Network Models of Frailty

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When people die, it is usually not from old age, but rather from illnesses that have accumulated over a life time. As a result of these accumulated deficiencies they become increasingly vulnerable to adverse health outcomes. In "Aging, frailty and complex Networks" by Mitnitski et al. [4], they model the accumulation of illnesses as damage that diffuses through a scale-free network with death occurring when the two most highly connected nodes become damaged. With this model they are able to explain Gompertz's law (an exponentially increasing mortality rate with age, observed across many species including single-celled bacteria [6]) without age-specific programming, but rather as an emergent phenomenon. The model simultaneously explains the success of the frailty index (FI) for predicting the vulnerability of individuals along with several other observed properties of the FI.

Ledberg proposes a model which explains Gompetz's law using queueing theory [2]. Damage accumulation is modelled as damage arriving in an M/M/1 queue and the ability to reduce the amount of damage in the queue is linearly decreasing in the age. The risk of dying is a function of the accumulated damage and is proportional to the probability that the queue length exceeds some thresh hold θ.

The model I propose is a combination of the model by Ledberg and Mitnitski et al., incorporating both views into a unified model.

1 Aging, frailty and complex networks model

Each individual is represented by a distinct network made up of N nodes, where each of the nodes $i \in [N] = \{1, \dots, N\}$ can either be damaged ($d_i = 1$) or not ($d_i = 0$), and undirected edges connect nodes. Deficits arise when nodes are damaged, but the nodes do not have to represent specific deficits. The network has a scale free distribution, which is characterized by a power law degree distribution $P(D = k) \sim k^{-\alpha}$, with D the degree of a randomly chosen node, and is created by a shifted linear preferential attachment model, which allows to adjust both the parameter α and the average degree $\langle k \rangle$. At time $t = 0$ all nodes are in an undamaged state. The local frailty f_i of node i is defined as

$$f_i = \sum_{j:\{i,j\}\in E} \frac{d_j}{k_i} = \frac{1}{k_i} \sum_{j:\{i,j\}\in E} d_j, \tag{1}$$

where k_i is the degree of node i and E is the edge set of the network. Frailty is a local property, the proneness of a node becoming damaged, which in words is the fraction of node i's neighbours that are damaged. So the authors claim that the propensity of a node damaging is going to be related to the fraction of its neighbours that are damaged. We can imagine that every node depends on each of its neighbours equally to stay healthy.

As time progresses, damage spreads through the network. There are three different types of nodes in this model.

1. **Mortality nodes** determine when an individual dies. There are two mortality nodes; as soon as both are damaged the individual dies. These are chosen to be the two most highly connected nodes (most central by degree centrality), reflecting the fact that mortality is impacted by many factors. Two were chosen because this provided the best fit with the data.

2. **Frailty nodes** are used to calculate the FI of our simulated individuals. These are n frailty nodes which represent the deficits that we use to calculate the FI's for real patients. These are chosen to be the next most highly connected nodes after the mortality nodes and as such provide a good representation of the "health" of the network without being directly related to mortality. The FI is calculated as

$$F = \sum_{i:\ i \text{ is frailty node}} \frac{d_i}{n} = \frac{1}{n} \sum_{i:\ i \text{ is frailty node}} d_i. \tag{2}$$

   So F is the fraction of the frailty nodes that are damaged.

3. **Normal nodes** are unobserved nodes in the network through which damage propagates to and from the observed parts of the network, represented by the mortality and frailty nodes. There are $N-n-2$ normal nodes, with $n << N$.

Healthy nodes i damage at a rate depending on the local frailty

$$\Gamma_+ = \Gamma_0 \exp(\gamma_+ f_i), \tag{3}$$

and repair at a rate

$$\Gamma_- = \frac{\Gamma_0}{R} \exp(-\gamma_- f_i) \quad . \tag{4}$$

2 Model extensions

Mitniski et al. use a shifted linear preferential attachment algorithm to generate the network representing the human body. This network does not exhibit properties typically observed in real networks, such as the fact that the average clustering coefficient is independent of the number of nodes in the network [1]. As discussed by Ravasz, Barabási [5] a further common feature of real world networks is a high degree of clustering which they argue is a consequence of hierarchical organization. This hierarchical structure also makes sense intuitively in the human body, as cells make up tissue, which make up organs, which make up organ systems. Therefore I believe that any realistic network model of the human body should exhibit hierarchical modularity.

The second change I wanted to implement was forcing the damage to start at the cellular level. Given that some of the high degree nodes are interpreted as deficiencies such as the ability to read or having a stroke, I believe the assumption that any node can randomly become damaged does not make much sense. A person with an otherwise healthy body does not randomly have a stroke but rather the stroke is a result of the underlying biological functions being damaged, which then results in a stroke. This also goes hand in hand with the hierarchical interpretation of the body and the low degree nodes representing cells of the body.

Given the importance of the exponential dependence of the damage rate on local frailty of a node (Equation 3) for this model, I believe that the emergence of this exponential damage rate should be explained. Using Ledbergs approach I interpret each node as an M/M/1 (first in, first out) queue at which damage arriving in the queue is a Poisson process with parameter λ and the time to service the damage is exponentially distributed with parameter μ. However, μ is dependent on the local frailty of the node and decreases linearly in the fraction of its neighbours that are damaged. The interpretation of this is that the body is continuously healing itself, but as more nodes become damaged its ability to do so decreases. If we assume that the queue is at the stationary distribution (and this exists under certain conditions), then we find the exponential dependence of a nodes damage rate on local frailty. As stated by López-Otín et al., "time-dependent accumulation of cellular damage is widely considered to be the general cause of aging" [3]. They propose 9 hallmarks that contribute to the cellular and molecular aging process, which I summarize in only one parameter λ. I also show that explicitly simulating the queues can explain Gompetz's law and it is not necessary to work with the stationary distribution of the queue.

In summary, damage arrives according to a Poisson process at the cells, which are interpreted as the low-degree nodes in the model. A cells ability to repair itself, which in our model means service the damage

waiting in the queue, worsens as its neighbouring cells become damaged. As highly connected clusters of cells become damaged, the tissue which is made up of these cells becomes damaged. From clusters of tissue the damage spreads to the organs that are made of the tissue, then to the organ systems depending on the organs and finally to higher order functions of the body that are dependent on the different organ systems functioning properly. In this way the model fully explains the process of aging, from the cellular level to the patterns observed in the frailty index, without requiring age-specific programming.

3 Discussion and extensions

- Add some heterogeneity in the damage rates λ since some nodes accumulate damage faster than others. This could by done by estimating the damage rates for different cell groups and applying these rates to different cell clusters in the network.
- Can we use this model for opinion dynamics? Say that nodes are now individuals and everyone has opinion A. λ is the rate at which arguments for a new opinion B, which contradicts A, arrive at a node. The repairing through neighbouring nodes can now be interpreted as the social pull towards conformity with friends, who argue against each new argument that arrives in the queue. So the same dynamics, with exponential damage rates, may apply to opinion dynamics. It would be interesting to investigate the dynamics when we make λ an increasing function in the proportion of nodes already of a certain opinion and investigate the attractors of the system. Furthermore, λ could be varied per cluster in the network, similar to cells having different damage rates. An example could be that λ is a function of the distance to the damaged nodes in the network.
- I am planning to further investigate where in the network it is best to measure in order to get an overview of the overall health of the network. Mitnitski et al. use the highest degree nodes for the FI, but my results indicate that selection nodes by other centrality measures may be more appropriate. This could also be applied to opinion dynamics, if we want to know how far opinions have penetrated a network, where is it best to measure?
- I would like to further investigate the self-similarity of the system. Gompetz's law is observed in many species with varying time scales including in single-celled bacteria. If this also holds true for the human body, then each of our cells exhibits Gompertz's law and these cells are inter-connected, healing each other in the hierarchical network structure I propose above. I would like to see if Gompetz's law also holds for any sub-cluster of nodes in the network. So Gompetz's law holds for the cells, which are clustered together as tissue, for which Gompertz's law also holds, and so on.

References

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