

## MICROFLUIDICS

## How to tame a giant oscillation

Experiments and simulations show that trains of droplets in microfluidic networks undergo synchronized oscillations, and that strategies to prevent these oscillations can help maintain uniform distribution of red blood cells in microcirculation.

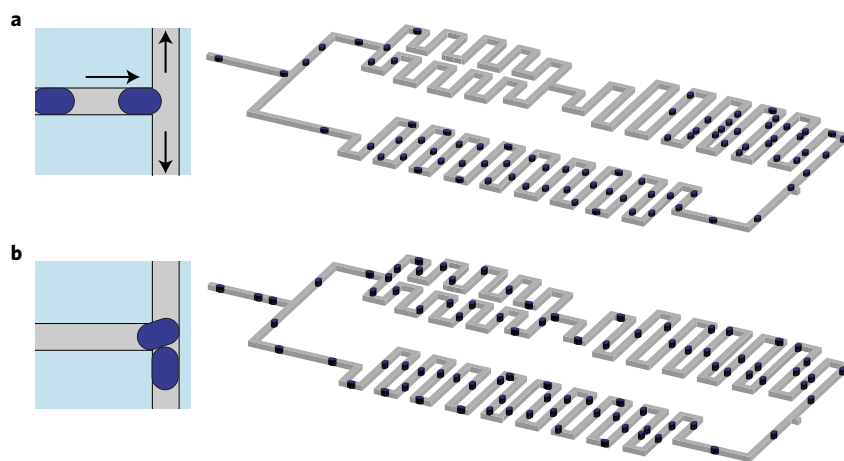
Siva A. Vanapalli

Oxygen-carrying red blood cells need to be distributed uniformly in both space and time in the branches of the microcapillary networks present in our vascular system. Large oscillations in the distribution of these cells can lead to pressure fluctuations causing hypertension or depleting surrounding tissues of oxygen, both of which can be fatal. And although fluctuations in capillary blood flow were noted almost a hundred years ago by the Nobel Prize-winning physiologist August Krogh<sup>1</sup>, the mechanisms underlying these fluctuations remain unclear<sup>2</sup>. But now, writing in *Nature Physics*, Olgierd Cybulski and co-workers have provided fresh insight into this problem by comprehensively studying the motion of trains of water droplets in microfluidic networks with vascular-like branching<sup>3</sup> — yet another demonstration of how a simple controllable system can inform our understanding of a complex biological phenomenon.

The systems studied by Cybulski and colleagues involved a single file of water droplets injected continuously into a microfluidic network such as that shown in Fig. 1, where a main branch emanating from the network inlet splits to form a daughter loop that rejoins at the network outlet. The key observation was that even though the droplets initially distributed themselves uniformly in the network, they gradually organized into a pack that then oscillated periodically between the two main branches (Fig. 1a).

The authors went to great lengths to establish experimentally that these synchronized oscillations were not just happenstance, but rather a robust phenomenon. They tested trains of droplets with varying intervals and sizes, and with different viscosity ratios. They also investigated networks that are more complex than those shown in Fig. 1. In all cases, packs of droplets alternated synchronously between branches of the network.

Why have these oscillations not been seen previously? Droplet traffic has been studied in microfluidic networks in the context of



**Fig. 1 | Droplets injected continuously into a simple microfluidic network form trains. a,** When there are no collisions at the junction, the trains oscillate between branches of the network. **b,** Droplet collisions at the junction can suppress these oscillations.

lab-on-chip devices, where there is a need to shuttle droplets to specific locations<sup>4</sup>. One explanation is that networks studied previously contain short branches in which droplet occupancy is low, in contrast to the authors' devices where the branches are rather long and can accommodate many droplets (see Supplementary Video 2 in ref. <sup>3</sup>). A related aspect is that fabrication of devices with large-scale networks is not easy — nor is ensuring the channels have robust wetting properties — and the authors implemented ingenious ways to overcome these issues.

But despite the robust demonstration of the self-sustaining oscillations, the general mechanism underlying this emergent behaviour remains to be fully elucidated. To explain their observations, the authors employed a resistive network model<sup>4</sup> where droplets were treated as independent point-load resistors, and the pressures and flow rates at every branch point were calculated using a system of linear equations analogous to Ohm's and Kirchhoff's laws of electrical circuits.

The simplicity of the resistive network model is certainly appealing and the

authors demonstrated good agreement between experiments and results from this model. However, what induces a uniformly distributed droplet flow to break open into packs of droplets that alternate between branches is unclear. When the droplets were distributed uniformly, the hydraulic resistance varied linearly with branch length, however, when packs of droplets began to form, the hydraulic resistance would vary nonlinearly with branch length. This crucial difference may need to be incorporated into the model to further unravel the mechanism.

The exciting finding from this study is that the oscillations in these networks are more of a norm than an exception. Therefore, Cybulski and colleagues sought to work out how to tame these oscillations. They showed that oscillations could be suppressed by inducing collisions between droplets at the junction, which prevented the droplets from deterministically choosing the branch with the highest flow rate (Fig. 1b). In addition, they showed that network topology could also be manipulated to suppress oscillations. For example, bridge


channels can be added between connected branches to harmonize the pressure fluctuations.

How do these findings impact our understanding of the mechanisms regulating fluctuations of capillary blood flow? In microcirculation, low-amplitude oscillations of  $O(0.1)$  Hz have been observed in the flow of red blood cells<sup>5</sup>. This is about an order of magnitude lower than a human heart beat. Arguments have been proposed that such oscillations may not be due to rhythmic control of heart or vasomotion, but are instead regulated by non-biological mechanisms.

Current physical approaches to explain these oscillations invoke continuum models of blood rheology<sup>6</sup>. However, the work of Cybulski and co-workers suggests that akin to trains of droplets, the discrete flow of red blood cells in vascular networks can

give rise to oscillations. To corroborate their premise, they scaled down the dimensions of the networks to individual cells and calculated a parameter that describes the degree to which decision making at the junction is deterministic. Strikingly, they found the low-amplitude oscillations occurred at parameter values that were consistent with in vivo data.

The study by Cybulski and colleagues highlights a rich system in which collective hydrodynamic resistive interactions give rise to fascinating spatiotemporal dynamics. (I would highly recommend readers to watch the visually stimulating videos that accompany ref. <sup>3</sup>. Given that the authors have identified the minimal network (Fig. 1) that exhibits synchronized oscillations, the ground should now be fertile for theoretical developments. And their work clearly provokes the need for more experiments

to elucidate the mechanisms underlying the long-standing problem of how and why oscillations arise in blood flow. 

**Siva A. Vanapalli**

*Department of Chemical Engineering, Texas Tech University, Lubbock, TX, USA.*

*e-mail: siva.vanapalli@ttu.edu*

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## References

1. Krogh, A. *Anatomy and Physiology of Capillaries* (Yale University Press, 1922).
2. Fung, Y. C. *Microvasc. Res.* **5**, 34–48 (1973).
3. Cybulski, O., Garstecki, P. & Grzybowski, B. A. *Nat. Phys.* <https://doi.org/10.1038/s41567-019-0486-8> (2019).
4. Schindler, M. & Ajdari, A. *Phys. Rev. Lett.* **100**, 044501 (2008).
5. Kiani, M. F., Pries, A. R., Hsu, L. L., Sævičius, I. H. & Cokelet, G. R. *Am. J. Physiol.* **266**, H1822–H1828 (1994).
6. Geddes, J. B., Carr, R. T., Wu, F., Lao, Y. & Maher, M. *Chaos* **20**, 045123 (2010).