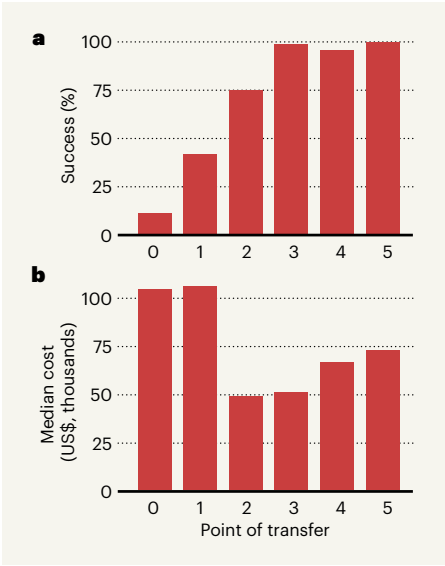

Figure 1 | A hybrid human–computer strategy for designing chip-fabrication processes. Using a virtual game, Kanarik *et al.*[1] tested how cost-effectively expert engineers and algorithms could design a step in the process of manufacturing semiconductor computer chips. The winning engineer completed 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.

Ying-Lang Wang and **Mao-Chih Huang** are in the Department of Electrical Engineering, National Cheng Kung University, Tainan City, Taiwan, Republic of China.
e-mail: ylwang@tsmc.com

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).

The authors declare no competing interests.

Virology

Influenza viruses don't play well with others

Mireille Farjo & Christopher B. Brooke

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

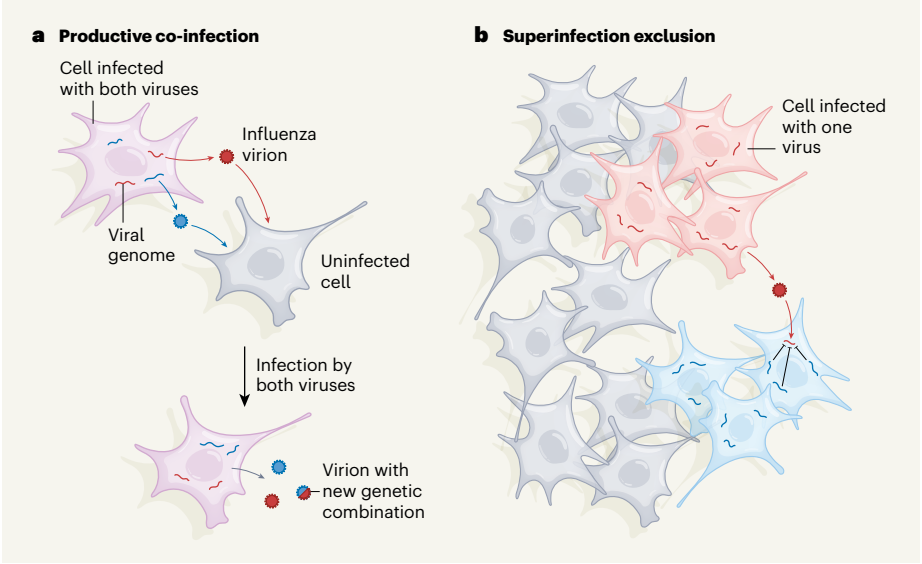

Figure 1 | Dynamics of influenza virus co-infection. To investigate the dynamics of co-infection by two different influenza viruses, Sims *et al.*[1] used viral particles (virions) engineered to express red or green fluorescent proteins. (Here, the virus carrying the green protein is depicted in blue.) **a**, The authors infected a single cell simultaneously with both viruses, which release their genomes into the cell. Virions produced in the infected cell enter a nearby cell within a short time of each other (less than two hours). Both viruses successfully infect the second cell and produce new virions, some of which are genetic combinations of the two strains. **b**, Next, the authors established different groups (foci) of cells infected by a single virus on a cell layer or in tissue. As the two foci expand and meet, virions from one virus attempt to infect a cell already infected with the other virus, but are blocked by a phenomenon called superinfection exclusion.

this effect — known as superinfection exclusion — and its consequences for infection dynamics in infected tissues are open for discussion. Given previous data suggesting that influenza virus spread in a host is highly spatially structured[8], Sims *et al.* hypothesized that superinfection exclusion at the boundaries of spreading foci of infection might lead to the emergence of a patchwork of spatially discrete virus populations in an infected host.

To investigate this possibility, the authors generated influenza viruses encoding either green- or red-coloured fluorescent proteins, allowing the viruses to be easily differentiated. By infecting cells with the green virus first and then with the red, the authors determined that superinfection exclusion begins about two hours after the initial infection, and that the effect increases exponentially as the infection runs its course. Notably, they also observed that the exclusion effect could not be overwhelmed by increasing the dose of the second virus.

The authors wondered whether the viral progeny released from an infected cell would interfere with one another's replication as they spread to nearby cells. To explore this scenario, the authors tracked the progression of infection initiated from a single cell that was simultaneously co-infected with both red and green viruses (Fig. 1a). They found that, under these conditions, red and green viruses released from the same cell could productively co-infect neighbouring cells — indicating that viruses released from the same parental cell did not interfere with each other.

Sims *et al.* then considered an alternative scenario, in which separately established foci of infection meet as they spread outwards (Fig. 1b). Imaging the spread of such infections, they observed that foci grew steadily — until they encountered another spreading focus. Then, the two viral populations would collide, but be prevented from mixing with each other by superinfection exclusion. The authors observed the same phenomenon in the lungs of infected mice, in which areas of infection were subdivided into discrete patches where only red or green viruses could grow, with minimal mixing of the two.

The balance of cooperation and exclusion described by Sims and colleagues probably profoundly influences the evolutionary potential of the virus. The discovery of non-overlapping regions of replication throughout infected tissue aligns with previous work demonstrating that genetically distinct 'infection islands' can arise in an influenza-infected host[8]. The current study provides further support for this model of infection, and introduces a specific, virus-mediated mechanism that might promote the spatial compartmentalization of viral populations.

This spatial structuring and compartmentalization is likely to influence the evolutionary potential of the virus in localized areas in several ways[9]. For instance, restricting the number of discrete viral genomes in an infected cell could limit a virus's effective 'ploidy' (gene copy number), which might influence the adaptability of viral populations and limit the potential for variants beneficial to the virus to emerge[10]. Restrictions on the spatial spread of viruses in tissues could also limit the chances that new beneficial variants that do emerge in one host can be transmitted successfully to another.

Sims and colleagues' findings also have implications for global viral evolution. By minimizing the extent of viral interaction during co-infection, superinfection exclusion will reduce the potential for genetic exchange and subsequent diversification. Chimeric viruses generated through co-infection have driven four of the five influenza pandemics of the past century[11]; understanding the specific factors that govern this process is crucial. Sims *et al.* reveal that spatial restriction of viral replication through superinfection exclusion might limit the generation of chimeric viruses, raising the possibility that superinfection exclusion curbs the pandemic potential of influenza viruses.

As with any good study, Sims and colleagues' paper raises as many questions as it answers. Perhaps the biggest is whether the superinfection exclusion effect is beneficial to the virus, and, if so, how? The role of the host in this process, if any, also remains unknown. Regardless of the answers, this exciting work establishes that superinfection exclusion is a key factor in shaping the dynamics of influenza virus infections, and emphasizes the need to better understand how collective interactions govern the behaviour of viral populations.

Mireille Farjo and **Christopher B. Brooke** are at the School of Molecular and Cellular Biology, University of Illinois at Urbana-Champaign, Urbana, Illinois 61801, USA. **C.B.B.** is also at the Carl R. Woese Institute for Genomic Biology, University of Illinois at Urbana-Champaign.
e-mail: cbrooke@illinois.edu

1. Sims, A. *et al. PLoS Biol.* **21**, e3001941 (2023).
2. Brooke, C. B. *et al. J. Virol.* **87**, 3155–3162 (2013).
3. Jacobs, N. T. *et al. Nature Commun.* **10**, 3526 (2019).
4. Martin, B. E., Harris, J. D., Sun, J., Koelle, K. & Brooke, C. B. *PLoS Pathog.* **16**, e1008974 (2020).
5. Neumann, G., Noda, T. & Kawaoka, Y. *Nature* **459**, 931–939 (2009).
6. Dou, D. *et al. Cell Rep.* **20**, 251–263 (2017).
7. Sun, J. & Brooke, C. B. *mBio* **9**, e01761-18 (2018).
8. Amato, K. A. *et al. Nature Commun.* **13**, 3416 (2022).
9. Gallagher, M. E., Brooke, C. B., Ke, R. & Koelle, K. *Viruses* **10**, 627 (2018).
10. Van de Peer, Y., Mizrachi, E. & Marchal, K. *Nature Rev. Genet.* **18**, 411–424 (2017).
11. Medina, R. A. & García-Sastre, A. *Nature Rev. Microbiol.* **9**, 590–603 (2011).

The authors declare no competing interests.
This article was published online on 5 April 2023.