Simulation of Neuronal Death and Network Recovery in a Computational Model of Distributed Cortical Activity

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Objectives: *The authors utilize a model of activity-dependent neuronal plasticity to study the interplay between synaptogenesis, neuronal death, and neurogenesis on the resulting pattern of neuronal connectivity.* **Design:** *A mathematical model of neuronal network activity was employed, with plasticity instantiated by an activity-dependent rewiring rule. In particular, the authors modeled a neural system as a collection of "nodes" (neural subsystems) connected by "links" (anatomical connectivity). Neuronal damage was simulated by deletion of nodes in this evolving network through either random or targeted attack. Neurogenesis was likewise simulated by insertion of new nodes with random connections.* **Measurements:** *Local and global structural network properties were characterized using the metrics of local and global "efficiency," and network "reachability."* **Results:** *Activity-dependent plasticity yields a network that is robust to random node deletion, with preservation of a "small-world" architecture, characterized by high local and global efficiency. In contrast, targeted deletion of central nodes leads to a drop in reachability and global efficiency, with a consequent loss of small-world properties. Simulated neurogenesis is able to compensate for this targeted cell loss even when rates of new cell formation are considerably slower than that of simulated cell death.* **Conclusions:** *The rapid growth of computational neuroscience enables to study the interplay between neuronal plasticity and cell death in computational models of brain network activity. Although the current simulations lack much of the rich physiology of real neuronal systems, they nevertheless allow us to make tentative hypotheses of the effects of neuronal lesions on the resulting neuroanatomical connectivity networks.* (Am J Geriatr Psychiatry 2009; 17:210–217)

Key Words: Brain plasticity, brain reserve, nonlinear dynamics, graph theory, small-world network, network robustness

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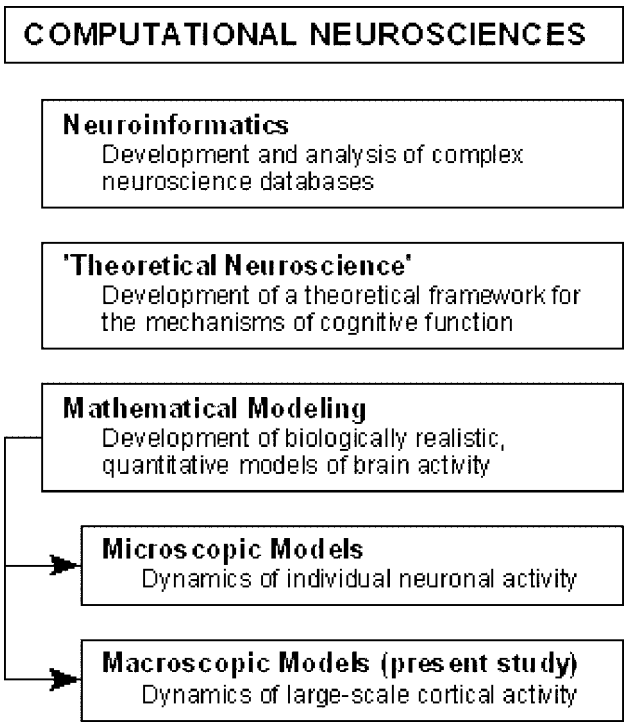
Over the last several decades, the idea that brain plasticity is a property that is maintained across the lifespan has become accepted. Early in development, neuro- and synaptogenesis and neural pruning are central in sculpting the emergence of normal cognitive function.[1,2] These same processes appear to extend to adulthood and may play a vital role in the reported capacity of the adult brain to reorganize following focal damage or to compensate for degenerative processes.[3–6] More recently, the observation of brain reorganization in adulthood has led to the development of brain reserve theory, which attempts to explain the variability in clinical presentation that is seen in neuropathologic, and especially neurodegenerative disorders.[7,8] In the present study, we employ recent advances in computational neuroscience to examine the potential underpinnings of this theory (Fig. 1). While a biologic characterization of this concept remains challenging, a simplified computational model may act as an auxiliary means for probing potential principles which underlie the theory of brain reserve. Mathematical models of neuronal biology are now available at a scale from the single cell through to the macroscopic scale of large cell populations.[9–11] Here, we use a recently developed neuronal network model to examine the effects of simulated synaptogenesis and the slower, simultaneous effects of neural death and neurogenesis on the resulting neuroanatomical architecture.

Our model simulates the dynamical activity of a coupled collection of neurons, linked together by a continually rewiring structural connectivity network. Neurocomputational models vary greatly in their physiologic complexity, but all invariably contain important mathematical complexities ("nonlinearities") arising from the voltage-dependent nature of neuronal membrane channels.[11] We utilize a simple one-dimensional nonlinear recursive function ("map"), which has been previously shown to approximate the behavior of a more complex neural mass model.[12,13] As dynamical activity evolves on an underlying structural network, this network is in turn continuously rewired, using an unsupervised, activity-dependent rewiring rule.[14] This rule upregulates modeled synaptic efficacy between neural elements that are firing synchronously (simultaneously), while pruning connections between asynchronous units. In this sense, it represents a crude approximation of Hebbian learning, as applied to a binary network without external stimuli.

FIGURE 1. The Present Study, as Placed in the Context of Computational Neurosciences



Notes: Computational neurosciences are a relatively new but rapidly growing collection of disciplines that employ mathematical techniques to elucidate brain activity and cognitive function. These disciplines may be subdivided into three broad areas: Neuroinformatics, theoretical neuroscience, and mathematical modeling. Our study belongs to the latter field. Mathematical brain models attempt to provide a representation of neuronal activity that is sufficiently accurate to match empirical observations (physiologic validity) while remaining considerably simpler than In Vivo Brain activity (computational simplicity). Accurate models of neuronal behavior at the neuronal microscale have existed since the 1950s (the seminal example is the hodgkin-huxley model). Biologically plausible models at macroscopic (whole brain) scales are more recent in their development but are quickly improving in their biologic complexity. These large-scale models offer the potential to provide a virtual quantitative laboratory, thus allowing to test empirically generated hypotheses, as well as to simulate the effects of focal lesions and global degenerative processes on large-scale brain activity. In this study, we illustrate an example of such a simulation, and briefly discuss its implications and usefulness for future empirical research.

Our study aims to characterize the effects of simulated neuronal death and neurogenesis on the resulting neuroanatomical connectivity. Neuroanatomical connectivity may be characterized using the methods of modern network theory.[15,16] A

network is defined by a collection of nodes (units) and internode links (connections). Depending on the spatial scale of interest, nodes may represent neurons[17] or cortical areas,[10] while links may represent synaptic connections or large-scale cortico-cortical tracts. The resulting networks may be quantitatively characterized by computing their local and global capacity for information transfer. These properties are well captured by the metrics of local and global efficiency.[18] Efficiency measures are based on the smallest number of links which are required to connect any pair of nodes within a specified neighborhood (local efficiency) or across the whole network (global efficiency). There are a number of conceptual advantages for the characterization of brain networks with local and global efficiency, compared with the more traditional metrics of clustering and path length.[19]

Neuronal network organization combines the competing demands of regional segregation and distributive integration.[20,21] Highly clustered (locally efficient), yet globally interconnected (globally efficient) "small-world" networks are considerably more effective in reconciling these opposing demands, when compared with artificially generated random or ordered networks.[22] A multitude of recent studies have reported that structural and functional brain connectivity exhibits small-world properties at multiple spatial and temporal scales, as recently reviewed.[23,24] Concurrent with these findings, simulations have previously shown that the present model self-organizes from a random to a small-world network configuration,[14] mimicking to an extent, events occurring in the developing nervous system. The system continues to slowly rewire once it has attained a small-world architecture, although the changes in network configuration become more subtle, emulating processes that may occur in the brain throughout the lifespan.

Recent analyses of functional connectivity networks extracted from electroencephalogram and magnetoencephalogram recordings have reported small-world disturbances in a number of neurologic and psychiatric disorders,[25] including in Alzheimer disease[26] and in schizophrenia.[27–29] Interestingly, network disorganization correlated with disease severity in Alzheimer disease[26] and with illness duration in schizophrenia.[29] On the other hand, medication dose was reported to have a normalizing influence on network architecture in first episode psychosis.[28] Hence, the organization of functional brain networks appears to reflect important aspects of the clinical presentation of several mental illnesses.

What are the neuropathologic mechanisms underlying the disruption of functional brain networks in psychiatric disorders? To our knowledge, this question has not yet been addressed. Here, noting that functional networks appear to strongly reflect the underlying structural connectivity,[10] we take the first steps in linking structural lesions to functional network disorganization. We extend the present model to study the effect of random or targeted node deletion on the network's connectivity properties, hence expanding on recent studies of targeted attack in small-world networks extracted from structural connectivity[30] and functional magnetic resonance imaging[31] datasets, as well as in "scale-free" networks on a theoretical (Hopfield) model of autoassociative memory.[32] In addition, we consider whether a slower, simulated neurogenesis (node addition) has a protective effect against the potential deleterious effects of node deletion.

METHODS

Adaptive Neuronal Model

The core model consists of a dynamical component, representing spontaneous neuronal activity, and a structural component, representing underlying neuroanatomical connectivity, on which the neuronal dynamics unfold. The dynamical component states how individual elements behave, in the absence of any inputs from other nodes, and is typically derived from physiologic study of core neuronal processes.[33] For the present purposes, we employ the nonlinear "logistic map," for which the current state of the system is derived from its most recent state through a strong nonlinear rule. The structural component represents a neuroanatomical connectivity network and determines how individual neural elements interact. In the present study, structural connections are represented by a directed binary network—that is, a connection from one node to another is either fully present or absent. Together, these two

components—structural and dynamical—provide a model for spontaneous activity in distributed cortical systems.

Synaptic Plasticity

To this model, we add a rule which introduces activity-dependent rewiring of connections at discrete points in time. We employ the simple rule introduced by Gong and van Leeuwen.[14] According to this rule, the structural connectivity is iteratively reshaped by dynamical activity through an unsupervised Hebbian rule. Following every 1,000 iterations of the dynamics, a node is randomly chosen and its connections are rewired such that it gains a link to a node with which it is most synchronous and loses a link to a neighbor with which it is least synchronous. If the most synchronous node is already a neighbor, a different node is chosen until a rewiring is made. In this way, the structural connectivity is continually rewired based on the dynamical activity it generates, hence mimicking Hebbian learning. The system can be considered symbiotic in the sense that the structural network determines how the neural subsystems interact on fast time scales, but is itself subject to rewiring on a slow time scale, according to the states of the underlying elements.[14,34] As with these previous studies, we start our networks with random initial connectivity, and we allow them to rewire until they reach a steady state. Formal mathematical details of the model are provided in the Appendix.

Neuronal Death and Neurogenesis

Neuronal death was simulated by node deletion, at a specified time interval. Nodes were deleted randomly or by targeting central nodes—defined as those nodes which lie on a large number of short paths (nodes with high values of "betweenness centrality"[35]). Neurogenesis was simulated by introducing new nodes into the system, also at regular intervals. Such nodes are initially randomly connected at the average network rate. These nodes henceforth obey the same adaptive rewiring rule for synaptic plasticity. Generally, the rate of neurogenesis was an order of magnitude slower than the rate of simulated cell death. Simulations were conducted with networks of 200 nodes, and 4,000 links (corresponding to approximately 1 in 10 possible connections), and proceeded until the network size was reduced by 50%. Results were averaged over 40 such simulations, hence providing estimates of the mean and standard errors of our principle network metrics.

Metrics of Network Structure

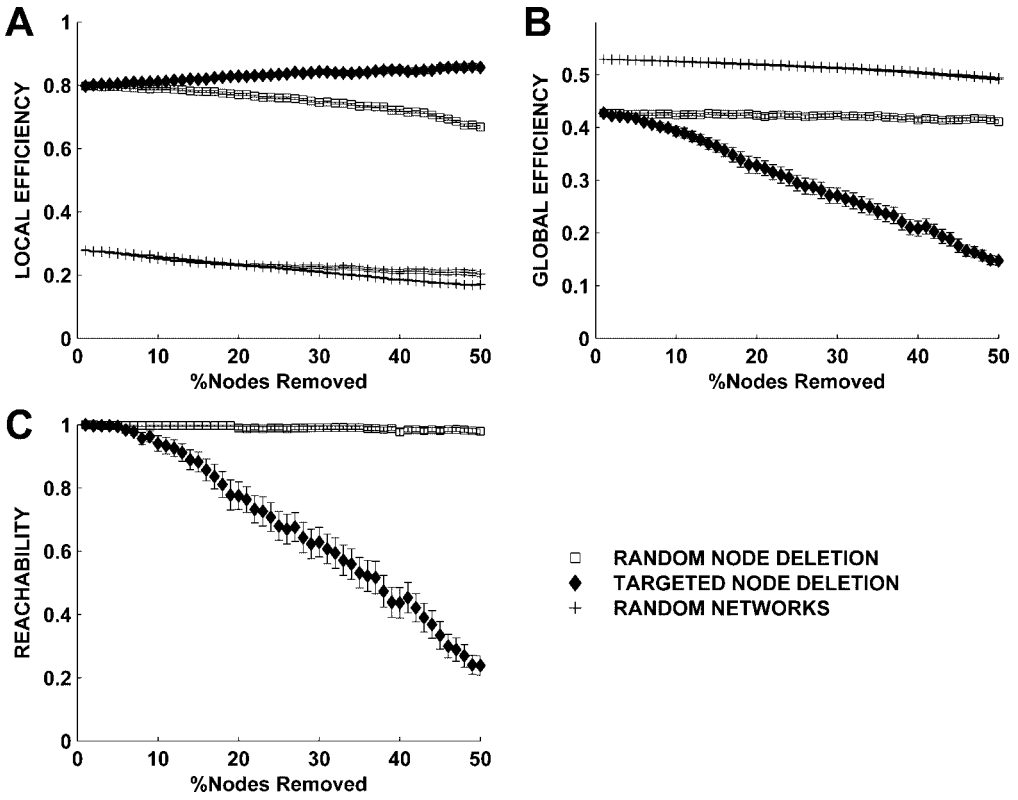
We evaluated structural network properties using local and global efficiency—defined as a harmonic mean of the characteristic path length within neighborhoods (local efficiency) or across the whole network (global efficiency). The metrics were compared against corresponding degree-preserved, random networks, to evaluate small-world properties. Small-world networks are known to manifest a significantly higher local efficiency, but only slightly lower global efficiency, when compared with random networks. In addition to characterizing the efficiency, it is also of interest to evaluate network disconnection directly. To this end, we measured network reachability—the proportion of all pairs of nodes which are connected by a sequence of links. Formal definitions of these metrics are provided in the Appendix.

RESULTS

As previously reported, the current modeled system evolves from a random to a small-world network configuration,[14] as characterized by a significant elevation of local efficiency, with a correspondingly small reduction in global efficiency. This small-world architecture hence optimally combines local information segregation (processing in small, clustered cliques) and global information integration (rapid integration of distributed activity).

After this evolution, we simulated neuronal death by deleting one node at every 1,000th rewiring step. The system continues to iteratively rewire according to the original activity-dependent rule. Figures 2A, B show the effects of random and targeted node deletions on local and global network efficiency. Random node deletions resulted in a gradual decrease in local efficiency, with a minimal effect on global efficiency. Hence, the net effect is a slight alteration in local

FIGURE 2. Effects of Random and Targeted Node Deletion on Local Efficiency (A) and Global Efficiency (B) of the Resulting Networks



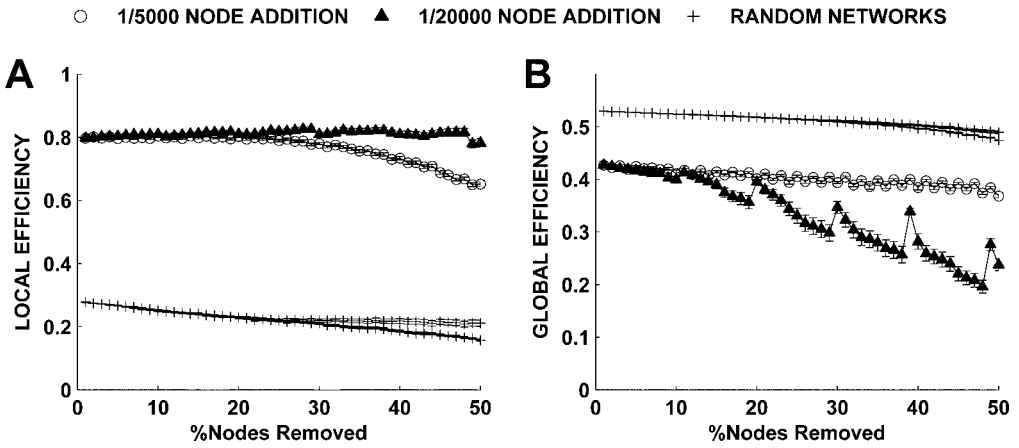
Notes: Corresponding randomized networks are shown for comparison. (C) The effect of random and targeted node deletion on network reachability (the proportion of node pairs which may be connected by a sequence of links). Note the close correspondence between a reduction in reachability (corresponding to network disconnection) and the loss in global efficiency. For all simulations, the deletion rate was one node in every 1,000 rewiring steps. Error bars represent the SE of the mean estimated over 40 repeated simulations.

structure, but invariance in global structure, with a preservation of small-world properties, when compared with random networks.

In contrast, targeted deletion of central nodes results in a moderate increase in local efficiency, but a marked reduction in global efficiency, after a short period of relative resilience to the insults. The reduced global efficiency is closely correlated to network disconnection (Fig. 2C). The combination of high local efficiency and low global efficiency are characteristic properties of ordered, non–small-world networks—networks which are hence not optimized for global integration of information.[22]

We next consider whether simulating neurogenesis by the addition of randomly connected nodes counteracts the effect of targeted node deletion. Figure 3A shows the effect of node addition on the resulting local and global efficiency. Nodes were added at a significantly slower rate compared with the rate of node deletion. Figure 3B shows that a relatively slow addition of one node for every five removed nodes is able to largely preserve a small-world architecture. On the other hand, an even slower frequency of addition failed to preserve small-world properties (Fig. 3B). Interestingly, the intermittent addition of nodes is evident as brief and partial rectifications in the system's global efficiency. Hence, as the frequency of node addition is reduced, so the overall properties of the system shift from a small-world system to a nonphysiologic overly ordered state.

FIGURE 3. Effect of Targeted Node Deletion, Together with Node Addition on Local Efficiency (A) and Global Efficiency (B) of the Resulting Networks



Notes: Corresponding randomized networks are shown for comparison. The system largely retains its small-world properties, when one randomly connected node was inserted at every 5,000 steps. On the contrary, node insertion at a slower frequency (1 in every 20,000 steps) was largely unsuccessful at counteracting the effects of targeted deletion, as evidenced by the values of local and global efficiencies that approximate the "targeted node deletion" networks from Fig. 1. The times of node insertion at this frequency is visually apparent, as prominent "Spikes" in global efficiency. Error bars represent the SE of the mean estimated over 40 repeated simulations.

DISCUSSION

Neurocomputational models attempt to simplify the complexity of real world systems while preserving sufficient plausibility, so as to allow a meaningful investigation (Fig. 1). In this spirit, our simple model captures the nonlinear nature of neuronal dynamics, as well as a mutually interdependent relationship between dynamics and structural connectivity, hence mimicking key physiologic processes. We find that the small-world properties of the model are resilient to random node deletion, but are significantly affected by central node deletion. However, a removal of a small proportion of central nodes is well tolerated, while a simulated neurogenesis at a relatively slow rate is able to largely restore a small-world architecture.

The distinct changes in global network structure that follow random or targeted insults provide a link between the clinical and neuropathologic features of mental illness and the disruptions in structural and functional networks of brain connectivity. Our present findings point to the importance of alternative hubs in the response to targeted attack. Such hubs are able to maintain global interconnectedness, and hence a small-world structure, in the face of targeted deletion. In our simulations, randomly added nodes are likely to restore small-world properties by assuming the role of such hubs. Hence, an increased number of such hubs is likely to confer increased network resilience in the case of targeted attack. Notably, the rapidly expanding network-based analyses of structural and functional cortical connectivity have already identified candidate hub locations and their putative roles in empirical data.[10,31] For instance, it is likely that heteromodal association regions act as hubs by integrating information from specialized cortical processing regions.[31]

The present study supports the hypothesis that synaptogenesis and possibly neurogenesis in candidate hub locations could confer a protective role in global system integrity, hence expanding on and complementing recent robustness analyses of static (nonrewiring) brain networks extracted from empirical data.[30,31] Consequently, we hypothesize that the early involvement of hubs in neurodegenerative disease will adversely affect the severity of clinical presentation, as well as the ensuing progression of illness. As the methodology of network acquisition and analysis improves, the extraction of functional brain

networks from neuroimaging investigations holds promise as a future aid in the establishment of psychiatric diagnoses and in monitoring the progression of illness.

A number of methodologic simplifications and assumptions necessarily underlie the current model. For example, the model lacks spatial constraints and conduction time delays. Notwithstanding explicit node removal and addition, the number of connections is kept constant throughout its temporal evolution. In addition, point-wise node deletion in itself does not embody the gradual deterioration in neuronal integrity and function that often precedes death. Despite these limitations, the model produced interesting and even unexpected results, such as a slight increase in local efficiency after a period of targeted node deletion. This increase is likely to come at the expense of functional dissociation into segregated neuronal "modules," after the deletion of globally interconnecting central nodes. Moreover, the gain in local efficiency may not translate directly into absolute functional gains, as the overall size of the network is greatly reduced. Findings such as these may therefore be used to test explicit hypotheses in real world scenarios, which in turn can further help develop neurocomputational models and so advance a profitable dialog between computational, biologic, and clinical neuroscientists.

APPENDIX

Technical Description of Neuronal Plasticity Model

The following appendix outlines the mathematical details of the present model. These details are provided for completeness, and we refer the reader to the Methods section for an informal and comprehensive description of the model and its neurobiologic underpinnings.

Structural and Dynamical Components of the Model. We represent the structural connectivity with a directed binary graph (network) $G = \langle N, L \rangle$, consisting of N, the set of n nodes, and L, the set of directed links (edges, connections) between pairs of nodes. G may be defined by a corresponding connectivity (adjacency) matrix H, in which a node j is said to neighbor node i ($i, j \in N$), when there exists a direct connection from i to j, as represented by $H_{ij} = 1$; the lack of such connection is denoted by $H_{ij} = 0$ (note that $H_{ii} = 0$ by definition). Let N_i represent the set of neighbors (neighborhood) of node i and let n_i be the number of neighbors (degree) of i; correspondingly let the complement $\bar{N}_i$ represent the set of all nonneighbors of i.[14]

The structural set of nodes N is assigned a corresponding dynamical ensemble $\mathbf{V}$; hence each node i has a corresponding dynamical unit V^i. The unit state at time t, $V^i(t)$, is governed by a commonly used quadratic logistic equation,

$$F_a(V^i(t)) = 1 - a(V^i(t))^2,$$

where the parameter a governs the nature of the dynamics. The neural ensemble is then constructed through coupling these maps, as

$$V^i(t+1) = (1-\epsilon) F_a(V^i(t)) + \frac{\epsilon}{n_j} \sum_{j \epsilon N_i} F_a(V^j(t)),$$

where ϵ represents the coupling strength ($0 \leq \epsilon \leq 1$) between dynamical units. Following Gong and van Leeuwen,[14] we set $\alpha = 1.7$ and $\epsilon = 0.5$. This choice of parameter values results in chaotic dynamics and allows for weakly synchronized oscillations but not complete synchronization.[36] The system has previously been shown to evolve to a small-world network across a range of parameter values.[14,34]

Activity-Dependent Rewiring Rule. A randomly chosen node $i \in N$ is rewirable if there exists a nonneighbor $k \in \bar{N}_i$ that minimizes $|V^i(t) - V^N(t)|$; that is, when i is not connected to a node, with which it is most synchronous. If rewiring is to occur, we select a neighbor $j \in N_i$ that maximizes $|V^i(t) - V^{N_i}(t)|$ (the least synchronous neighbor of i) and set the connections as $H_{ik} = 1$ and $H_{ij} = 0$. This rule exploits the fact that all nodes have identical parameter values so that the Euclidean distance $|V^i(t) - V^j(t)|$ accurately captures pair-wise synchronization.[14]

Global and Local Efficiency and Reachability. Global efficiency, E_{glob}, is defined as a harmonic mean of the shortest path length over the network. Hence, $E_{\text{glob}} = \frac{\sum_{i,j \epsilon N} 1/d_{ij}}{n(n-1)}$, where d_{ij} represents the shortest

path length between nodes i and j. Local efficiency, E_{loc}, is defined equivalently, but on individual neighborhoods, rather than on the whole network. Hence, for an individual node k, $E_{\mathrm{loc}}^{\mathrm{k}} = \frac{\sum_{i,j\in N_k} 1/d_{ij}}{n_{\mathrm{k}}(n_{\mathrm{k}}-1)}$. The reachability, R, represents the proportion of all pairs of nodes which are connected by a path of finite length. Hence $R = \frac{\sum_{i,j\in N} r_{ij}}{n(n-1)}$, where $r_{ij} = 1$ if d_{ij} is finite, and $r_{ij} = 0$ otherwise.[18]

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