mitochondria exploit a similar mechanism to generate ubiquinol and thereby repair oxidative damage to mitochondrial membrane lipids.

Mao and colleagues hypothesized that a system mitigating lipid peroxidation also exists in mitochondria. Given the close relationship between cellular metabolism and ferroptosis, the authors focused on metabolite molecules that are altered in cancer cells on lipid peroxidation. Surprisingly, they observed that peroxidation is associated with substantial changes in the abundance of metabolites in the pathway that synthesizes the pyrimidine bases that are a component of DNA and RNA. Building on this observation, the authors investigated the possibility that a component of this synthesis pathway is involved in preventing ferroptosis.

Most of the components of this pathway exist in the cytoplasm, but one enzyme, DHODH, is found in mitochondria. DHODH catalyses the conversion of the molecule dihydroorotate to orotate through an oxidation reaction that uses ubiquinone and thereby generates ubiquinol. Further experiments by Mao *et al.* revealed that DHODH protects cells against lipid peroxidation by regenerating ubiquinol, enabling ubiquinol-mediated repair of oxidative damage to mitochondrial lipids (Fig. 1). Supplementing cells with the end products of the pyrimidine-synthesis pathway did not affect lipid peroxidation, demonstrating that this anti-ferroptotic role of DHODH is independent of its function in pyrimidine synthesis.

These findings establish DHODH-mediated regulation of ubiquinol production as an efficient system for the mitigation of lipid peroxidation exclusively in mitochondria, in a mechanism that has echoes of the FSP1 system. Interestingly, a version of the GPX4 protein is found in the mitochondria of some cells, and its level of expression varies in different types of cancer. This mitochondrially localized GPX4 is not essential for mouse survival[7], indicating that it has a redundant role. By contrast, DHODH is ubiquitously expressed and has a role in cell proliferation owing to its function in nucleotide synthesis. Rapidly dividing cells, such as cancer cells, might therefore take advantage of this active pathway as a way to inhibit lipid peroxidation.

Indeed, Mao and colleagues found that if human tumour cells that expressed low levels of GPX4 were transplanted into mice treated with an inhibitor of DHODH, the resulting loss of DHODH function led to ferroptosis of the cells and impaired tumour growth. The effect was independent of DHODH's role in pyrimidine synthesis. It remains to be seen whether this mitochondrial ferroptosis-blocking antioxidant system contributes to the spread of cancer cells through metastasis[8] or to the tumour response to radiotherapy[9]. These are processes in which the induction of ferroptosis might help to thwart tumour progression. Potent DHODH inhibitors are being developed as anticancer agents, and are currently undergoing clinical trials. Perhaps they will be particularly effective in cancer cells that have low levels of expression of GPX4.

Mao and colleagues' discovery of a system for the specific protection of mitochondrial membranes suggests that dedicated mechanisms to counteract lipid peroxidation might exist in other subcellular compartments. Interestingly, squalene, which is an intermediate molecule in the biosynthetic pathway that generates cholesterol, protects cancers called lymphomas from lipid peroxidation, and is found in high concentrations in lipid droplets[10]. However, it is unclear whether squalene's protective function is due to this specific localization to droplets.

"Potent inhibitors of this enzyme are being developed as anticancer agents."

Organelles such as the endoplasmic reticulum and peroxisomes also harbour ROS-generating reactions. Glutathione and tetrahydrobiopterin are redox-active molecules (which can alter the oxidation state of other molecules), and thus might offer alternative ways to combat lipid peroxidation in such cases. However, the precise mechanisms and components that could enable the transport of these molecules to organelles are poorly understood. Advances in ways of assessing the molecular and protein compositions of organelles, through techniques such as metabolomics and proteomics, should provide insights into this fundamental issue, and improve our understanding of the role of antioxidants in tumour progression.

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Complexity science

Law of human travel uncovered

Laura Alessandretti & Sune Lehmann

An analysis of mobile-phone tracking data has revealed a universal pattern that describes the interplay between the distances travelled by humans on trips and the frequency with which those trips are made. **See p.522**

As a scientist, you sometimes come across a finding that is clear and robust, revealing a pattern that was right in front of you all along – and which makes you want to kick yourself for not noticing it before. The universal visitation law of human mobility, reported on page 522 by Schläpfer *et al.*[1], is just such a finding. The authors uncover a pattern of human behaviour that connects travel distance to the frequency of trips.

Consider any two places. Can we predict how many people travel from one to the other, and vice versa, on the basis of the position and simple characteristics of the two locations? This question is at the core of a large body of literature whose origin dates back to the mid-nineteenth century. In 1885, the geographer Ernst Ravenstein showed empirically that two key elements explain the number of individuals who move between any two places[2]: the distance between the places, and the socio-economic properties of the origin and destination. The number of travellers tends to decrease with distance, for example, and more-populated places attract more travellers.

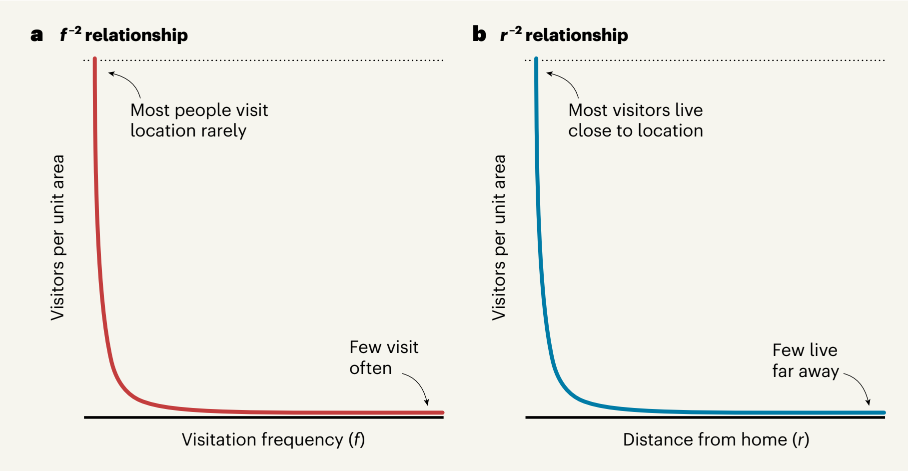

Figure 1 | A universal law of human mobility. Schläpfer *et al.*[1] analysed mobile-phone tracking data to determine the patterns of human journeys in several cities. **a**, The authors find that, for people who live at a specific distance r_0 from a particular location, the number of individuals per unit area who travel with a visitation frequency f to that location is inversely proportional to f^2. **b**, An inverse-square relationship is also observed for the distance from home, r, given a specific visitation frequency f_0. That is, for people who travel with a given frequency of trips f_0 to a particular location, the number of individuals per unit area who travel a distance r from home is inversely proportional to r^2. The observed relationships hold for any choice of location, r_0 and f_0. The graphs shown are illustrations of the observed relationships, and do not represent actual data.

These key observations were later integrated into the gravity law of human mobility, which states that the number of travellers between two cities increases with a power of the cities' population sizes, and decreases with a power of the distance between them[3]. A refinement of the gravity law, known as the radiation model, proposes that the number of travellers does not depend directly on the distance between two cities, but rather on the number of places between the cities at which people would realistically stop[4].

Research into human mobility has flourished in the past few years, as a result of data becoming available with increasingly fine spatial and temporal resolution[5]. This has allowed researchers to adjust the radiation and gravity models, and a plethora of variations, to capture travel patterns on a range of timescales, including home relocation (residential mobility), airline travel, urban transportation and commuting. Schläpfer and colleagues now report a fundamental discovery in this highly active area of research. They have identified a key component that was missing from existing theoretical frameworks of human mobility: visitation frequency (f), the number of trips that someone makes to a location per unit of time.

The authors made their discovery by reframing the challenge faced by modellers. Instead of focusing solely on distance and sociodemographic features, they asked a further question: 'How many people living in any given place travel to any other place exactly n times in a period T?' This change in perspective is possible because mobility data for individuals are now available from mobile-phone tracking. By studying mobility traces extracted from phones at seven urban locations around the world, the authors uncovered a phenomenological law that answers their question: the number decreases with r^{-2} (where r is the distance from someone's home to a given location), and with f^{-2}, where $f = n/T$ (Fig. 1).

Surprisingly, this law is valid for all the widely different urban systems considered in the study, and thus provides a general framework for describing and predicting mobility flows across timescales. Importantly, the model accommodates diverse mobility behaviours, from commuting to residential mobility, without requiring a change of parameters.

> **"The findings pave the way for a deeper understanding of how individual and collective mobility patterns are connected."**

To understand how the observed pattern emerges robustly from the multitude of individual behaviours, Schläpfer *et al.* developed a model of the mobility of individuals that incorporates realistic and well-understood mechanisms, such as people's tendency to explore places that are popular with other visitors, and preferential return — an empirical phenomenon in which the number of visits received by a location is proportional to the number of visits previously received[6]. This model reproduces the collective patterns of mobility observed in the phone data. By linking the mobility of individuals to collective outcomes, the authors' work helps to narrow the gap between two streams of literature that have previously been broadly distinct[5]. The findings therefore pave the way for studies that could deepen our theoretical understanding of how individual and collective mobility patterns are connected.

One unanswered question is whether the patterns of mobility observed in urban areas also apply outside cities. The geographies of rural areas are less centralized and contain fewer places of interest to visitors than do urban areas; these characteristics might result in travel patterns different from those observed by Schläpfer and colleagues. Another key question is whether mobility patterns are different for trips that are not anchored to people's homes.

In their modelling of travel patterns, the authors assume that people head straight home after visiting any location. But in the real world, geographical considerations and the need to minimize travel time tend to result in trips in specific reccurring sequences. People often visit places in a certain order, for example going from work to the supermarket and gym, and then home. We therefore anticipate that models that capture the ordering of trips will be key to providing a truly comprehensive description of collective mobility flows across space and time, and even more accurate predictions of real-world behaviour. In the meantime, we expect the mobility patterns uncovered by Schläpfer *et al.* to be useful for a variety of purposes, from epidemic modelling to transportation planning and urban design.

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