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DRUG DELIVERY

Closed-loop dynamic dosing

A system consisting of an aptamer-based microfluidic biosensor and a simple feedback-control algorithm adjusts therapeutic dosing in near real time in small animals.

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By accounting for physiological, genetic and other differences between patients, approaches in personalized medicine aim to tailor therapies to produce the most effective response and to ensure that target drug concentrations are maintained, regardless of pharmacokinetic variations resulting from differences in body weight, age, sex and other factors[1]. For many drugs, including chemotherapeutic agents, deviations from therapeutic doses can lead to toxicity (overdosing) or loss of efficacy (underdosing). Therefore, it is critical to maintain a narrow therapeutic window to ensure efficacy while minimizing adverse effects[2].

Closed-loop feedback control is widely used to maintain a system within a target range in the presence of perturbations. Three elements are key for effective feedback control: an effector mechanism to exert change in the variable, a sensor to measure its variation, and a regulator that 'closes the loop' by regulating the effector element on the basis of the information collected by the sensor. Such approaches are commonly used in medicine over short timescales (minutes to hours), such as when an insulin pump adjusts the level of insulin according to the concentration of blood glucose. Another example is the use of physiological parameters and breath analysers (for oxygen, carbon dioxide and, more recently, anaesthetic levels) to inform adjustments of anaesthetic dosage during surgery. However, for many drugs no simple technology exists that can provide quick and dynamic feedback control to ensure that the right drug levels are maintained. Reporting in *Nature Biomedical Engineering*, Hyongsok Soh and colleagues now show that an external closed-loop feedback-control device for drug infusion enabled by a near-real-time microfluidic biosensor maintains specific levels of a chemotherapy drug in animals regardless of variations in pharmacokinetics[3] (Fig. 1). This system could eventually enable tighter control over circulating drug levels in patients undergoing chemotherapy, thereby reducing toxicity while maintaining drug efficacy.

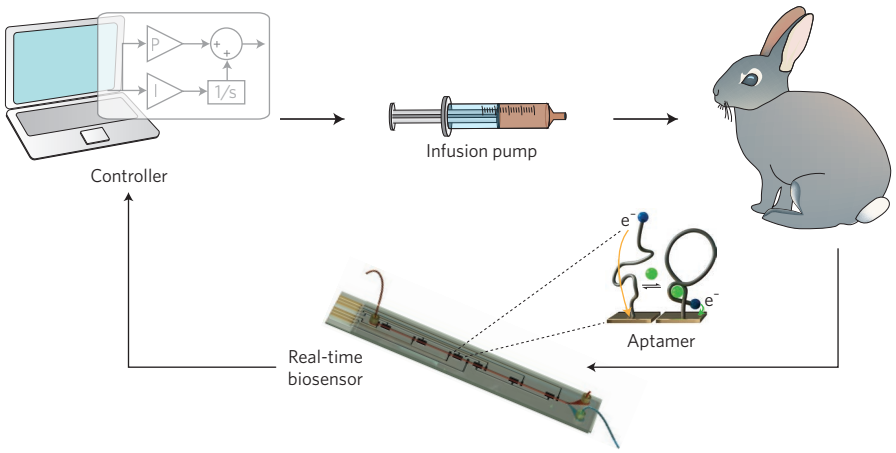

Figure 1 | Closed-loop control of drug infusion enabled by an aptamer-based microfluidic biosensor. Blood from the animal is continuously drawn and directed through a microfluidic biosensor bearing electrodes functionalized with a drug-specific aptamer that incorporates an electrochemical label (blue) at one end. Changes in the concentration of a chemotherapeutic drug (green) result in a reversible change in the configuration of the aptamer and a consequent change in the rate of electron (e^-) transfer, which is read out as an electric current by the proportional–integral controller and used to modulate the drug infusion rate to maintain *in vivo* drug levels at a target value. Figure adapted from ref. [3], Macmillan Publishers Ltd.

To enable reliable measurements of drug levels as well as quick responses, Soh and co-authors adapted an aptamer-based microfluidic biosensor that they had previously developed[4]. The sensor consists of a microfluidic channel lined with electrodes that are functionalized with aptamers specific for the chemotherapy drug doxorubicin. Binding of doxorubicin to the aptamer causes a reversible conformational change that brings a redox-labelled end of the aptamer closer to the electrode, generating a measurable electric current. To extend the sensor's operational time, the sensitive electrodes are isolated from the bloodstream by a continuous, thin buffer stream, which flows through the microfluidic channel in parallel to the bloodstream. The small molecule doxorubicin diffuses rapidly across the buffer stream and reaches the electrode. Fouling is minimized by the slower diffusion rate of platelets and proteins and by the heparin coating of the microfluidic channel and electrodes. The authors calibrated the sensor offline by spiking blood with known levels of doxorubicin, and minimized drift in the measurements by measuring the electrochemical signal at two different frequencies, 100 Hz and 10 Hz. At 10 Hz, the redox labels are depleted and a reference signal is obtained, which is then subtracted from the 100-Hz signal to provide a reliable readout. To enable near-real-time measurements, two additional developments were necessary. The microfluidics system minimizes the dead volume between the vein and the electrodes to approximately 0.01 ml, and limits the time that the blood takes to reach the sensing electrodes to approximately 1 min after exiting the body at a flow rate of 1.7 ml h^{-1}. This process is thus compatible with continuous monitoring of drug levels without significant blood loss. Additionally, the rapid on–off rate of the aptamer allows it to detect changes in doxorubicin levels within a few minutes[4]. The electrochemical signal measured by the biosensor is then routed to a computer, which provides a calibrated near-real-time measurement of the doxorubicin levels. The computer

also implements a simple feedback-control algorithm: proportional–integral control, which sets the doxorubicin infusion rate to be proportional to the weighted sum of the deviation of the drug level from its target value and the integral of the deviation over time. The proportionality constants are key parameters that determine how effective the control over drug levels is, including the extent to which the drug level overshoots the target level and the time required to achieve the target level. Because these parameters are determined by using simulations of a pharmacokinetic model of doxorubicin clearance in rabbits with population-averaged parameters, this approach does not require a priori knowledge of pharmacokinetic parameters from each individual.

In a set of experiments in rabbits, Soh and co-authors demonstrated that the closed-loop control of infusion was effective in maintaining the target concentrations of doxorubicin in circulation. In four rabbits, doxorubicin concentrations were measured to within 5% of the target value within 10 minutes of the start of intravenous infusion of the drug, and its levels were maintained within 20% of the target value over an infusion period of approximately an hour. By contrast, traditional infusion with dosage determined on the basis of body surface area was out of range for long periods of time in two out of three animals. The robustness of the device was demonstrated by assessing its ability to overcome changes in pharmacokinetics owing to drug–drug interactions: in rabbits that received doxorubicin and cisplatin (another chemotherapy drug that slows down the clearance of doxorubicin), the device maintained doxorubicin levels within the target range without a priori information about the altered pharmacokinetics, whereas infusion based on body area resulted in drug overdose. The authors demonstrated a similar level of control of doxorubicin concentration in rats, which illustrates the generality of their approach.

Conventionally, measurement of drug levels in blood is performed in a laboratory using techniques such as chromatography or mass spectrometry, which are hardly amenable to real-time measurement. Rather than attempting to miniaturize chromatographic separation, Soh and co-authors' clever approach integrates preliminary separation of the drug molecule from other blood components on the basis of differential diffusion and a molecularly engineered microfluidic electrochemical biosensor that responds reversibly and continuously to drug levels. Although microfluidics can trace its genesis to analytical chemistry[5], the integration of a drug-concentration sensor into a closed-loop feedback-control mechanism presents formidable challenges of robustness, continuous operation, and near-real-time readout while using very little blood. The authors' work addresses these challenges.

Before closed-loop drug administration can be used in patients needing chemotherapy, clinical studies that assess patient outcomes over current methods of dosing are required. The pathway to clinical application will also require further advances in the technology to ensure that the system is robust and incorporates fail-safe mechanisms to guarantee patient safety in the event of a malfunction (for example, sensor failure could result in ineffective drug administration, so redundant sensors are likely to be required to ensure safety). Furthermore, the sensor and controller will need to be packaged into a bench-top device that is sufficiently rugged and simple to operate. To extend the approach to other drugs, metabolites and drug complexes, the system will need to be equipped with new aptamers, as Soh and colleagues suggest[3]. New aptamers will enable multiplex measurements to simultaneously monitor several molecules in blood or other body fluids. Moreover, extensive clinical studies will be required to determine how to relate the system's parameters to the efficacy of a treatment, to account for compartmentalization of molecules within the body, and to understand how real-time information of concentrations of a number of molecules can be most effectively used.

In its current form, Soh and co-authors' closed-loop control device is only suitable for drug administration over relatively short periods of time and while the animal is catheterized. Longer-term monitoring of metabolites, antibiotics and other factors may eventually be possible for hospitalized patients with continuous blood draw, as this technology could be optimized to require less than 10 ml of blood per day. Also, future modifications may enable long-term drug monitoring in mobile patients, broadening the opportunities for new applications, such as the administration of mood stabilizers. For instance, the configuration of the parallel sample and buffer streams may be replaced by a static configuration in which a membrane or coating protects the aptamer-functionalized electrode surface in an implanted biosensor. In the future, such devices may relay information on the concentration of an array of analytes to devices outside the body or to other implanted devices. ❐

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