hyperactive. Increasing Wnt signals in McSCs induced their differentiation into melanocytes and prevented the cells from dedifferentiating in the bulge. The authors showed that the Wnt signals that activate McSCs come from surrounding cells in the hair germ and bulge – and genetically inhibiting this cell–cell signalling prevented McSCs from differentiating.

Melanocyte production is also stimulated by sunlight. Ito and colleagues found that irradiating mouse skin using ultraviolet light increased pigment production from melanocytes. But, again, the melanocytes retained the ability to yo-yo back to undifferentiated McSCs.

Finally, the authors asked how McSC behaviour was affected by ageing – a question pertinent to those of us with grey hair, which is caused by a lack of pigmentation. Analysis of follicles from aged mice revealed that McSC transit was diminished, meaning that fewer melanocytes were produced, thus leaving new hair shafts grey. This finding could open the door to new treatments to prevent greying by improving McSC activity.

It is worth noting that McSCs are thought to be key players in melanoma[14], a life-threatening cancer. Sun *et al.* suggest that the developmental plasticity they observed might explain why melanoma is so difficult to treat. It is also interesting to speculate that the reason hair greying is one of the first signs of ageing might be because the way in which McSCs produce progeny is more physically demanding than is the case for other stem cells. This would imply that the cells simply become worn out earlier. However, the premature ageing of McSCs could be an evolutionary strategy to prevent the formation of melanoma – if the cells stop replicating, they can't acquire the mutations that lead to cancer.

The unusual observations made in this study were possible only because the authors' innovative approach allowed them to monitor the same cells in their niche over time. Going forward, similar techniques should be applied where possible to take a fresh look at the behaviour of other populations of adult stem cells. Perhaps this yo-yoing behaviour will turn out not to be so unusual, after all.

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1. Sun, Q. *et al. Nature* **616**, 774–782 (2023).
2. Blanpain, C., Horsley, V. & Fuchs, E. *Cell* **128**, 445–458 (2007).
3. Greco, V. *et al. Cell Stem Cell* **4**, 155–169 (2009).
4. Azkanaz, M. *et al. Nature* **607**, 548–554 (2022).
5. Zhang, C. *et al. Nature Aging* **1**, 889–903 (2021).
6. Ito, M. *et al. Nature Med.* **11**, 1351–1354 (2005).
7. Overturf, K. *et al. Am. J. Pathol.* **151**, 1273–1280 (1997).
8. Ziv, O., Glaser, B. & Dor, Y. *Dev. Cell* **26**, 3–7 (2013).
9. Puri, S., Folias, A. E. & Hebrok, M. *Cell Stem Cell* **16**, 18–31 (2020).
10. Murata, K. *et al. Cell Stem Cell* **26**, 377–390 (2020).
11. Waddington, C. H. *The Strategy of Genes* 1st edn (Allen & Unwin, 1957).
12. Watanabe, A., Yamada, Y. & Yamanaka, S. *Phil. Trans. R. Soc. Lond. B* **368**, 20120292 (2013).
13. Takeda, K. *et al. J. Biol. Chem.* **275**, 14013–14016 (2000).
14. Moon, H. *et al. Cell Stem Cell* **21**, 665–678 (2017).

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Engineering

Human–AI team halves cost of chip-design step

Ying-Lang Wang & Mao-Chih Huang

Engineers and algorithms have competed in a virtual test to design a step in the process of manufacturing computer chips. Pairing human expertise with computational efficiency proves most cost-effective, but only when the timing is right. **See p.707**

Swift progress in semiconductor technology has lowered the cost of computer chips, but it has also introduced challenges for chip manufacturers. The operational dynamics associated with production processes have become increasingly complex, requiring that intelligent solutions be developed to maintain the quality of ever-smaller chips. On page 707, Kanarik *et al.*[1] explore how artificial intelligence (AI) can be used to decrease the cost of designing semiconductor processes without compromising quality. Their game-based approach shows that AI is best used during the late stages of process development, and that a hybrid strategy involving both humans and AI can markedly reduce costs compared with an AI-free production line.

The authors built a virtual game that tests how well humans and computers can design a single step in the chip-fabrication process. The step involves plasma etching[2], in which a gas of ions and electrons (a plasma) is used to etch features into the surface of a solid – in this case, a hole in a film of silicon dioxide. The team used existing data and a plasma-physics model to simulate a realistic etch output from a collection of input parameters, such as pressure and temperature, which were chosen by the player.

The goal of the game was to minimize the cost of producing an etched hole with a set of target characteristics, such as depth and diameter. Each player submitted batches of 'recipes' for the etch until they met the target. Recipes were each assigned a cost of US$1,000, with an extra $1,000 for the overheads associated with each batch – in other words, the typical costs incurred during process design.

Three senior engineers, three junior engineers and three players with no relevant experience participated in Kanarik and colleagues' experiment. The engineers all undertook a rapid initial phase of 'rough-tuning' before fine-tuning their designs, and the senior experts' strategies cost around half as much as those of their junior colleagues. The winning human player was a senior engineer, who spent just $105,000 to meet the target.

The authors then used a machine-learning method known as Bayesian optimization to design computer players that could compete with the humans without any previous training. These players were assigned a success rate on the basis of the percentage of their attempts that beat the winning engineer's low cost. Only 13 out of 300 attempts did so. Kanarik *et al.* concluded that the algorithms were no match for the winning human, and hypothesized that the computer players' lack of expert knowledge made them waste time exploring the full range of possible processes.

This hypothesis prompted the authors to test a 'human first–computer last' strategy, in which the expert undertook the rough-tuning and constrained the search, before handing over to the algorithms for fine-tuning. They found that this implementation reduced the cost of reaching the target, and that the amount by which the computer player's success rate improved depended on the point at which the human relinquished control of the game (Fig. 1). Specifically, as the algorithm gained access to more expert data, the cost decreased – but only up to a certain point. Beyond this point, further expert data increased the cost without aiding the algorithm. At the threshold, the most successful

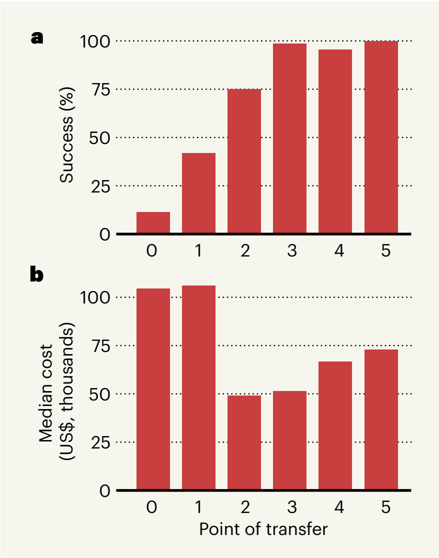

Figure 1 | A hybrid human–computer strategy for designing chip-fabrication processes. Using a virtual game, Kanarik *et al.*[1] tested how cost-effectively expert engineers and algorithms could design a step in the process of manufacturing semiconductor computer chips. The winning engineer completed the step at a cost of US$105,000, but the most successful algorithm matched this cost only 11% of the time. When the expert started the design process and the computer took over at a certain transfer point (where 0 indicates that no human was involved and 1 to 5 indicate little-to-large human involvement), the success rate increased (**a**) and the median cost decreased (**b**). However, this improvement was sensitive to the point of transfer: if it was too late in the game, the cost increased again. At the optimal transfer point (3), the human–computer team spent just $52,000. (Adapted from Fig. 3c of ref. 1.)

algorithm reached the target at a cost of just $52,000.

The implication is that algorithms need guidance from humans to improve semiconductor processes, but that human input can become costly if this guidance is prolonged. Applying Kanarik and colleagues' human first–computer last strategy to other processes in the semiconductor industry will therefore require careful consideration of the most advantageous point at which to switch from human-led to algorithmic development.

As well as designing processes, the authors' strategy could be applied as a means of monitoring equipment abnormalities during production. The increasing complexity of semiconductor technology has made it difficult to diagnose and classify faults using data-driven methods alone. Instead, intelligent devices with self-diagnosis and self-tuning capabilities are required to ensure that faults can be accurately detected and rapidly repaired. This, in turn, relies on integrating advanced AI algorithms and big-data analytics with the knowledge of engineering experts. Human input is also essential for monitoring these recovery processes.

For example, the ion-implantation process (in which impurities are deliberately injected into a chip device to improve its conductivity) involves targeting the semiconductor with a high-speed ion beam[3]. Accurate targeting is crucial for ensuring process uniformity and maintaining device yields, yet for manufacturers that prioritize product variety and customization over large output volumes, these beams must fulfil various device requirements. The ability to dynamically control the uniformity, strength and stability of the ion beam's electric current is therefore essential. Experienced human engineers are usually tasked with manually fine-tuning dozens of equipment parameters to achieve such control.

Over the past decade[4], several chip manufacturers have invested in and developed intelligent technologies such as the one reported by Kanarik and colleagues. Despite this, there are considerable challenges in implementing these technologies effectively. One key challenge is that the processes rely on external suppliers, many of whom are not able to provide integrated and intelligent equipment, especially in the software and data-engineering sectors. Transitioning from merely manufacturing hardware to also providing software solutions requires a mindset shift, but one that will ultimately propel the semiconductor industry into the digital future.

As fabrication processes improve, chip manufacturers must find ways of bridging the gaps between existing technologies and intelligent designs. Kanarik and colleagues have shown that combining AI with human experts is a fruitful strategy, but that careful timing is crucial to its success. By harnessing the power of AI and expert knowledge, hybrid approaches such as theirs will enable the semiconductor industry to maintain high-quality production standards in the era of digital transformation.

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1. Kanarik, K. J. *et al. Nature* **616**, 707–711 (2023).
2. Kim, K. *et al. Proc. SPIE* **8326**, 832605 (2012).
3. Williams, J. S. *Mater Sci. Eng. A* **253**, 8–15 (1998).
4. Kim, J. H. K., Lee, S. W. & Lee, S. *Int. J. Precis. Eng. Manuf.* **23**, 111–129 (2022).

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Virology

Influenza viruses don't play well with others

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Influenza viruses that infect the same host can interfere with each other's replication. This behaviour seems to result in spatial structuring of infected groups of cells in tissue, with implications for viral evolution.

Viral infections are often represented as a direct clash between a virus and its host. However, viruses that infect the same cell can also interact with each other, working jointly or in opposition. These collective interactions in viral populations are poorly understood, but are likely to be crucial in shaping infection dynamics and disease progression. Writing in *PLoS Biology*, Sims *et al.*[1] reveal one consequence of inter-virus interactions: influenza virus particles can restrict each other's spread, and, by doing so, partition a host into distinct territories of infection.

The idea of influenza viruses antagonizing one another is especially interesting given the many incentives that the viruses have to cooperate. The influenza genome comprises eight gene segments, but most individual viral particles (virions) lack functional copies of one or more segments, rendering them incapable of independent infection[2]. Co-infecting viruses can share gene segments, restoring their infectious capacity[3]. Co-infection can also accelerate viral replication kinetics, giving the virus a leg-up in its race to outrun the host's immune response[4]. Finally, viruses infecting the same cell can swap segments, to create progeny that are a genetic combination of the original strains. These reshuffling events build diversity in influenza populations, and sometimes result in the generation of new pandemic viruses[5].

However, despite the clear benefits of co-infection, once an influenza virus infects a cell, other virions are often blocked from infecting the same cell[6,7]. The mechanism underlying