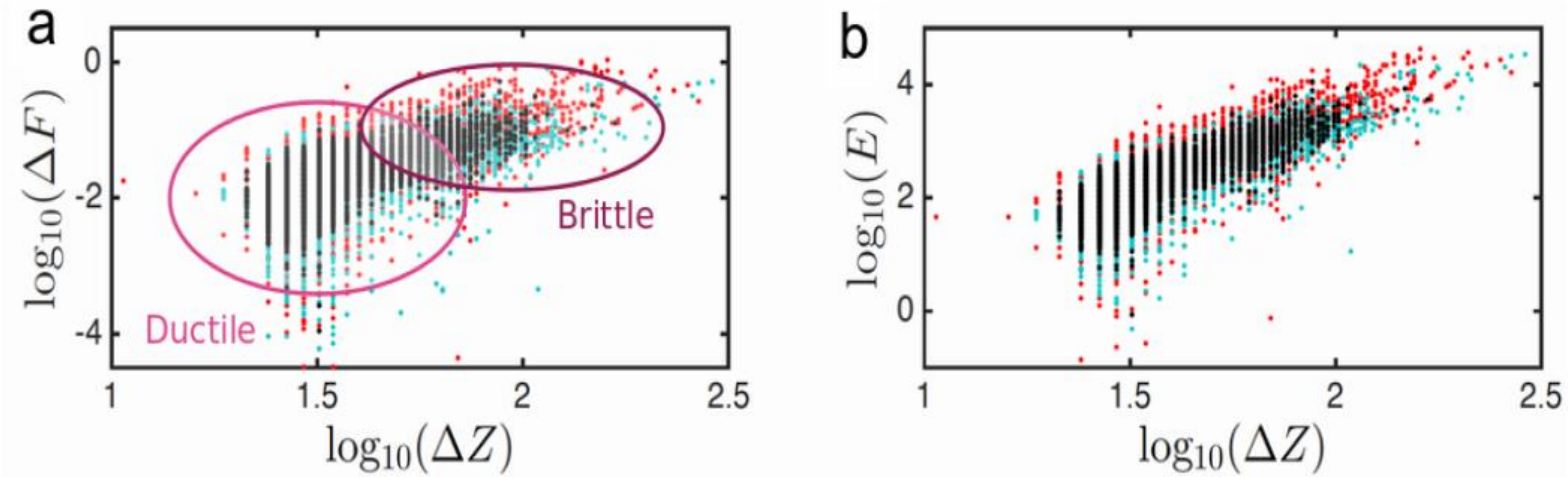


Maybe with Na-Alginate, pre-stressed networks?

Probability of breaking

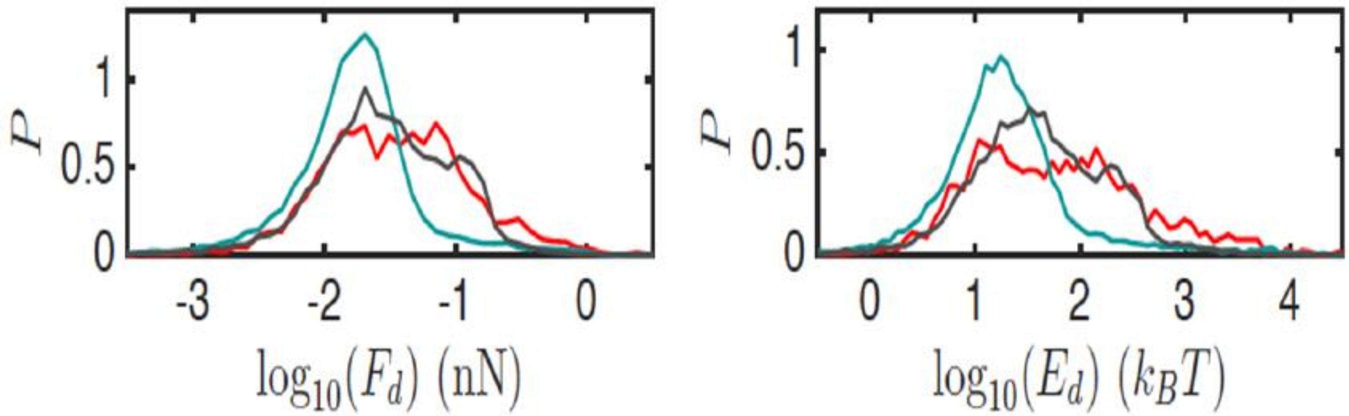


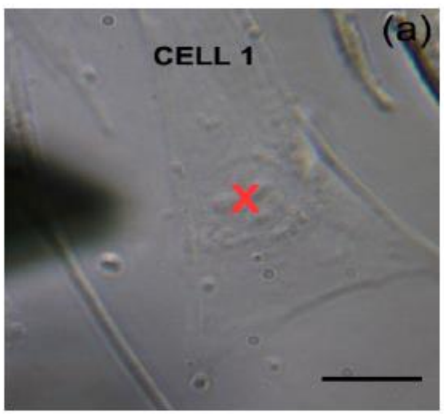
Brittle and ductile regimes



Correlation given by two clouds of events:

Generalization to other cells



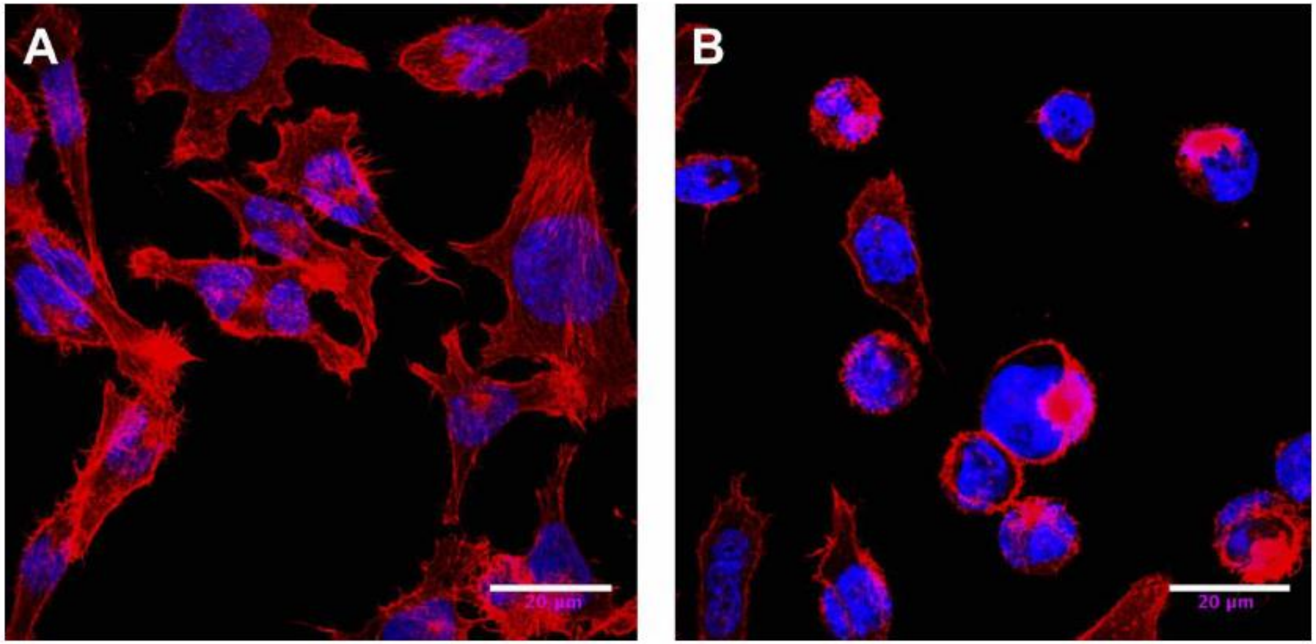


C2C12 myoblasts perinuclear actin stress fibers explain the brittle regime

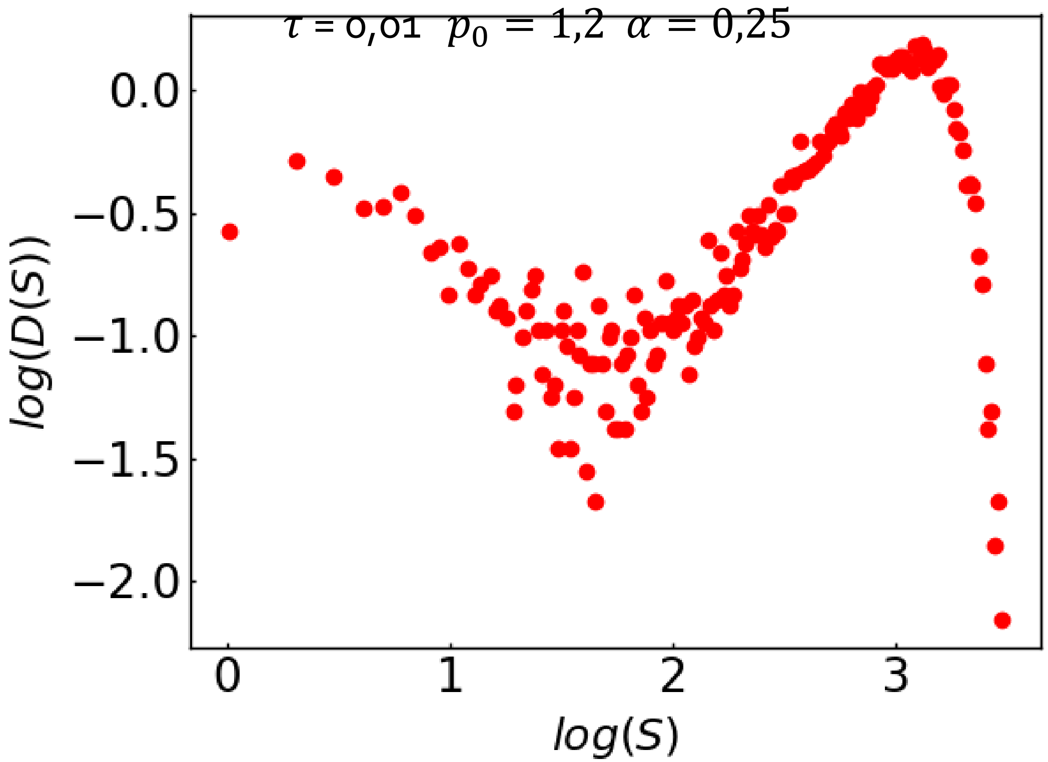
C2C12 myotubes no perinuclear actin stress fibers only the ductile regime

C2C12 myoblasts in ATP depleted culture medium ADP-myosin cross-links actin filaments in a freezed state (actin punctuate aggregates)

Fluorescence microscopy

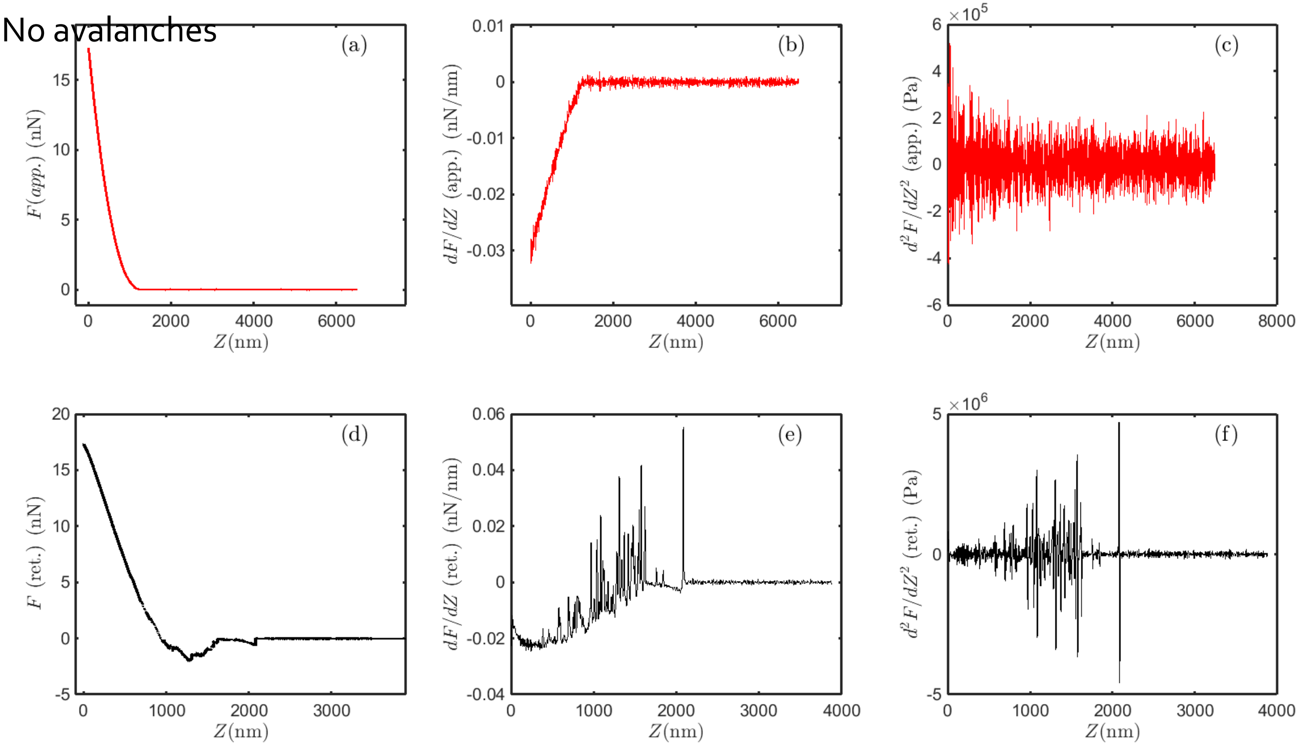


Preliminary results



FIC on a 40 kPa polyacrylamide gel

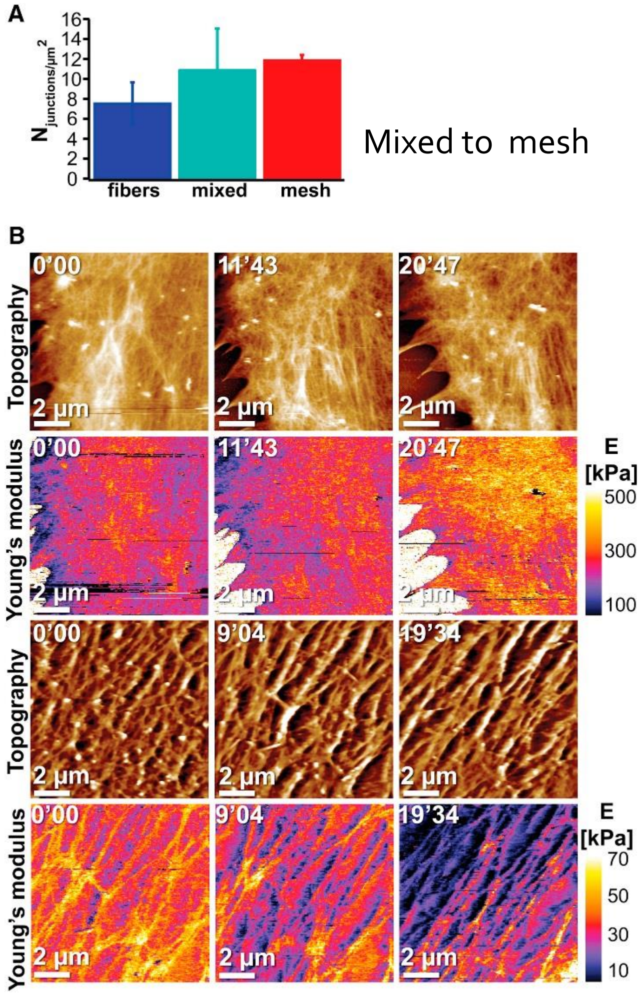
No avalanches



The actin cytoskeleton

Eghiaian, F., Rigato, A., & Scheuring, S. (2015). Structural, mechanical, and dynamical variability of the actin cortex in living cells. *Biophysical journal*, *108*(6), 1330-1340.

- cross-links between actin filaments and different cortex types by measuring the number of intersections between them through binary skeletonization of AFM topographs (~ 10)
- a parallel arrangement of long (10 μm) fibers
- a tightly connected meshwork of short (<1 μm) filaments. The latter presented a 100 nm average mesh size
- Thickness of actin filaments $\simeq 7\ nm$

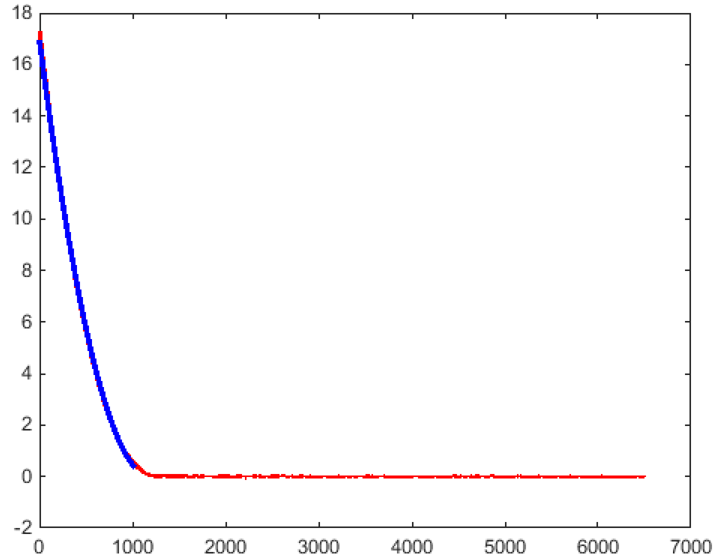


Mixed to mesh

Elastic fit

- $\sqrt{F} = 2\sqrt{\tan(\theta)/\pi(1-\nu)}\sqrt{G}\,(z - z_c)$ with $\theta = 11°$ and ν = 0,5

$E = 3G \simeq 69\ kPa$



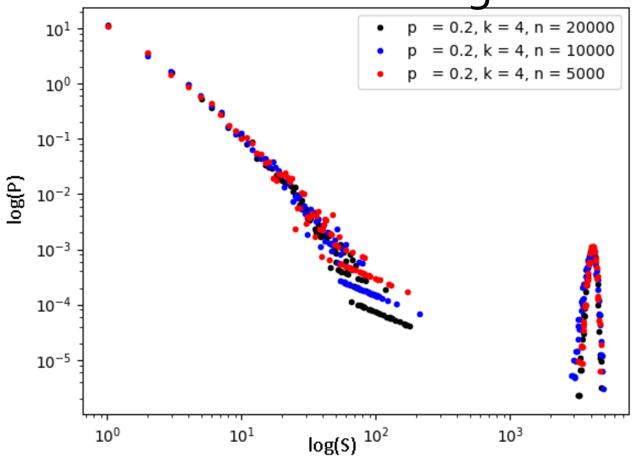
- Now p is varying like the Mittag-Leffler function:

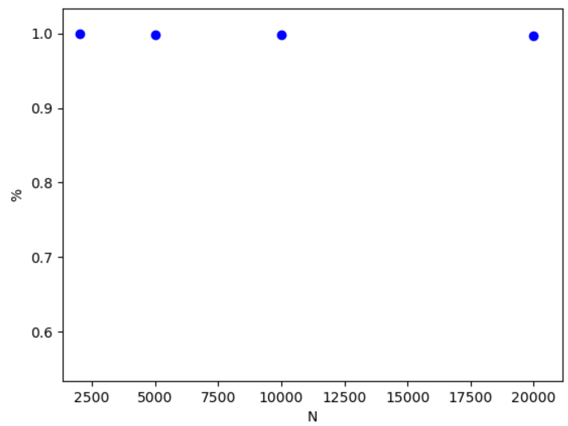
$$p_k^b(t) = \ p_0 \sum_{n=0}^{\infty} \left(-\left(\frac{t}{\tau}\right)^{\alpha} \right)^{n} / \Gamma(\alpha n + 1)$$

- α fixed at 0.25 so we have two parameters p_0 and τ

Finite size effects and statistical convergence

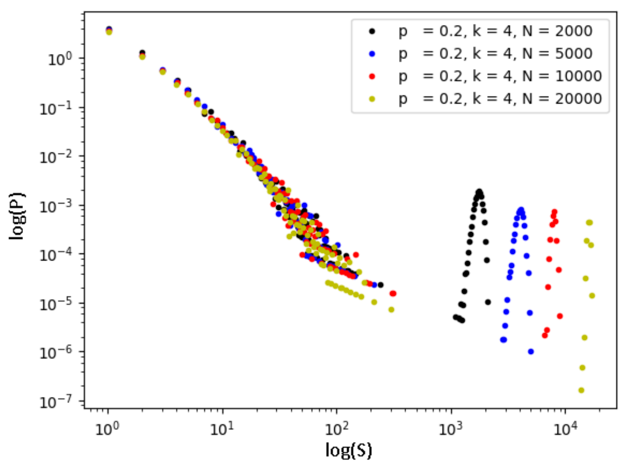
Statistical convergence

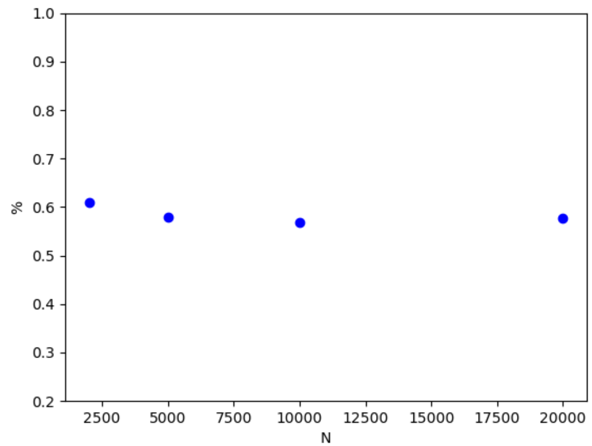




% of catastrophic events along purple- red boundary

Finite size effects

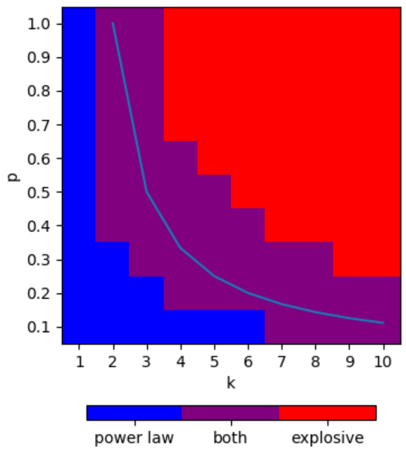




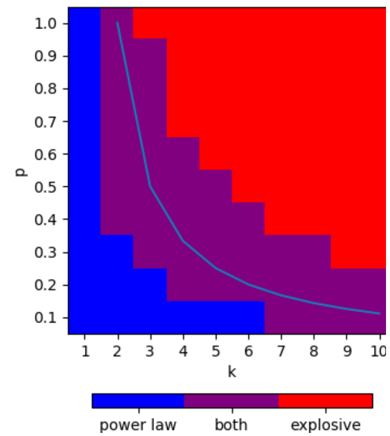
% of catastrophic events along blue-purple boundary

Finite size effects on the phase diagram

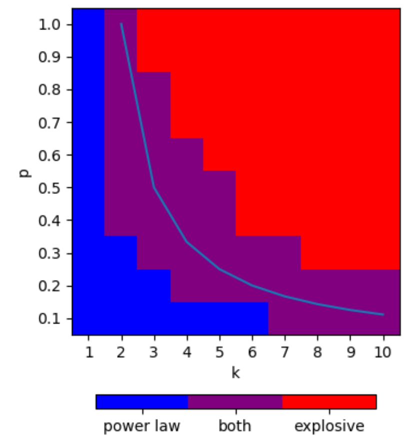
N = 5000



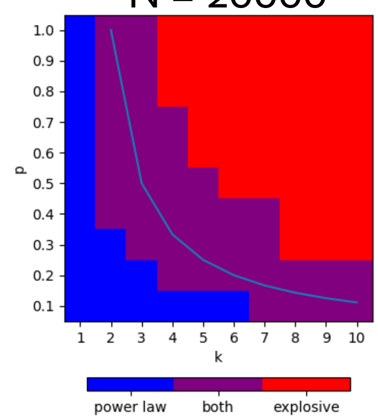
N = 2000



N = 10000



N = 20000



NO EFFECTS OF THE SIZE