Medical Xpress

Interview with Connectomics founder Olaf Sporns

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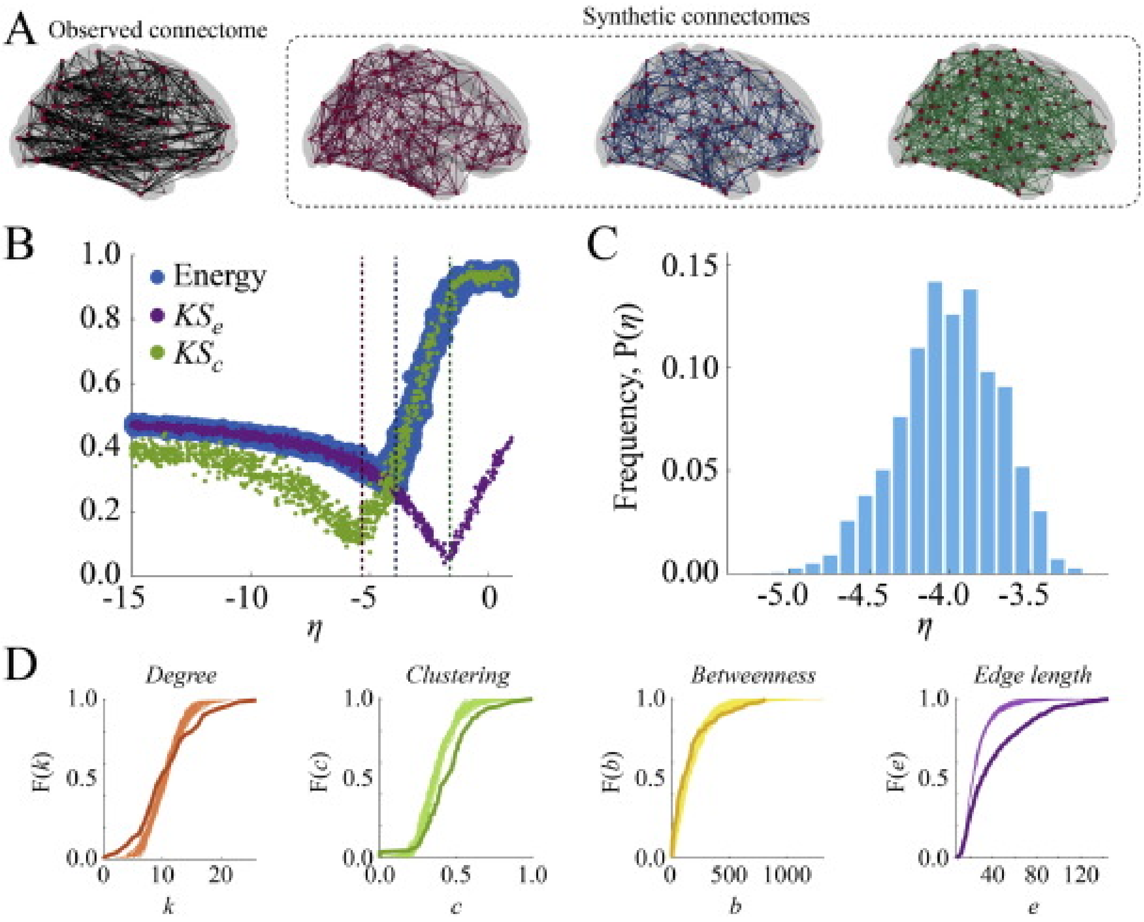

Fig 1. Summary of the geometric model.

Last month marked the 10th anniversary of the landmark paper that launched "connectomics", overthrowing the predominant approach to localizing individual functions in the brain in favor of mapping the entirety of the brain's connections. In the decade since, connectomics has redefined how we collect, analyzing, and interpret our data. Along the way numerous international endeavors like the Human Connectome Project have sprung up, spurring hundreds of institutions to amass never before seen volumes of brain data from thousands of individuals. This revolution has moved cognitive neuroimaging from a small scale endeavor, governed by many isolated labs conducting small scale studies in closed settings, to a massive open science bonanza of data sharing. Today most brain science institutes find themselves engaged in the collection of large scale datasets, whether to establish normative samples of particular patient groups or to bolster ongoing connectomics and computational approaches. This movement has not been without its detractors however, as many have raised concerns about the cost and long-term payoff of these massive scale projects, arguing that they come at the cost of more flexible and small scale hypothesis-driven research.

To get a feeling for how far we've come and how far we've yet to go, I met with PLOS ONE Section Editor and PLOS Computational Biology Deputy Editor-in-Chief, Olaf Sporns to discuss the first "decade of connectomics."

MA: Olaf, it's been 10 years since you published the paper in which you defined the connectome. What are some of the major advances that you've seen since?

OS: As we passed the 10 year mark just recently, I did spend quite a bit of time thinking back 10 years (or 20) – it is hard to believe how the field has changed. It is certainly true that studying the brain's connections has a long history – decades, if not centuries old. But mapping and modeling these connections in their entirety, across the whole brain, was at best a side-show a decade ago. For starters, there was very little data – almost none on the connections of the human brain. Everyone was working in isolated groups performing t-tests on small datasets, looking for localized activations. We had virtually no connectivity data to work with. And yet, through my many years of work as a computational neuroscientist I was keenly aware that dynamic patterns of neuronal activity were strongly shaped by the underlying anatomical connections (in addition to the biophysics of the neuronal elements).

These connections were crucial for building a realistic "forward model" of the brain. That triggered the idea of the "connectome" as a foundational data set for understanding brain function. Now with the Human Connectome Project and numerous other high-volume endeavors, we've got incredible amounts of data. The key going forward if we want to make sense of all this data is to work to discover the "laws" or theoretical principles that govern them. This is something myself and many others in the field are actively engaged in – and my bet is that network science will make important contributions to an emerging theory of the brain.

MA: What are some of the key findings of this approach? Have we learned anything new about the structure or function of the brain?

OS: I think that the insights connectomics has brought about are substantial – connectivity (both structural and functional) has been shown to form specific patterns that are both reproducible across individuals as well as predictive of individual variations in cognition and behavior. In structural connectomics, some of the most intriguing insights have revolved around highly central (from a network perspective) hub nodes and the connective core known as the "rich club". In functional connectomics, the connectivity-based decomposition of the brain into network communities (in both resting state and task co-activation data) has been perhaps most fruitful. While much recent work has focused on the resting state, I see strong potential for network-based approaches applied to specific cognitive operations, behavior, learning and plasticity.

One way to describe these findings is that we've begun to understand some basic architectural features of the brain. To make an analogy, it's a bit like saying, OK we know now that the architecture is that of a church, or an office building. From that knowledge you can work out, that there should be a certain number of rooms, a steeple, a watercooler, etc. Knowing something about the architecture, you can now refine the problem.

This knowledge is the key to working backwards from data to first principles – to working out the underlying "laws" that govern brain structure and function. This will help us to make the most of the massive data inflow inspired by connectomics – we actually begin to have insight into which questions are going to be the most fruitful. Connectomics is helping us to better define which questions to ask in the first place, whereas before the whole domain of brain connectivity was rather undefined and murky.

MA: That's very interesting, and reflects a lot of what I see in some of my colleagues work here in London. For example Karl Friston is quite interested in deriving the generative equations that describe the way any brain-like system must be, given some basic principles. This kind of normative approach – asking

why should the brain be one way and not another – is particularly interesting given growing awareness of a need for stronger theories in neuroscience. What are some of the ways your group is approaching this issue?

OS: This is something my group is quite interested in – understanding why certain kinds of brain architecture (e.g. Rich Club organization) are more prevalent than others. In fact, at least in principle, the brain could have taken on lots of different structures. An analogous problem in evolutionary biology is known as theoretical morphology – the study of why an organism typically takes one particular phenotypic shape when other shapes might also be geometrically possible. By systematically investigating the factors that make certain morphologies more likely than others, it's possible to gain insight into the generative forces that govern the brain . We believe this new approach to network morphospace will help us to understand how factors like wiring cost, metabolic demands, geometry, and potentially even information theoretic entities like the Free Energy Principle proposed by Karl govern emergent structure and function.

MA: That sounds like an extremely fruitful approach – and certainly speaks to worries that 'connectomics' isn't hypothesis or model-driven. For example, some have criticized connectomics for being overly exploratory or descriptive. One such critique is that the human genome project, an inspiration for the human connectome project, ultimately lead to more questions (e.g. what about the proteome) than

answers. One could ask, where does it end when you set out with a question like "what is the complete description of (some phenomenon)". Do you think there is a tension between smaller-scale, hypothesis driven research and big-data connectomics?

OS: I was a graduate student when the human genome project got off the ground, and I remember the discussion very well. People complained, it was too expensive. It was too exploratory. Some enthusiasts claimed at the time that the human genome would solve all biological problems – it certainly did not turn out that way. But enormous progress has been made. Mapping the genome has allowed biologists to ask better and more refined questions. Unquestionably, genomics has transformed biology and moved the discipline forward. I don't think anyone really wants to go back to the pre-genomic era and start over without the extremely fundamental knowledge that genomics has provided. In my opinion, progress does not necessarily mean finding final answers to complex questions, but it may instead mean being able to ask better questions. I think that will be the enduring contribution of connectomics. Connectomics is necessary for asking better questions about the brain. The basic knowledge of the layout and topology of the brain's connectome will allow us to develop more precise, more mechanistic hypotheses about brain function.

In my mind, there is no real tension between "exploratory" or "data-driven" and "hypothesis-driven" research – they're complementary and deeply interwoven. Exploration, for example in the form of assembling complete maps of connections in a nervous system, becomes a basis for creating better models and better hypotheses about specific aspects of brain function.

You can make an analogy here to the Voyager space probes. We really didn't know what we set out to find with those missions. They were exploratory in the sense that we sent them out to gather as much data as possible which then led to important new insights and understanding. While at first glance connectomics is similarly exploratory in nature, collection of connectomics data is increasingly tied to analysis and interpretation guided by mathematics, network theory, and computational neuroscience. Connectomics is not blind data collection – it deeply engages with an underlying theoretical framework rooted in complex systems and networks. Now, after ten years of connectomics, we are poised to begin to ask better questions – and we've got the data to accomplish this.

A general point: Model-based approaches are very important because they get us away from purely descriptive accounts of "what connects to what" and allow us to ask deeper questions, for example about what generative factors can account for the observed connection patterns.

We've taken a stab at building generative models for the human connectome in a recent study, and found that a mixture of spatial and topological factors could best capture the pattern of cortical projections. I think we'll see a lot more work in model-based approaches to connectomics.

MA: A point well taken. I think this also reflects a more general movement in neuroscience towards appreciating complexity, which motivates the need to integrate across data modalities and go beyond mere data features (ERPs, blobs, etc) towards the underlying biophysics and principles. What are some areas you see really changing in the next 10 years, and what might we be neglecting?

OS: Well, as you've mentioned there is a growing consensus that we need stronger theories. When I was a graduate student and postdoc the culture of neuroscience was very different from how it is now. Back then, there was a kind of extremely conservative empiricism and a strong distrust of theory that pervaded the day. Theories were widely viewed as something to be avoided. Today I think we are seeing the beginnings of a movement towards theories that embrace the complexity of the brain. Previously many neuroscience talks would start by making a passing reference to "the brain is highly complex", but then go on to say "now here is my very important molecule" and focus on that one aspect exclusively.

Now we are realizing that we have to move beyond just studying the components in isolation towards actually understanding how they interact with each other. This requires us to develop models that incorporate relational data – in other words, network models – in order to describe how neurons and brain regions connect and how information is dynamically integrated by the brain.

On that note, something we're still not really seeing is a full appreciation of how deeply embodied the brain is. Originally the plan for my book "Networks of the Brain" was to spend the first half talking about the brain and the second half on brain/body/environment interactions, but while writing the book, the brain took over. I strongly believe that the network perspective embraces the view that brain/body dynamics and morphology are critical to understanding cognition – neglecting the situatedness of the brain within the body misses a whole lot of what makes brains so powerful. We're just now beginning to understand the myriad ways in which information processing is grounded in the brain/body/environment interactions.

A radical network perspective views brain and body as fundementally part of the same extended integrated system. As neuroscience begins to embrace complexity and network theory, I hope to see this important aspect coming back to the forefront.

MA: I certainly agree – understanding cognition, consciousness and the brain in general requires that we view these elements as deeply interlinked units of a integrated network. I'm terribly excited by the idea that we might one day be able to derive generative principles that explain how the morphology of the brain and body go hand in hand, something i'm actively pursuing in my own research.

Last question – if I can muse a bit more abstractly – something I've noticed is that many of the 'grand scale thinkers' of cognitive neuroscience, such as yourself, Guilio Tononi, and Karl Friston all trained together at one point with Gerald Edelman. Although you've all developed your own unique approach, the philosopher in me wonders if there is a kind of 'Edelman' school that defines some commonalities. Information theory is something that for example seems to feature heavily in Tononi's Phi, Friston's Free Energy Principle, and your own work on dynamic brain networks and architechtures. Would you say you all found your own solutions to the same problem – and are these complementary?

OS: {Laughs} – Well I think you might be giving me a bit too much credit there – but thank you. And yes I suppose you can certainly draw some parallels between my work, Gerald's, and that of both Karl and Guilio. Guilio has really pushed the boundaries of information theory and connectivity in his work on consciousness, which I think links up with the notion of an integrative rich club. And I really admire what Karl is attempting to do with the Free Energy Principle. As we've discussed, I think that trying to work out the generative principles that underlie brain structure and function is a crucial future direction for theoretical neuroscience. Certainly all of us were greatly influenced by Gerald's incredible talent as a deep and visionary thinker. He left all of us with a lasting appreciation for the importance of a dynamic perspective on the brain that confronted its complexity head-on rather than brushing it aside. I think you can trace that line of reasoning through all of our work.

MA: It will definitely be exciting to see how these approaches continue to converge in the future, especially as neuroscience begins to warm up to complexity, embodiment, and more! Thanks so much for your time and a fascinating interview.

More information: "Generative models of the human connectome," *NeuroImage*, Available online 30 September 2015, ISSN 1053-8119, dx.doi.org/10.1016/j.neuroimage.2015.09.041

"The Human Connectome: A Structural Description of the Human Brain." *PLoS Comput Biol* 1(4): e42. DOI: 10.1371/journal.pcbi.0010042

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