centromeres differ in size, structure and DNA composition[3]. In some organisms, known as holocentric species, centromere activity is spread along the entire length of the chromosome rather than concentrated at a single site[5]. Other organisms, such as single-celled parasites called trypanosomes, use a completely different chromosome-segregation system that does not rely on the centromere protein CENP-A at all[6]. Whether the same principles of progressive evolution govern the appearance of this extreme diversity remains to be seen.

Another open question is why centromeres are subject to such rapid evolution. A leading explanation is the 'centromere drive' hypothesis[7], which proposes that stronger centromeres are preferentially transmitted to offspring when the reproductive cells (gametes) of females are produced through 'meiotic' cell division. During this process, cells divide asymmetrically – only one of the four cells produced by meiosis will become the gamete. However, this mechanism does not apply in yeasts, in which all of the products of meiosis are packaged into spores and retained. In the absence of such asymmetry, the evolutionary forces that drive rapid centromere evolution in yeasts remain unclear.

One possibility is that centromeres act as permissive landing sites for transposon insertions. Unlike insertions into essential genes, which would result in cell death, transposon integrations at centromeres might have only moderate effects on chromosome transmission. Many yeasts can also tolerate chromosomal imbalances that arise from occasional segregation errors, which can even enhance adaptability under certain conditions[8]. Under these circumstances, modest reductions in segregation efficiency caused by transposon insertions could be tolerated, enabling subsequent adaptation, including the co-option of transposon-associated DNA-binding proteins to help to specify centromeres. In this case, rapid centromere evolution could reflect a response to invasion by transposons and other 'selfish' DNA elements (such as those from viruses) that insert themselves into the genomes of their hosts.

Because many centromeres are large and made up of repeated sequences, their full sequences can be difficult to assemble with conventional DNA-sequencing technologies. With the advent of 'long read' sequencing that enables large, complex fragments to be read without interruption, scientists could begin to assemble even repetitive full centromeric sequences – bringing evolutionary genomics into an era that promises to answer some of these open questions.

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In retrospect

Forty-five years of evolving insights into cooperation

Sarah Mathew & Robert Boyd

A 1981 publication showed how cooperators can prevail over defectors, laying the foundation for how the evolution of cooperation between unrelated individuals is studied.

Ever since Charles Darwin, scientists studying evolution have grappled with how cooperative behaviours that are costly to an individual but beneficial to others can be consistent with maximal fitness. In 1981, writing in *Science*, Robert Axelrod and William D. Hamilton[1] presented key findings on how such cooperation can evolve. They accomplished this by weaving together two emerging ideas of the time in this area of research.

Evolutionary theorists John Maynard Smith and George Price had shown how game theory – a mathematical framework for studying interactions in which the outcome depends on the actions of an individual as well as those of others – could be used to identify social behaviours that arise through natural selection[2]. Separately, evolutionary biologist Robert Trivers had reasoned that individuals could gain long-term benefits by conditionally cooperating with partners if they had cooperated with them previously, reframing reciprocal altruism as forward-looking selfishness[3].

Combining the mathematical framework of evolutionary game theory with the logic of reciprocal altruism, Axelrod and Hamilton identified the conditions under which cooperators could outperform defectors and persist in a population when partners interact repeatedly. Notably, their analysis revealed that cooperation could evolve among unrelated individuals, a phenomenon that couldn't be explained by Hamilton's 1964 theory of kin selection[4], which showed how natural selection can favour helping relatives.

Fittingly, Axelrod and Hamilton's paper concluded: "Darwin's emphasis on individual advantage has been formalized in terms of game theory." Forty-five years and more than 50,000 article citations later, it is striking how well this closing remark foreshadowed the way in which cooperation would be studied in the ensuing decades – often for the better, although sometimes for the worse.

The key innovation of Axelrod and Hamilton's work was to predict which behavioural strategy (a rule that specifies which action to perform) would be favoured by selection in an iterated prisoner's dilemma (IPD) – a scenario in which pairs of individuals interact repeatedly and, in each interaction, can either cooperate (incur a cost to provide a benefit to the other player) or defect (incur no cost and provide no benefit). In any given interaction, cooperation pays less than defection, but cumulative pay-offs will depend on both players' strategies. By capturing the challenge of a scenario in which individuals seek long-term gains while facing the threat of immediate exploitation, the IPD has become the gold standard for modelling the evolution of cooperation. Inevitably, its simplifying assumptions have dominated and constrained the insights generated by the vast theoretical literature inspired by the 1981 paper.

Axelrod and Hamilton's analysis revealed one IPD strategy as the clear winner in the evolutionary competition. Termed tit-for-tat (TFT), it is intriguingly simple – start by cooperating, then do as your partner did in the previous interaction[5]. The dominance of TFT has important biological implications. More-complex strategies than TFT were not only unnecessary, but actually inferior, suggesting that reciprocity does not require

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Figure 1 | Chimpanzees (*Pan troglodytes*) engaging in the cooperative behaviour of grooming.

sophisticated cognition. The paper went on to detail how creatures ranging from micro-organisms to social animals could benefit from reciprocal cooperation.

The logic of cooperation that the paper revealed is so compelling that it leaves the following puzzle. Why don't we see cooperation in situations in which the theory predicts we should? Efficiency gains from specialization, trade, turn-taking, mutual aid and joint action can help to overcome time and energy constraints across diverse biological contexts, which should make cooperation ubiquitous. Shouldn't reciprocity therefore be widespread, at least in social species with the cognitive capacity to recognize individuals? Yet, evidence for reciprocal cooperation in animals other than humans remains scarce[6,7].

There are other discrepancies between theoretical predictions and what happens in the real world. According to the theory, it is the ratio of benefits and costs that matters, not their absolute magnitude. But reciprocal cooperation in species other than humans mostly involves low-benefit, low-cost exchanges such as grooming (Fig. 1), not high-stakes transfers of resources or services. Axelrod and Hamilton's analysis suggests that even a 50% chance of future interactions should yield levels of cooperation that are the same as those associated with individuals as closely related as siblings. However, in most animal societies, nepotism seems a much more potent driver of cooperation than do the potential gains from reciprocal cooperation with unrelated individuals.

Among the many extensions of the Axelrod–Hamilton model, two are especially relevant to explaining why reciprocal cooperation is less prevalent than predicted. The first extension concerns errors[8]. An individual who intends to cooperate can fail to do so for various reasons. For example, you could have planned to help your friend, but you arrived too late. Even worse, partners can have different perceptions of what occurred in previous interactions. For instance, you might think you defended your friend vigorously in a dispute, but your friend might think your defence was half-hearted. Errors radically reduce the pay-off of TFT by igniting an endless sequence of retaliatory choices.

Errors do not preclude the evolution of reciprocity, but taking them into account demands more-complex versions of the TFT strategy. One example, known as contrite TFT, restores cooperation after erroneous defections by attending to what is described as 'standing'— a variable that tracks whether the past behaviour of an individual and that of their partner were justified[9]. Divergent perceptions might require third-party adjudication in order for TFT-like strategies to achieve high rates of cooperation[10].

The second extension of the Axelrod–Hamilton model concerns what is termed indirect invasion. In a social environment dominated by 'nice' strategies such as TFT, indiscriminate cooperators can do just as well as those using TFT, and if indiscriminate cooperators increase in frequency, this eventually opens the door for defectors to rise in numbers. When the possibility for such indirect invasion is incorporated into the model, simple reciprocating strategies such as TFT do not prevail under the conditions assumed by Axelrod and Hamilton[11]. When errors and indirect invasion are considered together, multiple strategies can persist and, over time, cooperation tends to settle at intermediate levels[12].

Both extensions remain rooted in the IPD framework. To bring theory closer to what is observed in empirical results, fresh models are needed that move beyond the IPD's simplifying assumptions[13]. In the real world, costs and benefits vary across interactions. Opportunities to provide help can remain one-sided for extended periods. Individuals can leave unproductive partnerships and begin new ones. Long-term cooperation might require not only providing timely benefits, but also performing low-stakes behaviours — such as spending time with or grooming a partner to signal ongoing commitment to the relationship.

The challenge, then, is not just how to interact with a fixed partner, but deciding whom to cultivate as a long-term one. Modelling the dynamics of relationships in a world in which individuals can maintain only a limited number of close ties[14,15] might help to clarify particular questions. One is the puzzle of why, despite the dominance of scorekeeping strategies such as TFT in theory, when it comes to practice, close friends are reluctant to keep score[16]. Indeed, doing so would erode rather than help to sustain such a relationship.

Good theories must simplify reality, but in doing so, they can narrow the scope of scientists' imaginations. Axelrod and Hamilton's paper was transformative — perhaps too much so. It ignited vigorous theoretical explorations that extended evolutionary game theory within the confines of the IPD. A legacy of this work is that pairwise cooperation in repeated interactions became equated with reciprocity, and reciprocity with TFT-like scorekeeping.

It might be time for researchers to pause and return to the textured realities of cooperation in the natural world, so that we can reconceive models that capture the dynamics of cooperative relationships in new ways. After all, that is precisely what Axelrod and Hamilton did in 1981.

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