

Degrees of control

One might expect that social networks would generally be harder to control than naturally occurring systems such as biological networks. But this is not so, according to a new study. [SEE ARTICLE P.167](#)

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Networks can be found all around us. Examples include social networks (both online and offline), mobile sensor networks and gene regulatory networks. Such constructs can be represented by nodes and by edges (connections) between the nodes. The nodes are individual decision makers, for instance people on the social-networking website Facebook or DNA segments in a cell. The edges are the means by which information flows and is shared between nodes. But how hard is it to control the behaviour of such complex networks? On page 167 of this issue, Liu *et al.*¹ show that the answer to this question is anything but intuitive.

The flow of information in a network is what enables the nodes to make decisions or to update internal states or beliefs — for example, an individual's political affiliation or the proteins being expressed in a cell. The result is a dynamic network, in which the nodes' states evolve over time. The overall behaviour of such a dynamic network depends on several factors: how the nodes make their decisions and update their states; what information is shared between the edges; and what the network itself looks like — that is, which nodes are connected by edges.

Imagine that you want to start a trend by influencing certain individuals in a social network, or that you want to propagate a drug through a biological system by injecting the drug at particular locations. Two obvious questions are: which nodes should you pick, and how effective are these nodes when it comes to achieving the desired overall behaviour? If the only important factor is the overall spread of information, these questions are related to the question of finding and characterizing effective decision-makers. However, the nodes' dynamics (how information is used for updating the internal states) and the information flow (what information is actually shared) must also be taken into account. In their study, Liu and co-workers¹ do just this by combining the principles of network science with tools found traditionally in the domain of control theory^{2,3}.

Central to the question of how information, injected at certain key locations, can be used to steer the overall system towards some desired performance is the notion of



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Figure 1 | Tough job. Liu *et al.*¹ show that complex networks such as biological networks, metaphorically depicted by this locust swarm, are not at all easy to control.

controllability — a measure of what states can be achieved from a given set of initial states. Different dynamical systems have different levels of controllability. For example, a car without a steering wheel cannot reach the same set of states as a car with one, and, as a consequence, is less controllable.

Liu and colleagues¹ found that, for several types of network, controllability is connected to a network's underlying structure^{4–6}. The authors identified what driver nodes — those into which control inputs are injected — can direct the network to a given behaviour. The surprising result is that driver nodes tend to avoid the network hubs. In other words, centrally located nodes are not necessarily the best ones for influencing a network's performance. So for social networks, for example, the most influential members may not be those with the most friends.

The result of this type of analysis^{1,4} is that it is possible to determine how many driver nodes are needed for complete control over a network. Liu *et al.* do this for several real networks, including gene regulatory networks for controlling cellular processes, large-scale data networks such as the World Wide Web, and social networks. We have a certain intuition about how

hard it might be to control such networks. For instance, one would expect cellular processes to be designed to make them amenable to control so that they can respond swiftly to external stimuli, whereas one would expect social networks to be more likely to resist being controlled by a small number of driver nodes.

It turns out that this intuition is entirely wrong. Social networks are much easier to control than biological regulatory networks, in the sense that fewer driver nodes are needed to fully control them — that is, to take the networks from a given configuration to any desired configuration. Liu and colleagues find that, to fully control a gene regulatory network, roughly 80% of the nodes should be driver nodes. By contrast, for some social networks only 20% of the nodes are required to be driver nodes. What's more, the authors show that engineered networks such as power grids and electronic circuits are overall much easier to control than social networks and those involving gene regulation. This is due to both the increased density of the interconnections (edges) and the homogeneous nature of the network structure.

These startling findings¹ significantly further our understanding of the fundamental

properties of complex networks. One implication of the study is that both social networks and naturally occurring networks (Fig. 1), such as those involving gene regulation, are surprisingly hard to control. To a certain extent this is reassuring, because it means that such networks are fairly immune to hostile takeovers: a large fraction of the network's nodes must be directly controlled for the whole of it to change. By contrast, engineered networks are generally much easier to control, which may or may not be a good thing, depending on who is trying to control the network. ■

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CANCER

The flipside of Notch

Mutations that lead to increased activity of the Notch signalling pathway are well defined in human cancer. New work implicates decreased activity of this pathway in a type of blood cancer. SEE LETTER P.230

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Some of the most common and well studied mutations in human cancers affect signal-transduction pathways. For instance, mutations that lead to increased activity of the receptor protein Notch are frequently found in a type of blood cancer called T-cell acute lymphoblastic leukaemia/lymphoma¹. On page 230 of this issue, Klinakis *et al.*² report that mutations that lead to reduced activity of this protein are associated with another human blood cancer, chronic myelomonocytic leukaemia. This finding suggests that Notch can have either an oncogenic or a tumour-suppressive effect in blood cancers.

The Notch signalling pathway is evolutionarily conserved and has crucial roles in the development and maintenance of embryonic and adult tissues. Notch signalling is initiated when one cell expressing the appropriate ligand interacts with another cell expressing a Notch receptor. Ligand–receptor binding leads to a series of steps involving Notch processing. One such step requires the γ -secretase enzyme complex, which, through protein cleavage, generates a portion of the Notch receptor — called the Notch intracellular domain (NICD) — that is no longer bound to the cell membrane and that relocates to the nucleus (Fig. 1).

In the nucleus, the NICD interacts with DNA-bound protein factors (CSL/CBF1/RBPj γ) and recruits MAML proteins to modulate the expression of many genes³. One of the genes is the Notch target *Hes1*, whose increased

expression is part of the mechanism by which Notch signalling influences cellular physiology. The functions of the Notch pathway are highly cell-type dependent in different embryonic and adult tissues, as well as in cancers⁴. It therefore seems likely that Notch regulates diverse context-specific gene-expression programs that we are just beginning to understand.

To investigate the role of Notch in the haematopoietic system, Klinakis *et al.*²

specifically inactivated the Nicastrin gene in mouse blood cells. (Nicastrin is an essential component of the γ -secretase complex and so is required for the Notch-pathway function.) Surprisingly, the mice died relatively quickly — 20 weeks after birth — from a blood disorder similar to human chronic myelomonocytic leukaemia.

The γ -secretase complex has other functions besides processing Notch⁵. However, the authors confirm the significance of losing Notch signalling by showing that deletion of just the Notch1 and Notch2 receptors from blood cells is sufficient to produce the same cancer in mice. In addition, activation of the Notch pathway in cells lacking Nicastrin ameliorated the leukaemia, further supporting the crucial role of the Notch pathway.

Klinakis and colleagues also show that the effects of Notch loss on blood cells is cell-autonomous — that is, the cancer is due to the loss of Notch function in blood cells and not to its effects on other organs that then feed back to blood cells. This is an important demonstration, because the disruption of Notch signalling in mouse skin also leads to blood disorders in a non-cell-autonomous manner^{6,7}.

Klinakis *et al.* further report that Notch signalling actively represses a gene-expression program in blood stem and progenitor cells that is associated with differentiation of these cells along the myeloid lineage. Thus, loss of Notch signalling seems to ‘rewire’ early blood cells to inappropriately express genes specifying a myelomonocytic fate that, in mouse models, leads to leukaemia.

In addition to defining a new role for Notch signalling as a suppressor of leukaemia

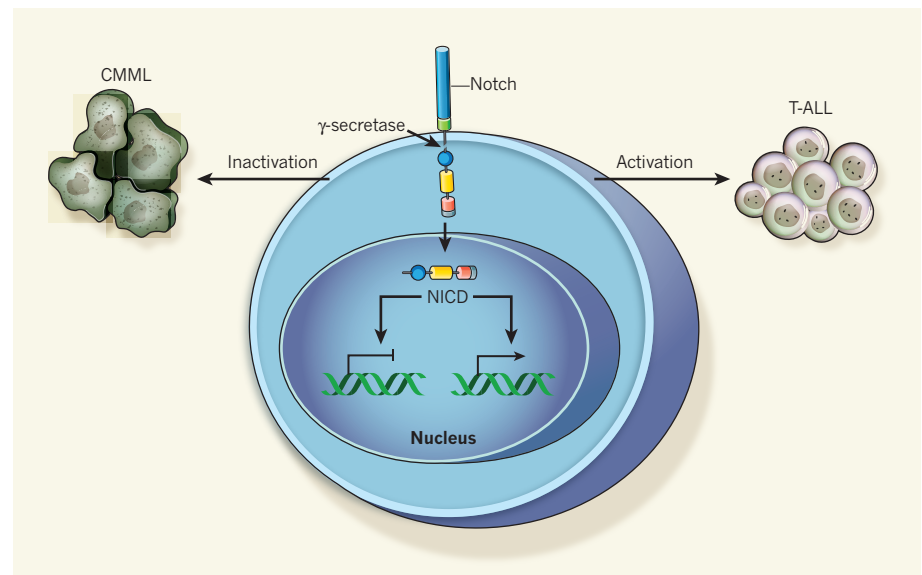


Figure 1 | The Notch signalling pathway and blood disorders. On interaction with an appropriate ligand (not shown) the Notch receptor is processed by the γ -secretase complex to form an intracellular domain (NICD), which accumulates in the nucleus to modulate gene expression. Activating mutations in Notch receptors have been described in T-cell acute lymphoblastic leukaemias/lymphomas (T-ALL), making the receptors an attractive drug target for this cancer. But Klinakis *et al.*² ascribe a tumour-suppressor role for Notch in another blood cancer, chronic myelomonocytic leukaemia (CMML).