The Journal of Physiology

PERSPECTIVES

Feedback and feedforward sympathetic haemodynamic control: chicken or egg?

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Aristotle first puzzled that 'there could not have been a first egg to give a beginning to birds, or there should have been a first bird which gave a beginning to eggs; for a bird comes from an egg' (Fénelon, 1726). This conundrum demonstrates the futility of attempting to disentangle individual paths in a closed-loop system. Feedforward effects are tightly coupled to feedback responses and so the behaviour of one cannot be interpreted without considering the behaviour of the other. This is true, for example, for sympathetic nervous control of blood pressure. Sympathetic outflow increases arterial pressure via vasoconstriction (feedforward), yet elevations in arterial pressure decrease sympathetic outflow via baroreflex feedback. It has been proposed that passive observation of spontaneous haemodynamic fluctuations is sufficient to understand (and quantify) the behaviour of each path. However, as Aristotle's conundrum suggests, without first decoupling the feedback and feedforward paths, the closed-loop system may not be fully understood. Nonetheless, the contention has been made that passive observations of spontaneous haemodynamic fluctuations in the closed-loop system provide information complementary to those when the feedforward and feedback paths are decoupled. If true, then open-loop feedback baroreflex responses should be predictable, at least to some extent, from closed-loop observations. However, a direct test of this corollary has been missing. In a recent issue of *The Journal of Physiology*, Kamiya *et al.* (2011) show, through cleverly designed experiments and innovative quantitative analyses, that the feedback responses of sympathetic haemodynamic control cannot be quantified unless the relation is assessed during open-, and not closed-loop conditions.

Kamiya *et al.* (2011) investigated the reflex control of sympathetic outflow and its vasoconstrictive effects on arterial pressure while actively manipulating the input to carotid sinus baroreceptors either irrespective of the prevailing systemic pressure (open-loop condition) or perfectly matching the systemic pressure (mimicking a closed-loop condition). They deployed transfer function models to quantify the feedback relation between carotid sinus pressure and sympathetic outflow and the feedforward relation between sympathetic outflow and systemic pressure. This allowed them to test whether closed-loop estimates of feedforward effects and feedback responses are sufficient to reliably quantify the behaviour of each path.

Their results demonstrate that although feedforward effects may be predicted from closed-loop observations two thirds of the time, feedback responses were highly inconsistent. In other words, Kamiya *et al.* (2011) provided unequivocal evidence that without opening the loop and actively perturbing the system, feedback, baroreflex-mediated sympathetic responses cannot be reliably assessed. In fact, when data from the closed-loop condition were used to predict responses to a modified Oxford baroreflex test, predicted feedback responses were the exact opposite of that observed. To explain this inconsistency, Kamiya *et al.* (2011) suggest that prevailing 'internal noise' in the neural processes of baroreceptor activation and sympathetic responses hinder accurate quantification of closed-loop feedback responses. This may be true. Another plausible interpretation is that at rest, sympathetic haemodynamic control is simply feedforward, and the feedback responses are engaged only in response to active perturbations.

Assessment of the degree and efficiency of feedback sympathetic responses is important for integrative physiology and pathophysiology. Nevertheless, there is no consensus on how baroreflex function can be reliably estimated. On the one hand, blood pressure fluctuations at lower frequencies (Mayer waves, ∼0.1 Hz in humans and ∼0.4 Hz in rats) are typically enhanced during sympathoexcitation (Guyton & Harris, 1951), and so it has been suggested that spontaneous Mayer wave magnitude is related to baroreflex control of sympathetic outflow (i.e. the feedback path). On the other hand, baroreceptor engagement is most apparent in response to rapidly changing pressures (Chapleau & Abboud, 1987), mostly absent in the resting (closed-loop) state, and so it has also been argued that resting arterial pressure is primarily under the influence of feedforward haemodynamic control. As a result, some researchers have exploited spontaneously occurring fluctuations in blood pressure to assess reflex function, while others argue that it is critical to perturb the system to clearly engage the reflex. Until now, clear, non-inferential evidence in favour of one or the other hypothesis has been lacking. A predominantly feedforward control of arterial pressure at rest, as unequivocally demonstrated by Kamiya *et al.* (2011), poses a significant challenge for the reliance on spontaneous blood pressure fluctuations as a surrogate for sympathetic function. It seems that one has to actively 'hatch' the eggs to know that they are chickens.

References

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DOI: 10.1113/jphysiol.2011.208199