# Why resting state functional connectivity must be restlessly dynamic?


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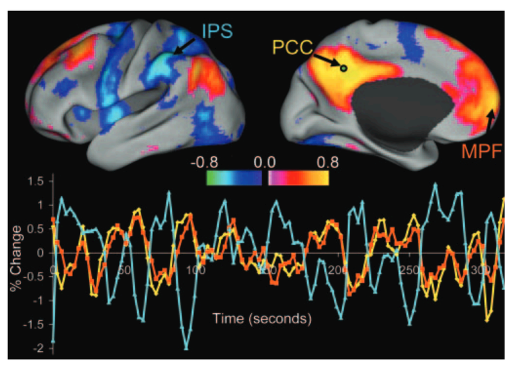
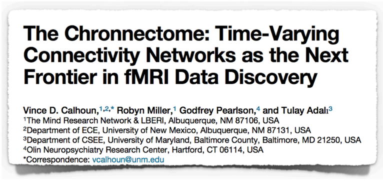
## Introduction

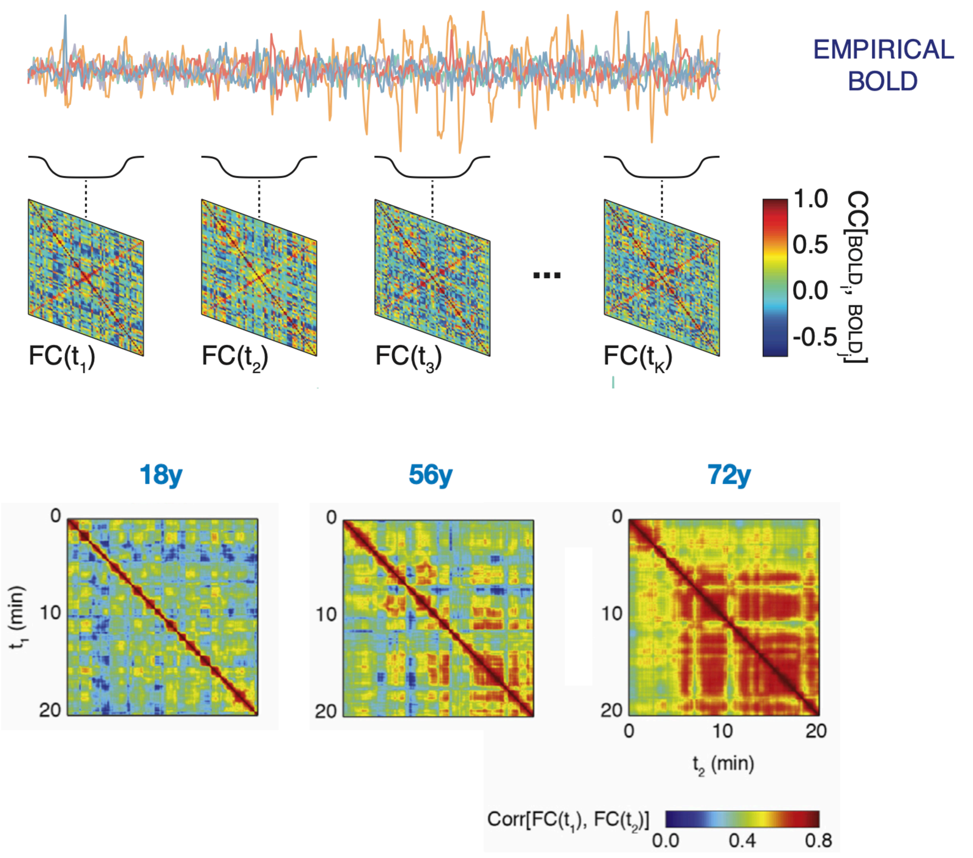
- **Functional connectivity** of the resting state describes patterns of correlation between distant regions working together
- Usually described as static, time-averaged network but it changes relentlessy through time as described by **dynamic Functional Connectivity (dFC)** analyses
- dFC fluidity is not only ubiquitous, it serves as **biomarker** of efficient cognitive performance and tracks different conditions (aging, pathology…)

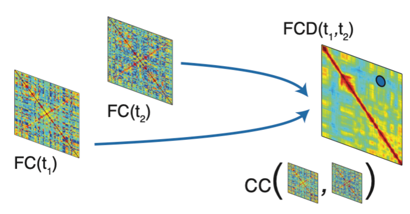



*Fox et al. (2005)*




*Calhoun et al. (2015)*




*Recurrence analyses to detect structure in temporal variability*

*Example: dFC slows down with aging or sleep deprivation, correlating with degraded cognitive assessments*

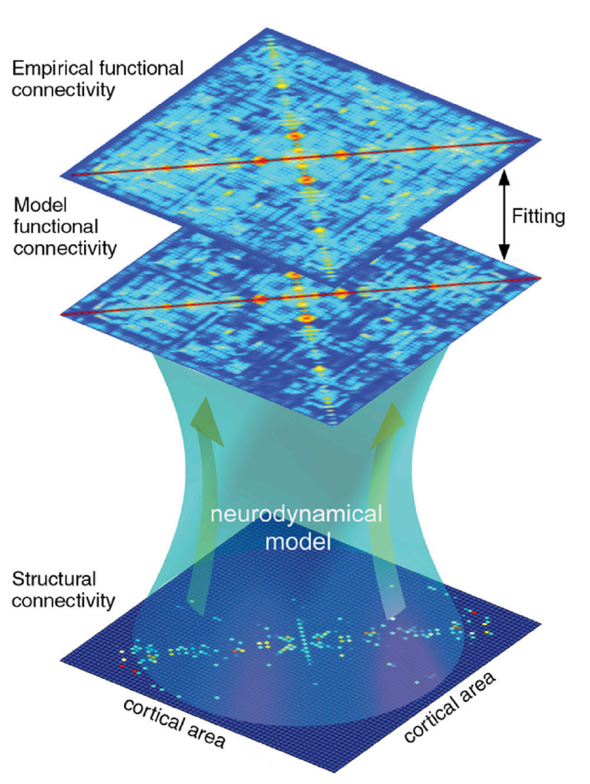
*Battaglia et al. NeuroImage (2020)*

*Lombardo et al. NeuroImage (2020)*

Functional connectivity supposedly reflects **inter-regional interaction and exchange of information**. If the aim of establishing FC is to enable communication why not generating a stable functional network infrastructure, optimized for information exchange efficiency?

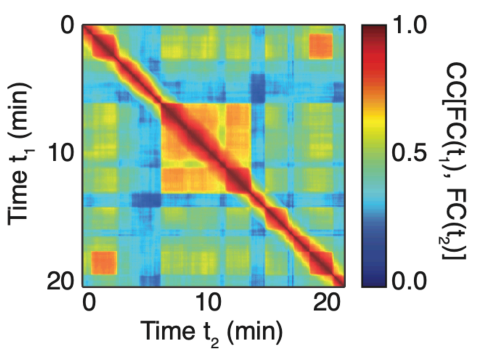
**In other words, why dFC should be "d" ?**

## "Why" as "how to": dFC is naturally occurring




*dFC recurrence matrix from simulated rs*

*Hansen et al. NeuroImage (2015)*



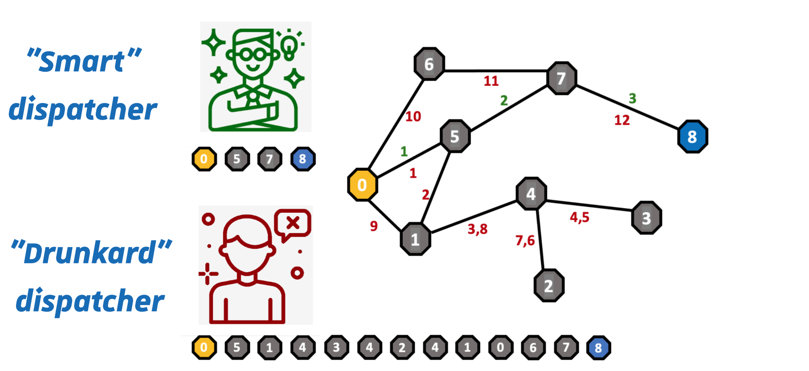

- **Mean-field models** of whole brain dynamics can be used to emulate resting state dynamics
- Simulations spontaneously give rise to a rich dFC because of the **sampling of an internal repertoire of dynamical states** near a critical instability
- Thus dFC is "d" "why"… **it would be unlikely to be otherwise**

## "Why" as "what for": dFC as an asset for info flow?

- Consider **FC networks as a communication infrastructure system** on which some unspecified **"information" can flow** moved by some unspecified dispatcher process. Information can move over a **static graph of FC** but also over a **temporal graph of dFC**
- Suppose that "keeping on" a **FC link at a certain time has some cost**, e.g. metabolic cost of high synchrony. We use **binary undirected networks** for simplicity (one link "on" at time *t* = cost 1; Tot cost = tot number of links over space *and* time)

If the system disposes of a **finite amount of resources**, how should it better spend them to dispatch info efficiently? By creating **fewer but long-lasting optimized links?** or, **at equal cost and duration, more transient links?** Is there an **optimum tradeoff** ?

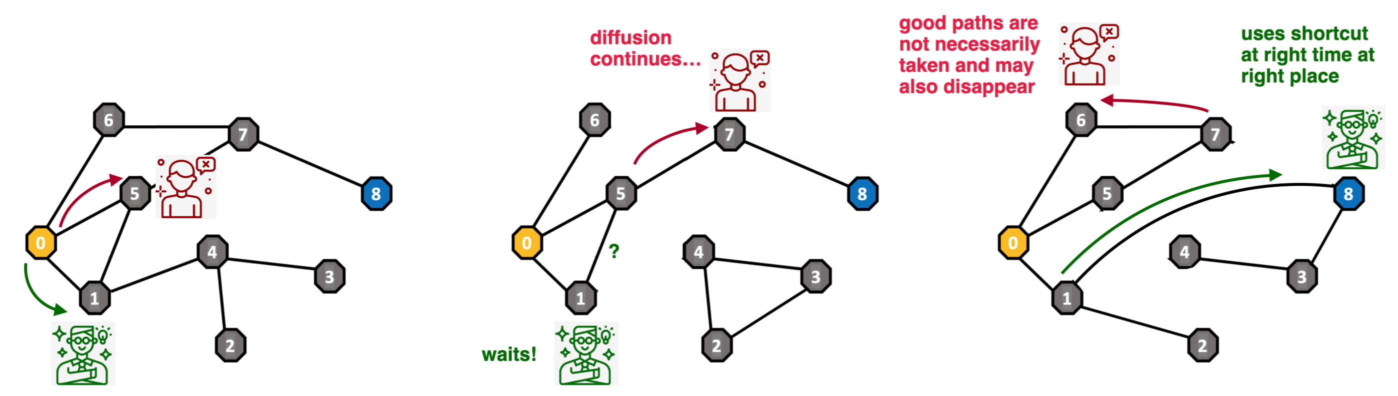
- We study **two strategies for info dispatch** on static and temporal graphs: the **"smart" scenario** corresponds to an *upper bound*, the **"drunkard" scenario** to a *chance expectation*




A smart dispatcher always chooses the **shortest path** to move info from a node to another (here "0" to "8")

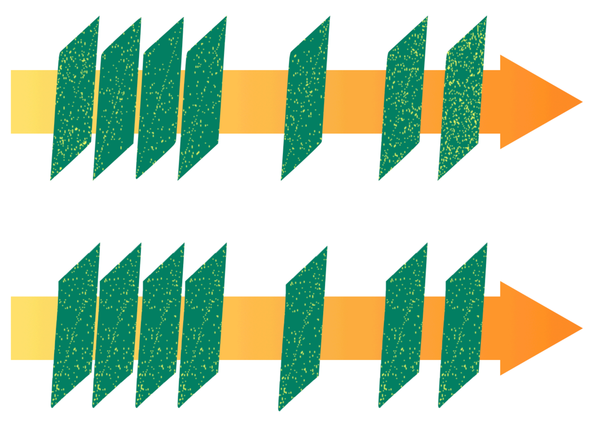
A drunkard dispatcher performs a **random walk** on the graph until the target is found

Even more complicated on a temporal net: **Time-respecting paths** !




## Toy dynamic Functional Connectivity: random temporal nets

$$\mathbf{A}(t) = \mathbf{A}_0 + \eta(t)$$



$$\mathbf{A}_{static}(t) \equiv \mathbf{A}_0$$

Toy Temporal network ***A(t)*** given by **random fluctuations around a common reference** $A_0$ (Erdös-Renyi ensemble) Specified by an average degree ***k*** and by a probability $p_{rew}$ of random rewiring

"Static temporal" network $A_{static}(t)$ given by the reference matrix $A_0$ repeated through time. ***A(t)*** and $A_{static}(t)$ are generated to have **same cost**

For both "smart" and "drunkard" scenarios, we monitor two properties to **quantify info dispatch efficiency**, as a function of average network frame degree, i.e. **for increasing network cost.**

**Irrigation,** i.e. the **amount of nodes reachable by info** initially at a source node over a given horizon of time ($T$ ~ $10^3$ frames, equivalent to empirical rs sessions below)

**Impermeability,** i.e. the **resistance to information diffusion** measured as the **time needed for info to reach a target node**, averaged all possible targets (targets that are not reached over the observation time *T* contribute a **penalty** of *T*+1)

### Analytical understanding

$$B(K) = \prod_{i=0}^{K-1} A_{t+i} \qquad B_{ij}(K)$$

number of paths from i to j lasting K

$$P_t(i,j) = \frac{A_t(i,j)}{\sum_j A_t(i,j)}$$

$$\Omega(K) = \prod_{i=0}^{K-1} P_{t+i} \qquad \Omega_{ij}(K)$$

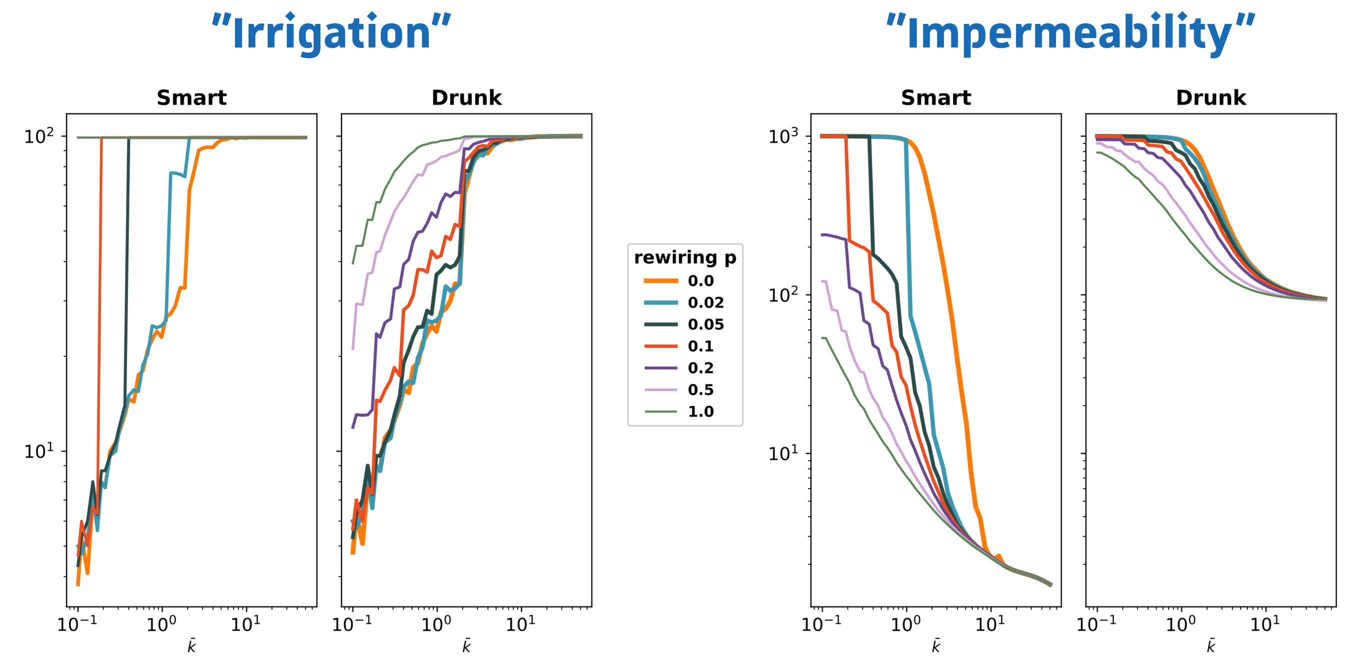
probability of taking a path from i to j lasting K

For SMART dispatch, **time-ordered products** of instantaneous adjacency matrices describe the existence of time-respecting paths. The smallest ***K*** for which $B_{ij}$ is not zero is the fastest SMART path

$$MFPT(i,j) = \sum_{k=1}^{T} k \cdot \Omega_{ij}(k)\Big(1 - \Omega_{ij}(k-1)\Big)$$

The **mean first passage time** in node *j* of DRUNKARD paths starting in *i* can be computed as a probability-weighed average

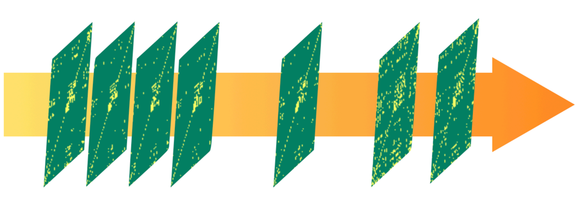
Improvement of info diffusion by dynamic rewiring are given by the **aggregate network reaching percolation** threshold



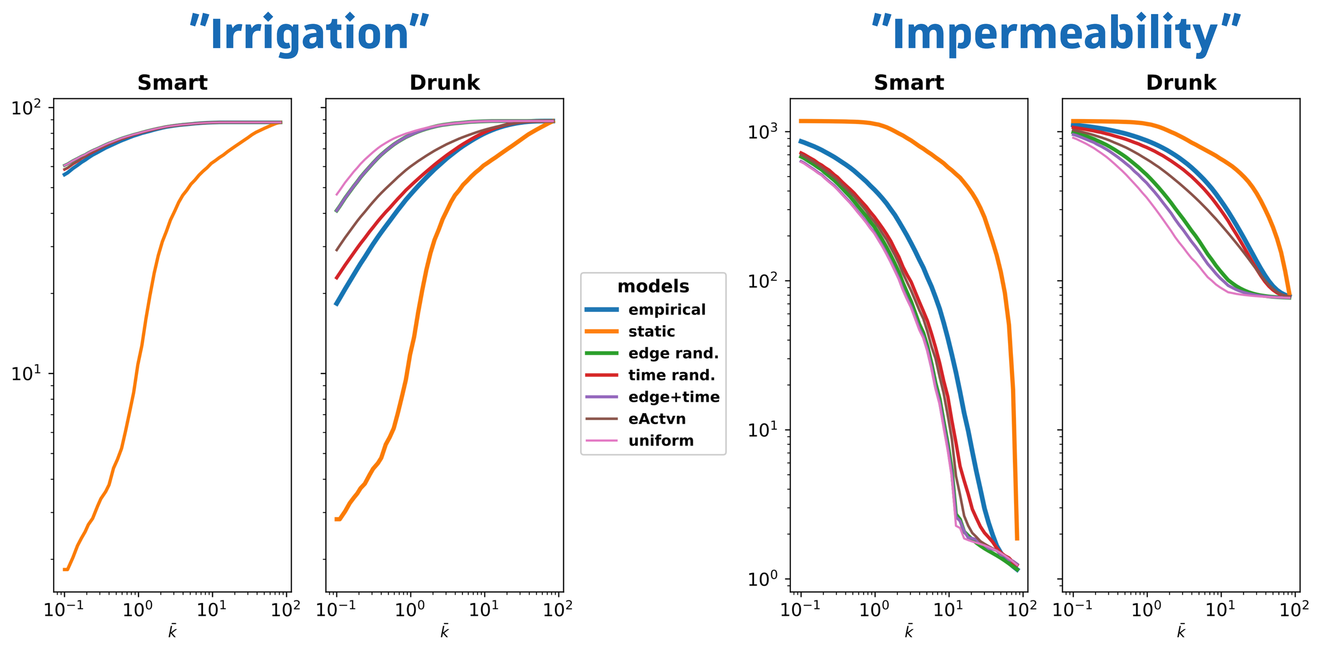

- Increasing network density, **irrigation increases.** Adding **random link rewiring boosts** overall **irrigation**
- Increasing network density, **impermeability decreases.** Adding **random link rewiring reduces** overall **impermeability**

## Empirical dynamic Functional Connectivity: human rs fMRI

$$\mathbf{A}(t) = \mathbb{I}\left[\mathrm{FC}(t) \geq \theta\right]$$



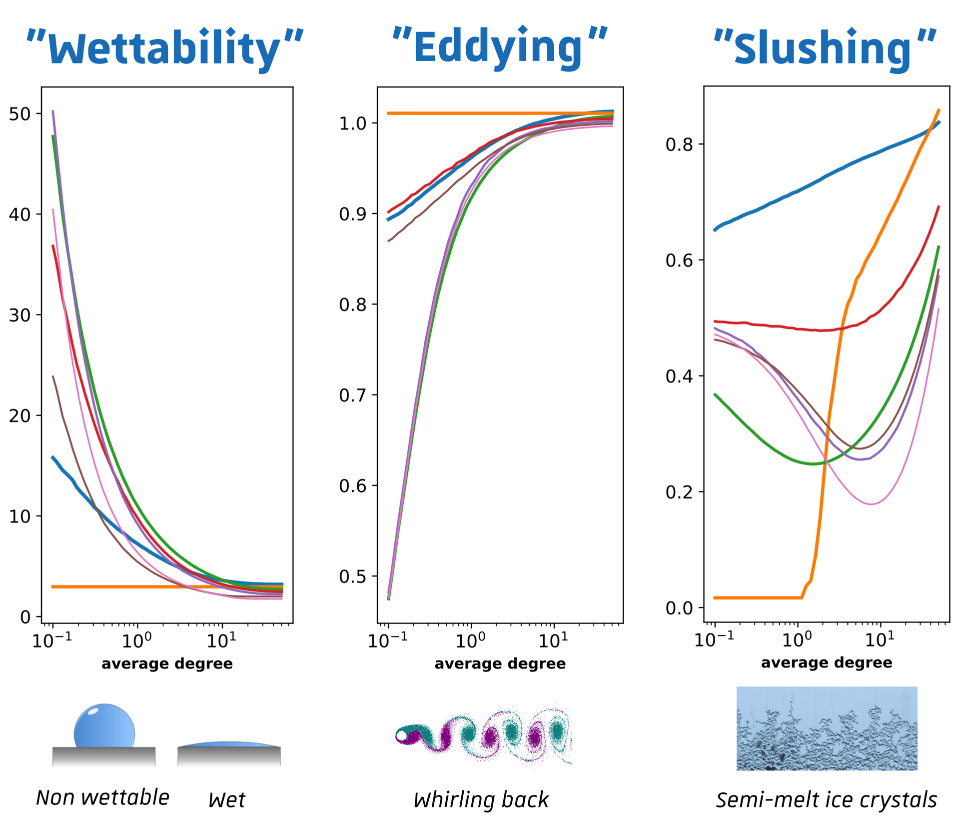
A binary temporal network ***A(t)*** is constructed from an **empirically measured dFC stream** from 20 min of human BOLD rs fMRI *(time window 20 s, data from Human Connectome Project, 99 subjects)* Application of a **sharp threshold *θ*** to control the obtained average degree. $A_{static}(t)$ is constructed from an **average temporal network frame**, rebinarized to obtain a temporal network with the **same cost**



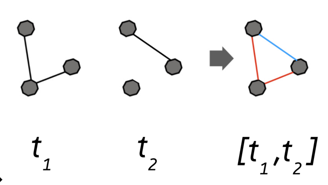

We compare **empirical** dFC streams with an equal cost **static** version. In addition we have a variety of null models. In **edge-randomized** link density is maintained frame-by-frame but links are randomly rewired, while in **uniform** every frame is regenerated from scratch with a homogeneous static-like link density in every frame. In **time randomized**, frames are kept identical but time-shuffled. In **"edge+time"**, after time shuffling, edges are rewired within each frame. Finally in **edge-activation**, every link is randomly generated with a link-specific activation probability matched to empirical.

- **Static dFC** has the **lowest Irrigation** among all considered models.
- **Empirical dFC** has **worse irrigation than more random** dynamic models.
- **Static dFC** has the **highest impermeability** among all considered models.
- **Empirical dFC** is **more impermeable than more random** dynamic models.

**Empirical dFC** dispatches information (*"integration"*) **more efficiently than** its **static** counterpart. However, **it does it less well than** the other **less structured null models. What else is empirical dFC optimizing** besides integrative dispatch?




- We define **wettability** as the time needed for information leaving a node to flow back to it, i.e. to stick to a place like a droplet that does not spread. **Empirical dFC is less wettable** than most other dynamic models
- Related to wettability, we define **eddying** as the probability that future neighbors of a node's neighbors at a reference time, still include nodes from the initial reference neighbor set, i.e. that the info flow tends to whirl back to a local neighborood (high cross-time Jaccard index). **Empirical dFC displays more eddying** than most other dynamic models.
- We also track **temporal clustering**, i.e the tendency to have high clustering when over-laying temporally close frames, even when individual frames may be more poorly clustered. Like in an icy slush, where crystals are melting and refreezing fluidly. **Empirical dFC has the highest temporal clustering** of all dynamic models.




Temporal clustering

**Empirical dFC** has the **highest capacity to retain and mix Information locally** among all tested dynamical models. Other dynamic models may be more integrative, but, unlike empirical dFC, they lack these *"segregation"* properties.

### Some open questions

- Can we **understand analytically** the scaling of irrigation curves ?
- Can we construct a **null-model** capturing more precisely **both integrative and segregative properties** of empirical dFC? Or a **virtual brain** model?
- Are the frame-by-frame fluctuations in network density of empirical dFC interpretable as an **avalanching phenomenon**? Power-laws?
- Are our info flow features useful as **biomarkers of cognitive (dys)function**?

## Conclusions

- The **"d" in dFC confers superior information dispatch properties** in terms of both number of irrigated nodes and time needed to receive a broadcasted information. Such **integrative advantages are more evident** when networks are more diluted, i.e. when creation and maintainance through time of a **FC link have a high cost**
- **Between static FC and more random null models, empirical dFC** exhibits a **complex tradeoff** between advantages for **integration** conferred by dynamicity and the simultaneous preservation of **segregative properties.**