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Explaining anaesthetic hysteresis with effect-site equilibration

Alex Proekt* and Max B. Kelz

Department of Anesthesiology and Critical Care, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

*Corresponding author. E-mail: proekt@gmail.com

This article is accompanied by an editorial: Resisting neural inertia: an exercise in floccinaucinihilipilification? by Eleveld et al., *Br J Anaesth* 2021:126:31–34, doi: 10.1016/j.bja.2020.09.025

Abstract

Background: Anaesthetic induction occurs at higher plasma drug concentrations than emergence in animal studies. Some studies find evidence for such anaesthetic hysteresis in humans, whereas others do not. Traditional thinking attributes hysteresis to drug equilibration between plasma and the effect site. Indeed, a key difference between human studies showing anaesthetic hysteresis and those that do not is in how effect-site equilibration was modelled. However, the effect-site is a theoretical compartment in which drug concentration cannot be measured experimentally. Thus, it is not clear whether drug equilibration models with experimentally intractable compartments are sufficiently constrained to unequivocally establish evidence for the presence or absence of anaesthetic hysteresis.
Methods: We constructed several models. One lacked hysteresis beyond effect-site equilibration. In another, neuronal dynamics contributed to hysteresis. We attempted to distinguish between these two systems using drug equilibration models.
Results: Our modelling studies showed that one can always construct an effect-site equilibration model such that hysteresis collapses. So long as the concentration in the effect-site cannot be measured directly, the correct effect-site equilibration model and the one that erroneously collapses hysteresis are experimentally indistinguishable. We also found that hysteresis can naturally arise even in a simple network of neurones independently of drug equilibration.
Conclusions: Effect-site equilibration models can readily collapse hysteresis. However, this does not imply that hysteresis is solely attributable to the kinetics of drug equilibration.

Keywords: effect-site concentration; hysteresis; mechanisms of anaesthesia; pharmacokinetics; modelling

Editor's key points

- Whether anaesthetic induction occurs at higher drug concentrations than emergence, known as hysteresis, occurs in humans and its mechanism are unclear.
- Modelling studies described here show that one can construct an effect-site equilibration model such that hysteresis always collapses.
- As concentration in the effect-site cannot be measured directly, the correct effect-site equilibration model and the one that erroneously collapses hysteresis were experimentally indistinguishable.
- Thus hysteresis can arise even in a simple network of neurones independently of drug equilibration mechanisms owing to neuronal network dynamics. These neuronal dynamics can be obscured by models of effect-site equilibration.

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Pharmacokinetic and pharmacodynamic (PK–PD) principles are indispensable for successful and safe practice of anaesthesiology. Without them, it would be impossible to maintain sufficient anaesthetic depth for the duration of surgery and then rapidly restore consciousness. PK–PD models for intravenous[1–6] and volatile[7,8] anaesthetics, opioids,[6,9,10] neuromuscular blockers,[11,12] and local anaesthetics[13] have been developed over the past three decades. Target-controlled infusions (TCIs),[14–20] based on the pharmacokinetic parameters, are used throughout the world to deliver intravenous anaesthetics and opioids. PK–PD models are also a key component of the newer closed-loop anaesthesia delivery systems.[21–25]

The key assumption of the PK–PD approach is that concentration of the drug at the *effect-site* is the sole determinant of the anaesthetic state. This relationship between concentration and its effect is expressed in the familiar concentration–response curve. In a seeming contradiction to this assertion, experiments in mice[26,27] and in fruit flies[28] suggest that induction of anaesthesia occurs at a higher brain anaesthetic concentration than emergence. Thus, there appear to be at least two concentration–response curves: one for induction and another for emergence. This phenomenon is variably referred to as either anaesthetic hysteresis or neural inertia.

One interesting consequence of anaesthetic hysteresis is that at the same anaesthetic concentration one can be either anaesthetised or awake. As an example, consider a patient at the end of surgery with an end-tidal anaesthetic concentration of 0.1 MAC (minimum alveolar concentration) breathing spontaneously through a tracheal tube with eyes closed who does not appear to be conscious. A gentle stimulus such as calling their name can be observed to trigger an abrupt change as the patients' eyes open, they begin to follow simple commands, and appear to be conscious. Although this phenomenon is frequently observed, no pharmacokinetic model would predict that the concentration of the anaesthetic changed appreciably over a course of a second that it took the person to transition from the state of unconsciousness to the awake state. Thus, it appears that one can indeed be both awake and anaesthetised at approximately the same anaesthetic concentration.[29]

Many experimental findings support the conclusion that knowing just the drug concentration is insufficient to define the response. Experiments in rats,[30] primates,[31,32] and patients undergoing surgical anaesthesia[33] show that at a fixed anaesthetic concentration, brain activity fluctuates between several discrete states. Fluctuations in the level of consciousness occur in both mice and in zebrafish exposed to mechanistically distinct anaesthetics[34,35] at pharmacokinetic equilibrium. Similar fluctuations were also observed in humans.[36] In neurophysiological recordings[30] and in behavioural responses,[34] fluctuations between different states exhibit an inertial tendency that manifests as a propensity for the system to stay in its previously observed state. Mathematical models show that such fluctuations are sufficient to give rise to anaesthetic hysteresis independently of effect-site equilibration.[37] Different mathematical models of cortical circuits[38–40] converge on the concept that neuronal dynamics, in addition to drug equilibration, contribute to the observed anaesthetic hysteresis.

All of the above evidence suggests that hysteresis should be present in humans, but human studies of hysteresis are contradictory.[29,41,42] Although notable methodological differences exist, a basic paradigm is to first expose subjects to escalating doses of anaesthetics. Once loss of consciousness is attained, anaesthetic concentration is lowered until restoration of consciousness is observed. Although straightforward in the experimental design, interpretation of such data is not trivial.

To show definitive evidence for hysteresis, one would have to show that loss and recovery of consciousness occur at different *effect-site concentrations*. Critically, however, the effect-site is a theoretical compartment such that drug concentration in the effect-site cannot be experimentally measured. Instead, the kinetics of equilibration are inferred by estimating the time lag between plasma concentration and the anaesthetic effect, typically measured on the basis of the EEG. Effect-site equilibration kinetics are estimated using an algorithm that specifically attempts to eliminate the hysteresis between the observed plasma concentration and the effect.[43] It is thus unclear whether effect-site equilibration models are best suited to establish evidence for or against hysteresis.

Here we show mathematically that effect-site equilibration models can always be constructed such that hysteresis collapses. This is true for systems in which hysteresis is entirely attributable to drug equilibration, but is also true for systems where neuronal dynamics play a key role. The main reason for this is that effect-site models are underconstrained by experimental observations. The fact that effect-site equilibration models can collapse hysteresis does not imply that the observed hysteresis is indeed attributable solely to drug equilibration. We suggest a novel experimental approach successfully implemented in animals[34] that can definitively establish whether neuronal dynamics contribute to anaesthetic hysteresis in humans. Unequivocally demonstrating hysteresis in humans has fundamental implications for how we think about the relationship between exposure to anaesthetics and subsequent recovery of cognition.

Methods

All simulations were performed in Matlab (Mathworks Inc., Natick, MA, USA) using custom written software.

A standard three-compartment model was constructed using the following system of equations:

$$\frac{dx_1}{dt} = -(k_{1-2} + k_{1-3} + k_{1-0})x_1 + k_{2-1}x_2 + k_{3-1}x_3 + I(t)$$

$$\frac{dx_2}{dt} = k_{1-2}x_1 - k_{2-1}x_2$$

$$\frac{dx_3}{dt} = k_{1-3}x_1 - k_{3-1}x_3$$

where, x_i is amount of drug in the ith compartment (compartment 1 is assumed to be plasma). Compartments 2 and 3 are the effect-site and 'rest of body' compartments, respectively; k_{x-y} is the rate constant that governs transit from compartment x to compartment y; k_{1-0} is the rate constant for drug elimination; and $I(t)$ is the infusion rate. There is some variability in the PK–PD approaches for modelling the effect-site. In Figures 1–5, we chose to have the effect-site models maintain mass balance. Other approaches model the effect-site compartment as having zero volume and therefore disrupting mass balance (reviewed by Gambus and Troconiz[44]). This does not affect the conclusions concerning collapse of hysteresis as we show in Figure 6.

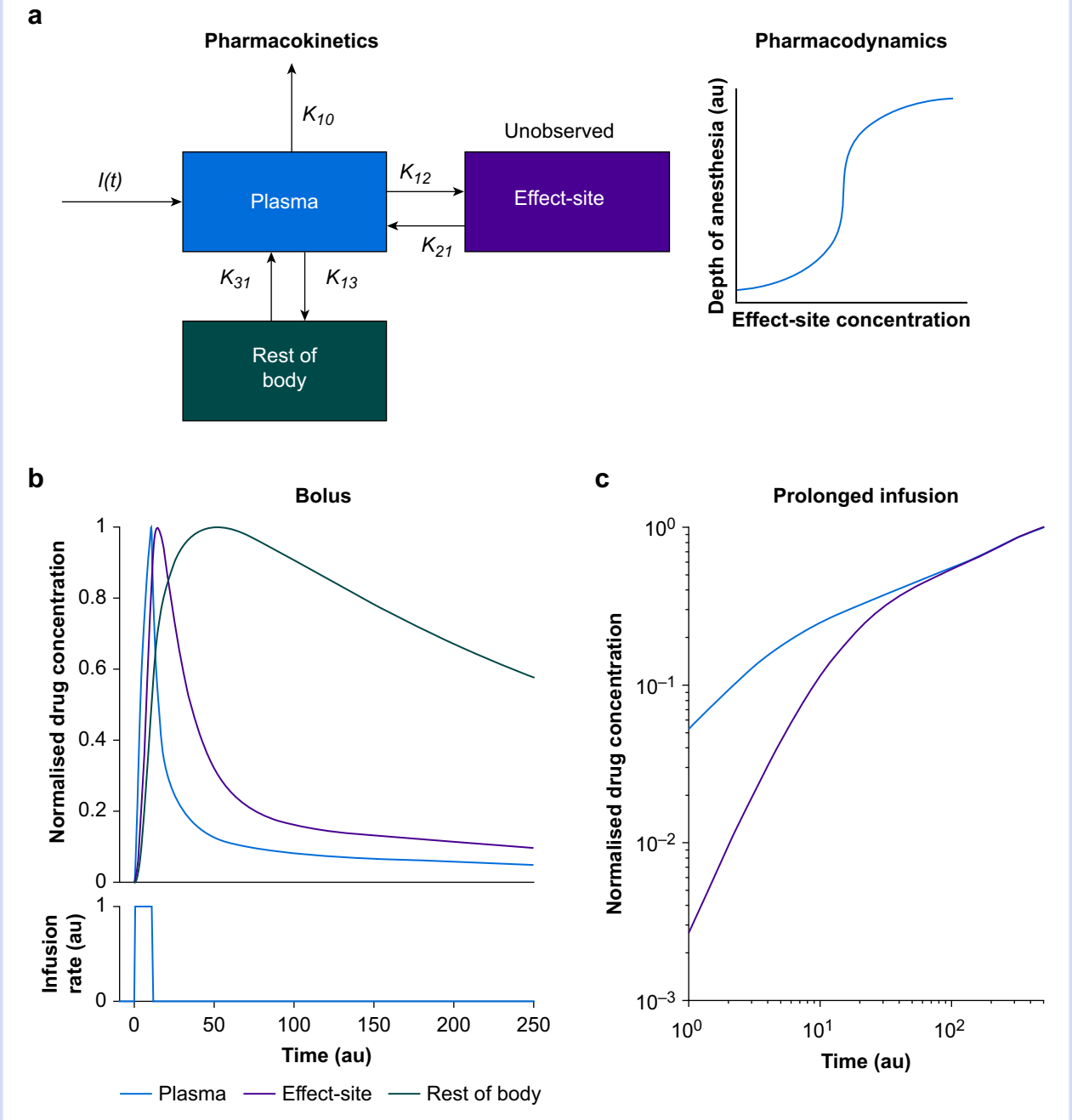

Fig 1. Pharmacokinetic–pharmacodynamic (PK–PD) model. (a) The general structure of the PK–PD model used in Figures 1–5. Infusion $I(t)$ is administered into the plasma compartment. The drug distributes to other compartments labelled 'effect-site' or 'rest of body' or be eliminated. The distribution and elimination are modelled using standard first order chemical kinetics with the rate constants k_{xy} denoting the rate constant governing distribution from compartment x to compartment y. This constitutes the PK module of the PK–PD model. The PD model is a sigmoid concentration–response curve that relates the concentration in the effect-site compartment to 'depth of anaesthesia'. (b) Time course of concentration changes after a brief infusion (10 time steps) of the drug (bottom panel). All drug concentrations in this and other figures are normalised to the maximum concentration in the compartment. (c) After a prolonged infusion, the normalised concentration in the effect-site and plasma compartments converge. au, arbitrary unit.

The rate constants used to simulate data in Figures 1–3 are:

k_{1e} 0.1

k_{eo} 0.1

k_{13} 0.1

k_{31} 0.01

k_{10} 0.05

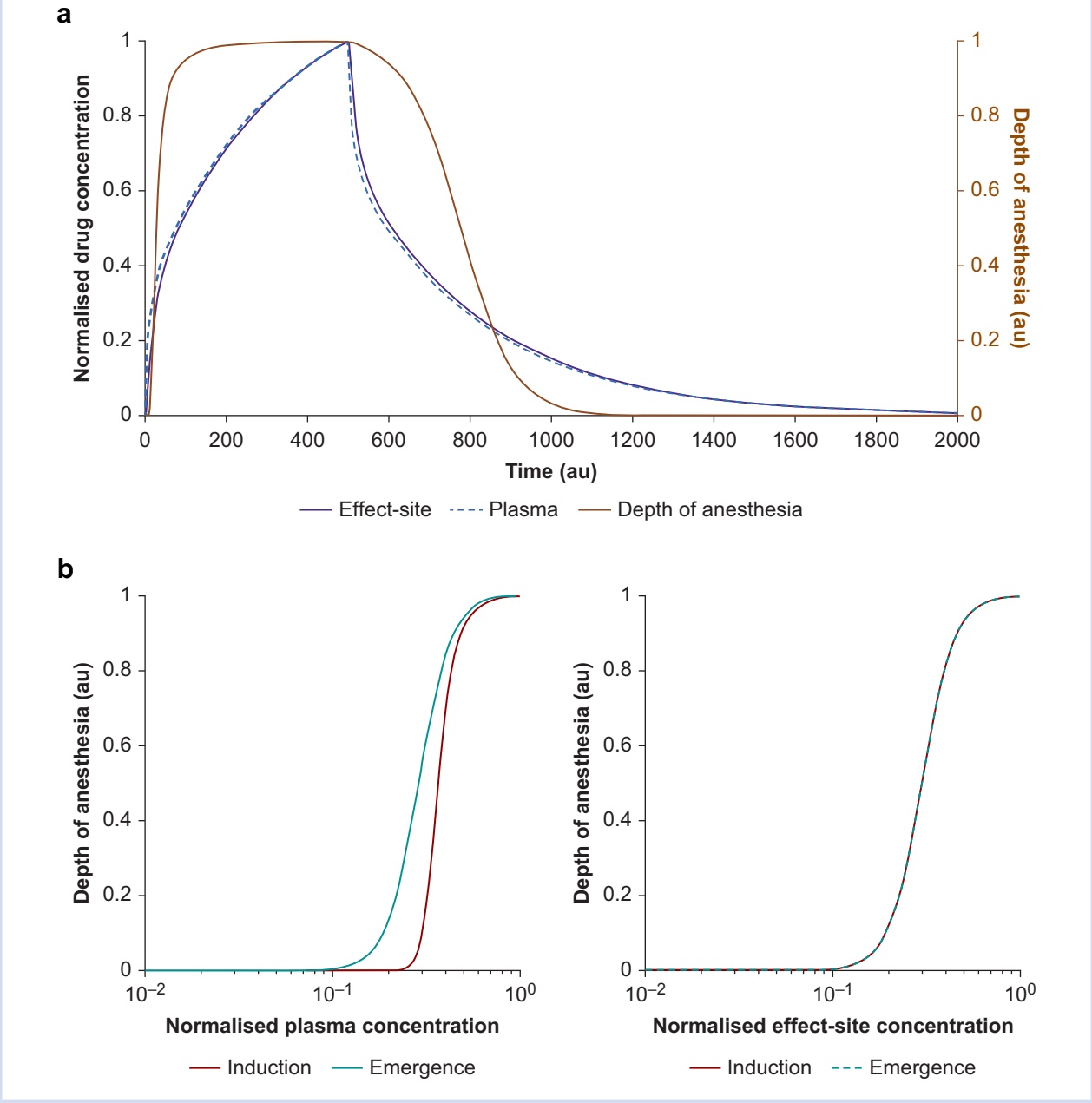

Fig 2. Pharmacokinetic–pharmacodynamic (PK–PD) mechanism of anaesthetic hysteresis. (a) Combined PK–PD model is simulated for a fixed rate infusion (as in Fig. 1c) of drug followed by discontinuation. Note that effect-site concentration lags behind plasma concentration. Depth of anaesthesia is computed as a sigmoid function of the effect-site concentration. (b) When depth of anaesthesia (from a) is plotted as a function of the plasma concentration, hysteresis is readily observed (left). However, when the same data are plotted as a function of the concentration in the effect-site, hysteresis collapses (right). Thus, in this case anaesthetic hysteresis is solely attributable to drug equilibration. au, arbitrary unit.

The rate constants for the incorrect model used in Figure 4 to collapse hysteresis are:

k_{1e} 0.1

k_{eo} 0.01

k_{13} 0.1

k_{31} 0.1

k_{10} 0.05

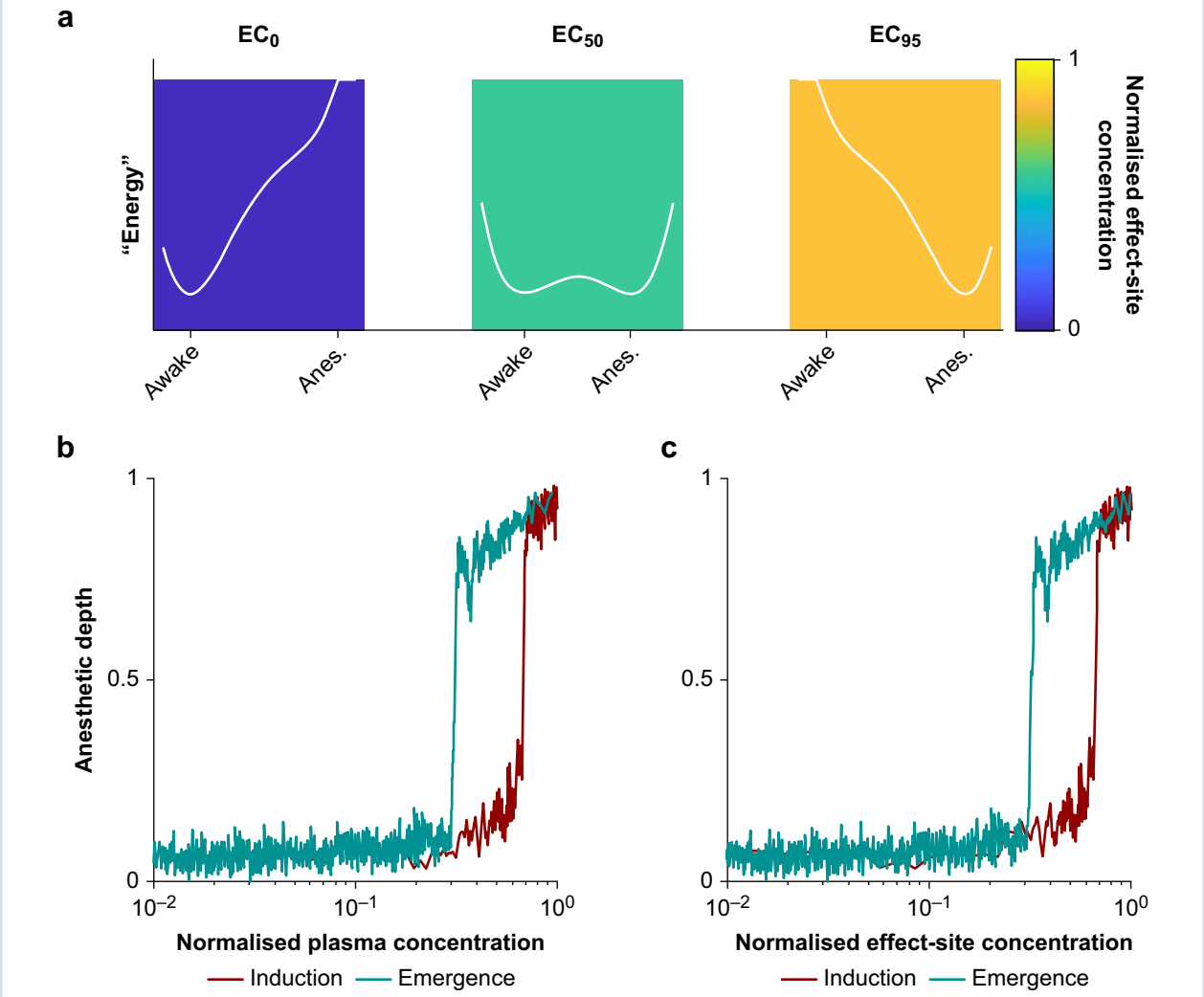

Fig 3. Neuronal dynamics mechanism of anaesthetic hysteresis. (a) 'Energy' landscape plotted as a function of anaesthetic concentration in the effect-site (colour bar). When there is no anaesthetic only the awake state is stable. At high anaesthetic concentrations, only the anaesthetised state is stable. At intermediate anaesthetic concentrations both the awake and anaesthetised states are equally stable. This corresponds to EC_{50} as such a system will spend 50% of the time being awake or anaesthetised. Rather than using the sigmoid concentration–response curve (Fig. 2) we simulated the system where effect-site concentration (driven by the same pharmacokinetic–pharmacodynamic [PK–PD] model as in Figs 1 and 2) changed the shape of the energy landscape. The fraction of time spent anaesthetised is plotted on the ordinate in (b) and (c). Because relaxation of the system to the steady-state in this case is given by neuronal dynamics, here hysteresis is observed when anaesthetic depth is plotted as a function of both plasma (b) and the effect-site (c) concentrations. Thus, in this case, hysteresis is not attributable solely to drug distribution. anes., anaesthetised.

For the sake of simplicity, and without any loss of generality, concentrations are given in arbitrary units. Note that the only difference between the correct and incorrect rate constants is mathematically equivalent to a change in the naming convention such that compartment 3 becomes the 'effect-site' compartment, whereas compartment 2 becomes 'rest of body'. Because the only difference between the two models is naming convention, it is trivially true that the concentration in the plasma compartment (the only one that is experimentally observed) is exactly the same in both the correct and incorrect model.

The concentration of the drug in the effect-site (c) was related to effect (E) using a standard sigmoid concentration–response curve:

$$E(c) = \frac{c^h}{\mathrm{EC}_{50}^h + c^h}$$

where h=5 is the Hill slope and EC_{50}=0.5 is the concentration sufficient to elicit half-maximal response. Note that in this case the effect is an invertible function of the effect-site concentration. In other words, there is one-to-one

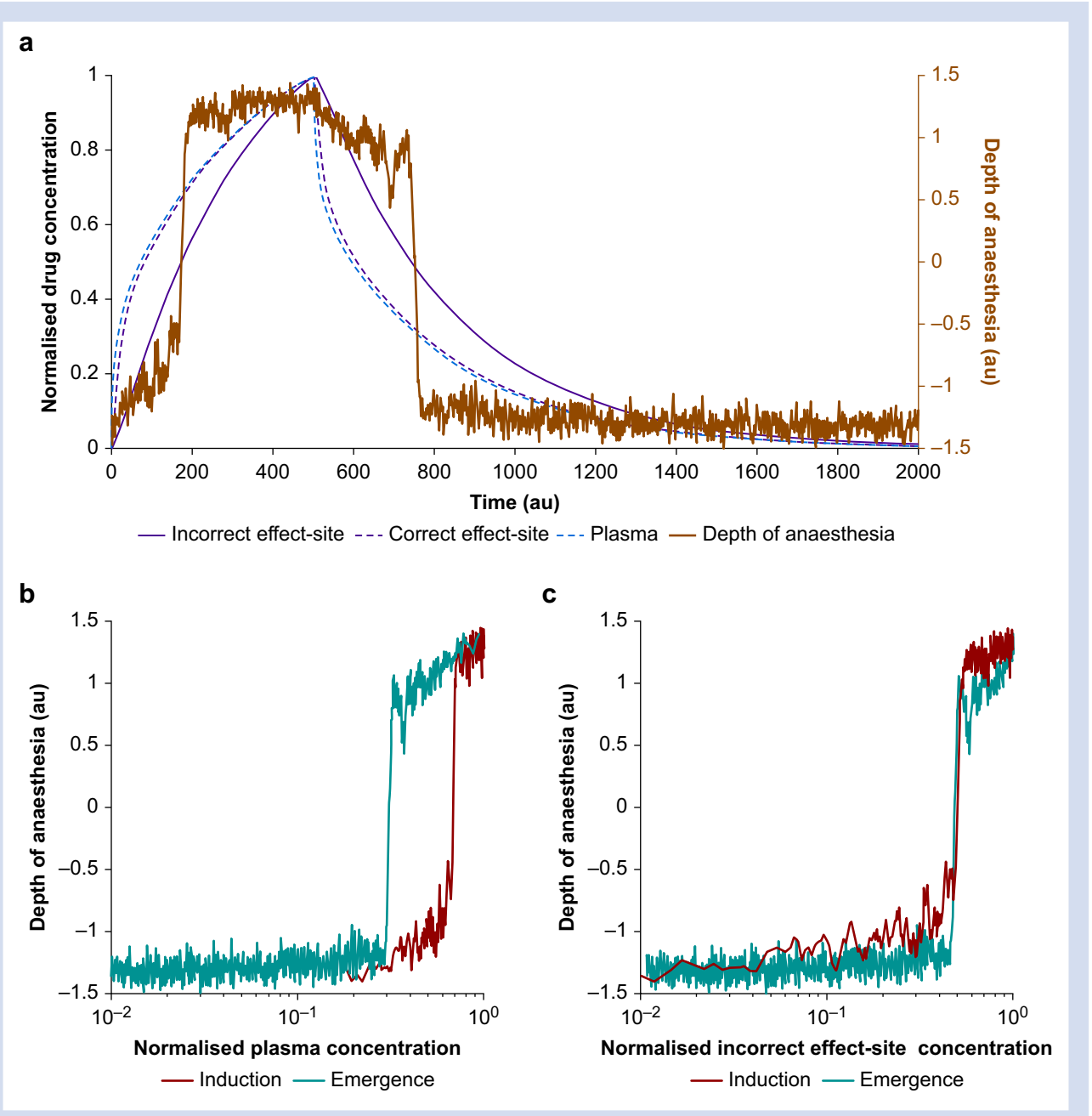

Fig 4. Pharmacokinetic–pharmacodynamic (PK–PD)models can collapse hysteresis caused by neuronal dynamics. (a) Time evolution of drug concentration and depth of anaesthesia. Data are identical to that in Figure 4. Here, a new PK–PD model is created such that plasma concentration and depth of anaesthesia are identical. However, the effect-site concentration is now different. That is effect was produced as a function of correct effect-site concentration (dashed red line), but the new model predicts the incorrect effect-site concentration (red solid line). Because this new model produces identical plasma concentration and effect, it is experimentally indistinguishable from the correct model used to generate the data. (b) Hysteresis exhibited with respect to plasma concentration. (c) Hysteresis collapses with respect to the incorrect effect-site concentration. In this way, PK–PD models can be used to minimise the effect of neuronal dynamics. anes., anaesthetised. au, arbitrary units.

correspondence between the effect-site concentration and the effect.

To incorporate neuronal dynamics into the model, we adapted a formalism as described.[37] The only difference from the standard approach is that rather than specifying the effect directly, the concentration in the effect-site sets the probability of being awake (or anaesthetised). Mathematically, this corresponds to constructing an energy landscape that has two potential wells (one representing awake and the other representing anaesthetised). This assures that the system spends most of its time near the wells rather than in between them. Anaesthetic in the effect-site compartment acts to

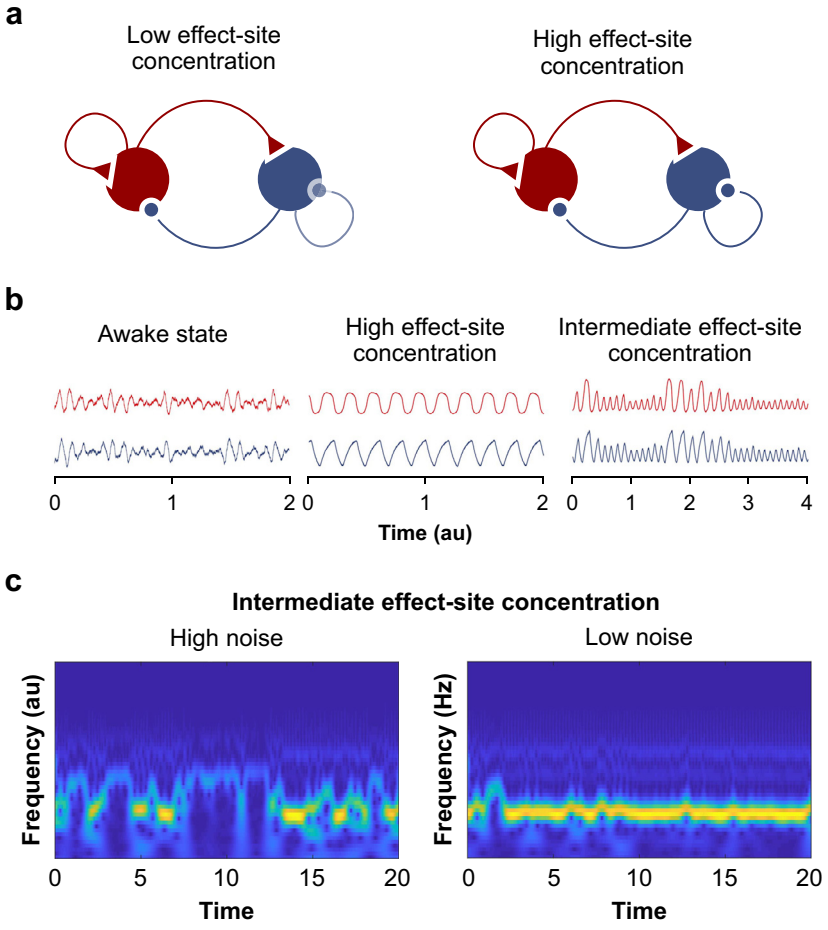

Fig 5. A simple neuronal network can produce stochastic switching between different states at a fixed anaesthetic concentration. (a) The network consists of two neurones, *A* and *B* (excitatory and inhibitory). At the low effect-site concentration, self-inhibition is minimal. Strength of self-inhibition is related to the effect-site concentration according to the PK–PD model in Figure 1. (b) Examples of activity produced by the network at three anaesthetic concentrations. At an intermediate anaesthetic concentration the network flips between two distinct oscillatory regimes. (c) Wavelet spectra of neuronal activity in a network simulated at the high (left) and low (right) levels of noise. Power in log units is shown by colour (blue low power, yellow high power). In the high noise regime, the system fluctuates frequently between two oscillatory patterns. In the low noise regime, the system tends to persist in one state. This resistance to state transitions manifests as anaesthetic hysteresis.

deepen (stabilise) the anaesthetised well and destabilise the awake well according to the following equation:

$$E(s,c) = s^2\left(\frac{s^2}{2} - 2\right) + c(s-1)^2 + (1-c)(x+1)^2$$

where E is the energy, c is the concentration in the effect-site compartment, and s is the state akin to 'depth of anaesthesia'. The dynamics of such a system are well described by Brownian motion on this energy landscape simulated as described,[37] which we will briefly outline below.

The Boltzmann relationship between energy and probability distribution assures that at each anaesthetic concentration c, the probability of a system being in any state s (depth of anaesthesia in this case) is $\pi(c,s) \propto e^{-E(s,c)}$. Thus, much like the standard approach, a given effect-site concentration always yields only one distribution of states. The key difference, however, is that diffusion on an energy landscape also has dynamics. The simplest case is Brownian motion in which the time evolution of the state of the system at a fixed concentration c is given by:

$$\left.\frac{\partial s}{\partial t}\right|_c = D\frac{\partial E(s,c)}{\partial s} + \varepsilon$$

where D is the diffusion constant and ε is noise, computed as random normal variable $\varepsilon \sim N(0,\sigma)$ with zero mean and variance given by σ. Note that neither D nor σ plays any role in setting the ultimate distribution of states (depth of anaesthesia); these variables only determine the rate at which the system given by the energy landscape E approaches the steady-state distribution. If ε is high relative to D, then the system approaches steady-state quickly. If, conversely, ε is small, then the system takes longer to decay to steady-state. To simulate the system with neuronal dynamics, we integrated the Brownian motion equation computed for each anaesthetic concentration using standard numerical Runge–Kutta methods implemented in Matlab.

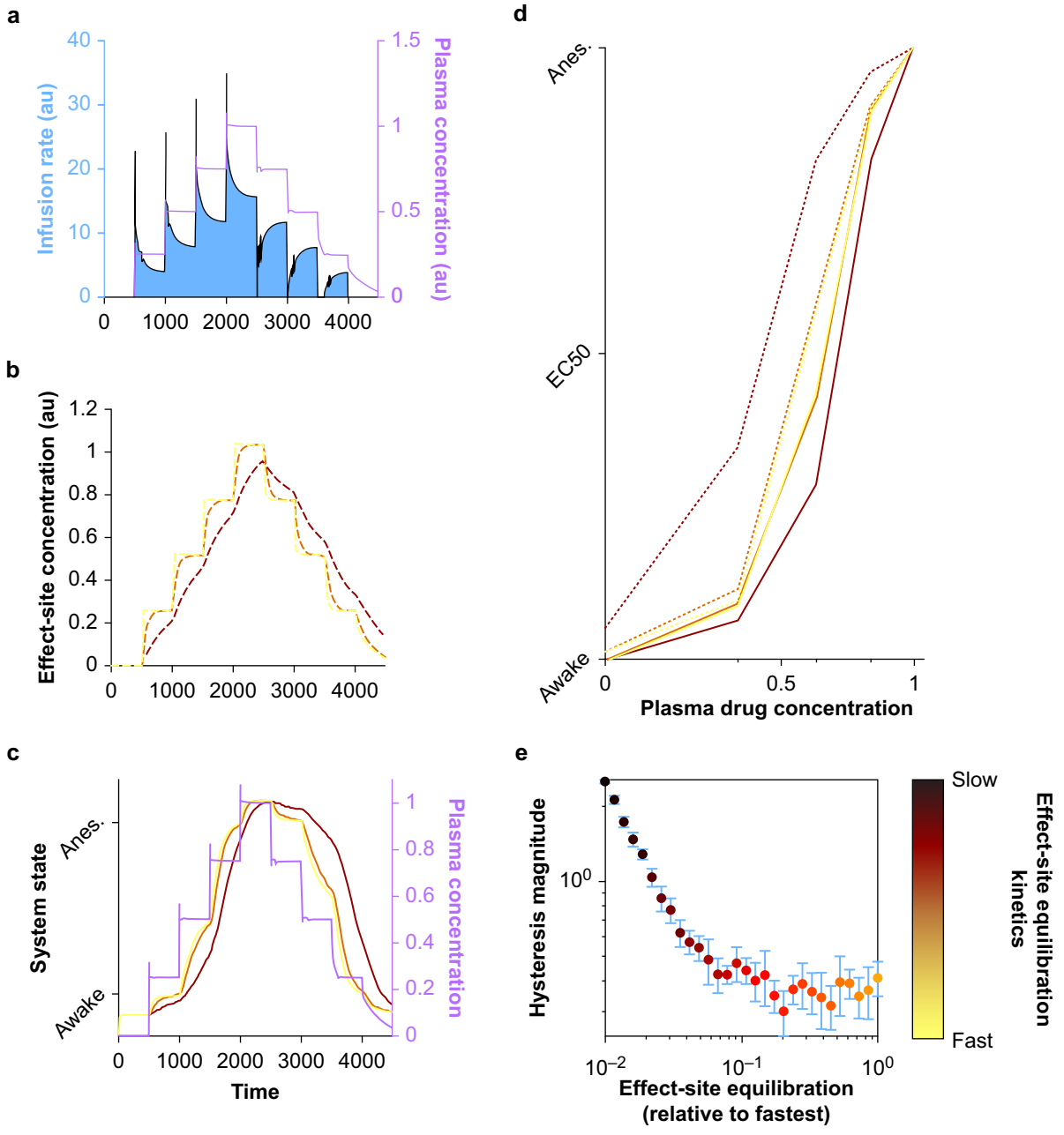

Fig 6. Simulation of target-controlled infusion. (a) Simulation of target-controlled infusion (TCI). Infusion rate is adjusted such that effect-site concentration is constant at every step. The TCI algorithm assumes that the effect-site equilibrates rapidly such that during each concentration step effect-site concentration is at steady-state. (b) Dynamics of effect-site concentration under the infusion scheme in (a). Different effect-site concentration curves (that assume different equilibration kinetics) are shown. Colour coding is the same for panels (b)–(e) (colour bar). TCI was computed assuming that equilibration kinetics are rapid relative to step duration (yellow). Slower kinetics of effect-site equilibration (orange and red) are shown for comparison purposes. Because effect-site concentration is assumed rather than measured, it is shown by dashed lines. (c) Mean of 500 simulations of the noisy two well potential system driven by effect-site concentrations shown in (b) colour coded by the equilibration kinetics. Observed plasma concentration is replotted from (a) to facilitate evaluation of the relationship between plasma concentration and the effect. (d) Concentration–response curves computed from data in (c) colour coded by effect-site equilibration kinetics. If the effect-site equilibration is fast, little to no hysteresis is observed because the two well potential is simulated in the noisy regime (Supplementary Fig. S1 demonstrates behaviour as a function of noise). When slower effect-site equilibration is assumed hysteresis is clearly present (induction curves solid lines, emergence curves dotted lines). (e) Magnitude of hysteresis computed as area between induction and emergence concentration curves in (d) over a range of equilibration kinetics (shown by colour). Error bars show standard deviation computed across multiple simulations. One can conclude that hysteresis is either present or absent depending on the assumed kinetics of effect-site equilibration. au, arbitrary units.

In the complete absence of noise, the system will be found at steady-state at all times (local energy minimum). Because at intermediate anaesthetic concentration $c \approx 0.5$, the energy landscape has two stable states (local minima), the system will stay at its current well until the state loses stability. Such bistable systems generically give rise to anaesthetic hysteresis as described.[37]

Because the energy landscape model is mathematically abstract and devoid of biological realism, we constructed a simple neuronal network consisting of excitatory neurone (A) and inhibitory neurone (B). The simplified biophysics of these neurones were modelled as described[46 47] according to the following equations:

$$\frac{dA}{dt} = -A + \psi(w_{11}A - w_{12}B - b_1) + \varepsilon$$

$$\frac{dB}{dt} = -B + \psi(w_{21}A - w_{22}B - b_2) + \varepsilon$$

where $\psi(x) = \frac{1}{1+e^{-x}}$ is a sigmoid function describing how inputs into the neurone affect its output, w_{ij} is the strength of the synapse from neurone i to neurone j, b_i is a bias term for the ith neurone which determines the level of activity in the absence of input, and ε is noise. Noise was implemented as a normally distributed random variable with zero mean. The level of noise was controlled by setting the standard deviation of the normal distribution to 0.05 or 0.01 for high and low noise conditions, respectively. In the model, the effect-site anaesthetic concentration acts to potentiate self-inhibition (w_{22}) such that in the absence of anaesthetic in the effect-site compartment $w_{22}=0$, whereas at high anaesthetic concentration w_{22} saturates at 4. This was accomplished using the following concentration–response relationship between w_{22} and effect-site concentration, c:

$$w_{22} = 4 + \frac{4}{1 + 10^{2-c}}$$

Other parameters were as follows: $w_{11}=8$; $w_{12}=6$; $w_{21}=16$; $b_1=0.34$; $b_2=2.5$.

Activity of neurones A and B was added for the purposes of computing the wavelet transform. This is meant to mimic the fact that EEG and local field potential signals average neuronal activity over some volume of brain tissue.[47] The wavelet transform using Morse wavelet was computed using the standard *cwt* function implemented in Matlab.

To better approximate the experimental design used in human hysteresis studies,[42] we simulated TCIs (data in Fig. 6) by implementing the standard STANPUMP algorithm in Matlab.[48] In a small departure from the model used in Figures 1–3, we made effect-site compartment to have zero volume. In this way, effect-site concentration, consistent with the approach of Sheiner and colleagues,[20] does not influence plasma concentration. Effect-site concentration in this TCI simulation is used to modulate the shape of the energy landscape in the same way as described above.

Results

Figure 1a illustrates the basic model used throughout this work. Pharmacokinetics, modelled using a standard approach, govern how the drug distributes among the three compartments. Drug is administered into and eliminated from the plasma compartment, with drug concentration directly measured only in the plasma compartment. Drug concentrations in the 'effect site' and 'rest of body' compartments are not directly measured. The pharmacodynamic part of the model relates the concentration of the drug in the effect-site compartment to the effect (depth of anaesthesia) using a standard Hill equation. Because the drug does not instantaneously distribute into the effect-site compartment from the plasma, effect-site concentrations peak after the plasma concentration (Fig. 1b). When drug is administered continuously, the effect-site and plasma concentrations equilibrate over time dictated by the rate constants k_{12} and k_{21} (Fig. 1c). The behaviour of the combined system during a simulated experiment aimed at detecting anaesthetic hysteresis is shown in Figure 2a.

If depth of anaesthesia is plotted as a function of plasma concentration, the system is seen to exhibit hysteresis (Fig. 2b). Consistent with experimental findings in animals[26–28] and humans,[41] the concentration–response curve for emergence is left-shifted with respect to induction (Fig. 2b, left). However, if depth of anaesthesia is plotted as a function of the unobserved effects-site concentration, the hysteresis is collapsed (Fig. 2b, right). This observation is the basis for the contention that anaesthetic hysteresis is solely a consequence of the delay in equilibration between the plasma and effect-site concentrations. Note, that in animal models of anaesthetic hysteresis,[27,28] the emergence concentration–response curve has a shallower Hill slope relative to that for induction. This decrease in the Hill slope is related to the magnitude of hysteresis[37] and cannot be readily explained by effect-site equilibration kinetics.

Differences in Hill slope notwithstanding, to examine the merits of the claim that effect-site equilibration accounts for hysteresis, we created a model that, in addition to the drug equilibration component (Figs 1 and 2), has a neuronal dynamics component. This corresponds to relaxing the assumption that at a given concentration of drug in the effect-site the effect is completely determined. In this case, we chose the simplest form of neuronal dynamics: Brownian motion on an energy landscape. The only difference between this model and that described in Figures 1 and 2 is that rather than a simple concentration–response curve, the effect-site drug concentration affects the shape of the energy landscape. This model is consistent with the experimentally observed fluctuations in behavioural responsiveness at pharmacokinetic steady-state.[34] In both mice and zebrafish exposed to mechanistically distinct inhalation and intravenous anaesthetics at pharmacokinetic steady-state at ~MAC-awake, the ability to respond to stimuli fluctuates from trial to trial.[34,35] Furthermore, these behavioural fluctuations exhibit inertia. If the animal failed to respond to the previous stimulus, the probability of response to the next stimulus is dramatically decreased.[34] The simplest model that can account for both fluctuations in responsiveness and inertia is a two-well potential system, which is why this system was chosen in this case.

When the anaesthetic concentration at the effect-site is low, only the awake state is stable (Fig. 3a, blue). Conversely, when anaesthetic concentration in the effect-site compartment is high, only the anaesthetised state is stable (Fig. 3a, yellow). In the intermediate range of anaesthetic concentrations, both awake and the anaesthetised states are stable. Correspondingly, the system spends half of the time in the awake and anaesthetised states (Fig. 3a, green). In this case,

the rate of switching between states is dictated by the amount of noise in the system rather than anaesthetic concentration. When the noise level is low, there is a high propensity to stay in the current state. Consequently, in the low noise regime hysteresis is observed.[37] As in the original drug equilibration model (Fig. 2), when the probability of being in the anaesthetised state (depth of anaesthesia) is plotted against plasma concentration, anaesthetic hysteresis is readily observed (Fig. 3b). In contrast to the original system, however, hysteresis does not collapse when the depth of anaesthesia is plotted against the true effect-site concentration (Fig. 3c). Thus, Figures 2 and 3 present two paradigmatically different mechanisms for anaesthetic hysteresis: delay in drug distribution into the effect-site and relaxation of neuronal dynamics. As Figure 3 illustrates, the two mechanisms are not mutually exclusive; the data in Figure 3, in addition to neuronal dynamics, also has effect-site equilibration kinetics.

It is trivial to distinguish between hysteresis in Figures 2 and 3 in a mathematical model when the drug concentrations in all compartments are known. However, in most experimental settings, only the drug in the plasma compartment can be measured.[1,2,8] To compute the equilibration time for the effect-site compartment in addition to the plasma concentration, the effect (e.g. EEG) is measured. Figure 4a shows plasma concentration and 'depth of anaesthesia' simulated for the system equipped with both drug equilibration and neuronal dynamics (the same data as in Fig. 3). Given just these two measurements, a new effect-site equilibration time constant can be found such that when depth of anaesthesia is plotted against this newly derived incorrect effect-site concentration, hysteresis is collapsed (Fig. 4b and c). This new model is constructed such that plasma concentration is identical to the correct model (Fig. 3). Thus, there would be no experimental basis by which to distinguish this incorrect model (Fig. 4) from the correct model (Fig. 3). Therefore, even when the system is influenced by neuronal dynamics, one can nevertheless construct a model devoid of neuronal dynamics that will make hysteresis collapse. Based on such a model, one could erroneously conclude that the hysteresis is a consequence of delay in drug equilibration. The only difference between the correct model (Fig. 3) and the incorrect model (Fig. 4) is the naming convention. Although this was chosen as the most mathematically elegant demonstration of the indeterminacy of PK–PD parameters, many combinations of rate constants can be used to produce similar plasma concentration dynamics if the model parameters are not constrained by explicit experimental measurements. In contrast to experimental observations that show significant differences in Hill slopes for induction and emergence of anaesthesia,[27,28] the energy landscape model that contains just two wells predicts that the Hill slope for induction and emergence will be the same. However, Proekt and Hudson[37] showed that adding more potential wells in keeping with the experimental observations of brain activity[30] gives rise to the experimentally observed shallower Hill slope for emergence. For the sake of simplicity, and to focus the analysis on the effect-site equilibration dynamics, these more sophisticated models were not considered here.

Figure 4 shows an abstract model of stochastic switching between two states. In order to make a more realistic model, we consider a simple network of two neurones (Fig. 5a) modelled by simplified biophysics as described,[45,46] chosen as one of the simplest neuronal network models that can exhibit oscillations. Oscillations in neuronal activity, measured using EEG, are commonly used as a measure of effects of anaesthetics.[1,49,50] Thus, this simple neuronal network serves as an instructive example of how neuronal dynamics can give rise to hysteresis. Anaesthetics are known to affect gamma aminobutyric acid (GABA)-ergic synaptic transmission.[51,52] Yet, when the brain is deeply anaesthetised, there is a paucity of inhibition in the cortex.[53] These observations are modelled by having anaesthetics potentiate self-inhibition (Fig. 5a). Thus, when anaesthetic concentration in the effect-site is low, there is no self-inhibition (light-coloured synapse). Increasing effect-site concentration is modelled as an increase in the strength of self-inhibition (darker coloured synapse) using the same concentration–response curve (Figs 1–3).

At low anaesthetic concentrations (Fig. 5b, left), the network of two neurones exhibits complex high frequency, low amplitude fluctuations in activity commonly seen in the awake brain. Conversely, when the anaesthetic concentration in the effect-site is high (Fig. 5b, middle), the neuronal network exhibits large amplitude slow oscillations that typically characterise states of anaesthesia and sleep.[50] At intermediate anaesthetic concentrations (Fig. 5b, right), the network switches between more anaesthesia-like large amplitude oscillations and more awake-like fast low amplitude oscillations. Switching arises because at this particular strength of the self-inhibition, the two cell network can exhibit two different oscillatory modes depending on the initial conditions.[45] When noise is added to the system, the neuronal network spontaneously switches between the two oscillatory patterns at a constant anaesthetic concentration. Correspondingly, the two neurone network can be thought of as a biologically plausible network that can give rise to stochastic switching between two oscillatory states at constant effect-site concentration. In other words, the network in Figure 5 is a specific example of the more abstract description of the energy landscape (Fig. 4).

To illustrate the dependence of frequency of state switching on noise, the amount of noise added to the simulated network of neurones was varied whereas effect-site anaesthetic concentration (EC_{50}) was held constant (Fig. 5c). To illustrate switching between different oscillatory patterns, we computed the wavelet transform of neuronal activity. Consistent with observations in the time domain (Fig. 5b, right), when the noise level is high, the system switches frequently between different oscillatory modes (Fig. 5c, left). When the same network is simulated at the same effect-site concentration with less added noise, the switching is less frequent (Fig. 5c, right). The system tends to stay in its current oscillatory state. This resistance to state transitions is *sine qua non* of hysteresis. Much like the abstract two well potential, this simple neuronal network gives rise to hysteresis that depends on neuronal dynamics rather than just drug equilibration.

The point of this model is not to suggest that cortical dynamics can be adequately modelled by two neurones or that anaesthetic effects on the brain can be simply modelled by potentiation of self-inhibition. Rather, even in dramatically simplified models consisting of just two neurones, multistability is the norm. In the more realistic models of the cortex, one finds many more than two stable states. However, as long as the system has more than one stable state at a fixed

anaesthetic concentration, hysteresis will automatically be observed.

One of the important critiques of the findings of Warnaby and colleagues[41] that supports the presence of anaesthetic hysteresis in humans described by Colin and colleagues[54] is that Warnaby and colleagues[41] allowed the concentration of propofol to decay passively during the emergence arm of anaesthetic administration. As argued by Colin and colleagues,[54] this may introduce bias into the experimental findings. Indeed, they show that by assuming a different effect-site equilibration model, they can collapse the hysteresis observed by Warnaby and colleagues.[41]

Kuizenga and colleagues[42] found limited evidence for hysteresis in humans; their study has several distinct methodological advantages: TCIs to attain specific target concentrations during induction and emergence and use of the measured plasma drug concentrations rather than assumed effect-site concentration in construction of the concentration–response curves. Therefore, we simulated an experimental study design as implemented by Kuizenga and colleagues[42] to determine whether such an experimental paradigm can also lead to equivocal conclusions concerning anaesthetic hysteresis depending on the unobserved effect-site concentration.

Figure 6a shows a simulation of TCI steps. The TCI algorithm was constructed such that the effect-site concentration rapidly reaches the target level without overshooting. Critically, in these simulations we assumed that the effect-site compartment equilibrates rapidly with plasma concentration relative to the duration of each TCI step (yellow curve in Fig. 6b). We simulated the two-well potential system (as in Figs 2 and 3) driven by these concentration steps (Fig. 6b). For the purposes of illustration, the two-well potential system was simulated in a noisy regime such that equilibration between the observed state of the system and effect-site concentration is rapid (Fig. 6c, yellow curves; plasma concentration is shown in green to illustrate the relationship between plasma concentration and the observed effect). When concentration–response curves for induction and emergence are plotted with respect to the observed plasma concentration (Fig. 6d, yellow curves), no appreciable hysteresis is observed because neuronal dynamics equilibrate rapidly. Decreasing noise would increase the observed hysteresis[37] (see also Supplementary Fig. S1).

Because the effect-site concentration is not experimentally observed, we examined how the conclusions concerning hysteresis are affected by changes in the assumed effect-site equilibration time constant (orange and red curves in Fig. 6b–d). When the kinetics of effect-site equilibration are commensurate with the duration of each TCI step (red curves, Fig. 6b–d), a clear hysteresis between induction and emergence curves is observed. This observation is quantified for a range of possible effect-site equilibration time constants (Fig. 6e). Given the same experimental data that relate plasma concentration to the observed effect, one can conclude that hysteresis either does or does not exist depending on the choice of the effect-site equilibration kinetics. No one particular choice of effect-site equilibration time constant can be either supported or refuted on the basis of any experimental measurement. Thus, even exemplary experimental work by Kuizenga and colleagues[42] unfortunately cannot be used to establish unequivocal evidence for or against hysteresis in humans so long as the theoretical framework used to administer anaesthetics relies on unobservable rate constants. Supplementary Figure S1 shows that one can also make hysteresis arbitrarily large or small given the same experimental observations by changing the amount of noise that drives neuronal dynamics. In contrast to the effect-site concentration that cannot be measured, the methodology for measuring noise-driven fluctuations in responsiveness at a constant drug concentration has been developed.[34,35]

Discussion

A standard effect-site modelling approach can be used to collapse anaesthetic hysteresis even when hysteresis is in part attributable to neuronal dynamics. In practice, the effect-site equilibration time constant is explicitly estimated such that hysteresis is minimised. Thus, any model that involves an experimentally unconstrained estimate of effect-site equilibration time constant is bound to conclude that effect-site equilibration completely accounts for the observed hysteresis whether that is true or not. We could interpret 'effect-site equilibration' as a catchall time constant that quantifies the delay between plasma concentration of the drug and its effect, rather than specifically the transit time of the drug from the plasma to the receptor(s) where it exerts its actions. However, this may be misleading, as it implies that drug equilibration alone is responsible for hysteresis, when in fact neuronal dynamics may play a pivotal role.

Many degenerate parameter sets can produce model behaviours that cannot be distinguished on experimental grounds. For instance, this degeneracy has been demonstrated for models of signal transduction cascades,[55] and for simple systems such as radioactive decay[56] similar in mathematical structure to those that govern standard PK models. One can readily find models whose parameters vary over several orders of magnitude but nevertheless produce similar quality fits to experimental data (see Supplementary Fig. S2). This is not a consequence of uncertainty in measurement of drug concentration or inter-subject variability. This 'sloppiness'[55] is a consequence of the mathematical structure of the equations used to model many systems including pharmacokinetics. The fact that a complex multi-parameter model can faithfully reproduce limited experimental observations does not validate any specific parameter value of the fitted model. The parameters can be individually measured to constrain the fits. Unfortunately, this experimental validation is explicitly precluded by the assertion that the effect-site is a theoretical compartment devoid of specific physical interpretation.

Before addressing how anaesthetic hysteresis can be experimentally established in humans, it is important to underscore why this is an important issue. Traditional pharmacological explanations maintain that recovery of consciousness is entirely attributable to drug washout. In contrast, a neuroscience-based approach maintains that recovery of consciousness is fundamentally distinct from loss of consciousness and cannot be explained by drug washout alone. To see why this is the case, consider a seemingly unrelated example of protein folding. It is well known that proteins can be denatured by heat. Upon cooling, some denatured proteins will refold back into their native conformation. As was pointed out by Levinthal[57] in the 1960s, if the protein were to sample the conformational space at random to recover its original fold, the folding process would take longer than the time of the known universe. This observation known as Levinthal's paradox implies that protein folding must necessarily be structured, and occur by a sequence of

metastable intermediates.[58] These folding intermediates, found in local minima of the energy landscape, greatly constrain the conformation space and allow the protein to rapidly restore its native conformation. This protein folding example illustrates a general principle: whereas going from the structured to the unstructured state is trivial, the restoration of structure is not generically expected after a dramatic perturbation.

There is an obvious parallel between protein folding and restoration of consciousness after anaesthesia. Many mechanistically distinct compounds can extinguish consciousness.[51,52] However, once consciousness is lost, the brain is faced with attempting to restore itself into its previously structured state. Much like protein folding, restoration of consciousness in the brain proceeds via transiently stabilised intermediates.[30,59–61] Thus, drug washout alone is no more of an explanation of recovery of consciousness than cooling is an explanation of protein folding.

Most proteins do not spontaneously recover their native conformation after denaturation. This is because *en route* to recovery the denatured protein can become trapped in one of the folding intermediates or assume a totally different conformation altogether. Although most patients recover consciousness uneventfully after anaesthesia, some exhibit transient and potentially long-term alteration in cognitive function such as postoperative delirium[62] and cognitive dysfunction.[63] It is possible that such short- and long-term alterations in cognition are a manifestation of the brain becoming trapped in one of the intermediates *en route* to recovery of consciousness. However, before addressing this hypothesis,[64] the role for neuronal dynamics in recovery of consciousness must be experimentally demonstrated in humans.

How can this be accomplished? There are two complementary experimental approaches that can be translated from animal experiments to humans. The first approach involves direct measurement of anaesthetic concentration in brain for comparison with estimated effect-site concentration kinetics.[65] All such measurements of brain anaesthetic concentration in animals unequivocally favour presence of anaesthetic hysteresis. Across species loss of consciousness is observed at a higher brain anaesthetic concentration than recovery of consciousness.[27,28] In animal work on hysteresis, concentration measurements have been performed using methods that cannot be applied to humans. However, brain concentration of one anaesthetic, xenon, can be measured in humans, albeit indirectly, using neuroimaging. Experiments that address whether loss of consciousness occurs at higher brain xenon concentration than recovery of consciousness are currently being performed.[66]

Measurement of brain xenon concentration cannot unequivocally rule out an effect-site equilibration model. Because the effect-site is a theoretical compartment, one could claim that imaging-based xenon concentration measurements do not reliably estimate the concentration at the effect-site, and different effect-site models would eliminate hysteresis. Thus, even if the xenon experiments show that loss of consciousness occurs at higher brain xenon concentration than recovery, it is unlikely that the debate concerning existence of anaesthetic hysteresis in humans will be settled. The second experimental approach, motivated by recent animal experiments,[34,35] can offer definitive evidence concerning the role of neuronal dynamics in anaesthetic hysteresis and does not depend on specific choices of effect-site equilibration constant.

It is assumed that at pharmacokinetic equilibrium each individual will exhibit a consistent anaesthetic depth. There are two interpretations of this statement. One interpretation is that at the EC_{50} for wakefulness (MAC-awake), half of individuals will be awake, whereas the other half will be anaesthetised. The second interpretation is that each individual will respond to a randomly chosen 50% of stimuli. Remarkably, recent experiments on mice and on zebrafish with both intravenous and inhalation anaesthetics are not consistent with either one of these interpretations. At pharmacokinetic equilibrium, each individual's ability to respond to stimuli fluctuated. But these fluctuations were not random; the probability of failing to respond increased dramatically if the subject failed to respond to the previous stimulus. In other words, even at drug equilibrium, behavioural dynamics still exhibit inertia.[34] Such behavioural inertia automatically results in hysteresis independent of effect-site equilibration.[37] The results of McKinstry-Wu and colleagues[34] and Wasilczuk and colleagues[35] are consistent with simulations of the two-well potential and of the simple neuronal network presented herein.

With minor modifications, the same approach can be readily applied to human subjects exposed to either volatile or intravenous anaesthetics around MAC-awake at pharmacokinetic equilibrium. Whereas a clear strength of the work by Kuizenga and colleagues[42] was that they exposed subjects to steady-state concentrations of anaesthetics, the key distinction from the work by McKinstry-Wu and colleagues[34] and Wasilczuk and colleagues[35] is that the focus of the analysis is on the fluctuations in responsiveness in each individual rather than averages across population. Establishing that humans, much like mice and zebrafish, exhibit behavioural inertia at pharmacokinetic steady-state will offer definitive evidence that neuronal dynamics play a pivotal role in recovery of consciousness. This, in turn, will clear the way for investigating whether aberrant neuronal dynamics can help explain why restoration of consciousness after anaesthesia in some patients is complicated by delirium and other cognitive disturbances.[64]

The famous statement by George Box[67] that 'all models are wrong but some are useful' applies to both the effect-site models and to the neuronal dynamics models presented here. Effect-site models, despite their limitations, are useful as purely empirical tools for administering anaesthetics. However, because effect-site concentration cannot be measured experimentally, these models offer little in the way of insight into anaesthetic hysteresis. The neuronal dynamics models are clearly much simplified relative to their biological counterparts and cannot be used to infer the mechanisms of anaesthetic action, but are useful in analysing behavioural fluctuations.[34,35] Critically the two models make fundamentally different predictions about responses at a fixed drug concentration. Box[67] further states that 'science is a means whereby learning is achieved, not by mere theoretical speculation on the one hand, nor by the undirected accumulation of practical facts on the other, but rather by a motivated iteration between theory and practice'. There is an accumulation of experimental findings that point to the importance of neuronal dynamics in restoration of consciousness after anaesthesia. The 'black box' models that shape how we think about loss and recovery of consciousness must be amended to incorporate neuronal dynamics.

Authors' contributions

Designed and analysed experiments: AP
Wrote and edited manuscript: AP, MPK

Declarations of interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

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References

1. Schnider TW, Minto CF, Shafer SL, et al. The influence of age on propofol pharmacodynamics. *Anesthesiology* 1999; **90**: 1502–16
2. Minto CF, Schnider TW, Gregg KM, Henthorn TK, Shafer SL. Using the time of maximum effect site concentration to combine pharmacokinetics and pharmacodynamics. *Anesthesiology* 2003; **99**: 324–33
3. Schüttler J, Stanski DR, White PF, et al. Pharmacodynamic modeling of the EEG effects of ketamine and its enantiomers in man. *J Pharmacokinet Biopharm* 1987; **15**: 241–53
4. Schnider TW, Minto CF, Gambus PL, et al. The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. *Anesthesiology* 1998; **88**: 1170–82
5. Stanski DR, Hudson RJ, Homer TD, Saidman LJ, Meathe E. Pharmacodynamic modeling of thiopental anesthesia. *J Pharmacokinet Biopharm* 1984; **12**: 223–40
6. Hughes MA, Glass PSA, Jacobs JR. Context-sensitive half-time in multicompartment pharmacokinetic models for intravenous anesthetic drugs. *Anesthesiology* 1992; **76**: 334–41
7. Olofsen E, Dahan A. The dynamic relationship between end-tidal sevoflurane and isoflurane concentrations and bispectral index and spectral edge frequency of the electroencephalogram. *Anesthesiology* 1999; **90**: 1345–53
8. Cortínez LI, Trocóniz IF, Fuentes R, et al. The influence of age on the dynamic relationship between end-tidal sevoflurane concentrations and bispectral index. *Anesth Analg* 2008; **107**: 1566–72
9. Scott JC, Ponganis KV, Stanski DR. EEG quantitation of narcotic effect: the comparative pharmacodynamics of fentanyl and alfentanil. *Anesthesiology* 1985; **62**: 234–41
10. Bouillon T, Bruhn J, Radu-Radulescu L, Andresen C, Cohane C, Shafer SL. A model of the ventilatory depressant potency of remifentanil in the non-steady state. *Anesthesiology* 2003; **99**: 779–87
11. Sheiner LB, Stanski DR, Vozeh S, Miller RD, Ham J. Simultaneous modeling of pharmacokinetics and pharmacodynamics: application to d-tubocurarine. *Clin Pharmacol Ther* 1979; **25**: 358–71
12. McCoy EP, Mirakhur RK, Maddineni VR, Wierda JMKH, Proost JH. Pharmacokinetics of rocuronium after bolus and continuous infusion during halothane anaesthesia. *Br J Anaesth* 1996; **76**: 29–33
13. Tucker GT, Mather LE. Clinical pharmacokinetics of local anaesthetics. *Clin Pharmacokinet* 1979; **4**: 241–78
14. Gustafsson LL, Ebling WF, Osaki E, Harapat S, Stanski DR, Shafer SL. Plasma concentration clamping in the rat using a computer-controlled infusion pump. *Pharm Res* 1992; **9**: 800–7
15. Glass PSA, Jacobs JR, Smith LR, et al. Pharmacokinetic model-driven infusion of fentanyl: assessment of accuracy. *Anesthesiology* 1990; **73**: 1082–90
16. Connor SB, Jacobs JR, Quill TJ. Accuracy of drug infusion pumps under computer control. *IEEE Trans Biomed Eng* 1992; **39**: 980–2
17. Russell D, Wilkes MP, Hunter SC, Glen JB, Hutton P, Kenny GNC. Manual compared with target-controlled infusion of propofol. *Br J Anaesth* 1995; **75**: 562–6
18. Shafer SL, Gregg KM. Algorithms to rapidly achieve and maintain stable drug concentrations at the site of drug effect with a computer-controlled infusion pump. *J Pharmacokinet Biopharm* 1992; **20**: 147–69
19. Guarracino F, Lapolla F, Cariello C, et al. Target controlled infusion: TCI. *Minerva Anestesiol* 2005; **71**: 335–7
20. Struys MMRF, De Smet T, Glen JB, Vereecke HEM, Absalom AR, Schnider TW. The history of target-controlled infusion. *Anesth Analg* 2016; **122**: 56–69
21. Jaklitsch RR, Westenskow DR. A model-based self-adjusting two-phase controller for vecuronium-induced muscle relaxation during anesthesia. *IEEE Trans Biomed Eng* 1987; **34**: 583–94
22. Struys MMRF, De Smet T, Versichelen LFM, Van De Velde S, Van Den Broecke R, Mortier EP. Comparison of closed-loop controlled administration of propofol using Bispectral Index as the controlled variable versus 'standard practice' controlled administration. *Anesthesiology* 2001; **95**: 6–17
23. Locher S, Stadler KS, Boehlen T, et al. A new closed-loop control system for isoflurane using bispectral index outperforms manual control. *Anesthesiology* 2004; **101**: 591–602
24. Gentilini A, Schaniel C, Morari M, Bieniok C, Wymann R, Schnider T. A new paradigm for the closed-loop intraoperative administration of analgesics in humans. *IEEE Trans Biomed Eng* 2002; **49**: 289–99
25. Ching S, Liberman MY, Chemali JJ, et al. Real-time closed-loop control in a rodent model of medically induced coma using burst suppression. *Anesthesiology* 2013; **119**: 848–60
26. Kelz MB, Sun Y, Chen J, et al. An essential role for orexins in emergence from general anesthesia. *Proc Natl Acad Sci U S A* 2008; **105**: 1309–14
27. Friedman EB, Sun Y, Moore JT, et al. A conserved behavioral state barrier impedes transitions between anesthetic-induced unconsciousness and wakefulness: evidence for neural inertia. *PLoS One* 2010; **5**, e11903
28. Joiner WJ, Friedman EB, Hung HT, et al. Genetic and anatomical basis of the barrier separating wakefulness and anesthetic-induced unresponsiveness. *PLoS Genet* 2013; **9**: 1–12
29. Proekt A, Kelz M. Schrödinger's cat: anaesthetised and not! *Br J Anaesth* 2018; **120**: 424–8
30. Hudson AE, Calderon DP, Pfaff DW, Proekt A. Recovery of consciousness is mediated by a network of discrete metastable activity states. *Proc Natl Acad Sci U S A* 2014; **111**: 9283–8
31. Ishizawa Y, Ahmed OJ, Patel SR, et al. Dynamics of propofol-induced loss of consciousness across primate neocortex. *J Neurosci* 2016; **36**: 7718–26

32. Patel SR, Ballesteros JJ, Ahmed OJ, et al. Dynamics of recovery from anaesthesia-induced unconsciousness across primate neocortex. *Brain* 2020: 1–11. 0
33. Chander D, García PS, MacColl JN, Illing S, Sleigh JW. Electroencephalographic variation during end maintenance and emergence from surgical anesthesia. *PLoS One* 2014; **9**, e106291
34. McKinstry-Wu AR, Wasilczuk AZ, Harrison BA, et al. Analysis of stochastic fluctuations in responsiveness is a critical step toward personalized anesthesia. *eLife* 2019; **8**, e50143
35. Wasilczuk AZ, Harrison BA, Kwasinewska P, et al. Resistance to state transitions in responsiveness is differentially modulated by different volatile anaesthetics in male mice. *Br J Anaesth* 2020; **125**: 308–20
36. Wong KFK, Smith AC, Pierce ET, et al. Statistical modeling of behavioral dynamics during propofol-induced loss of consciousness. *J Neurosci Methods* 2014; **227**: 65–74
37. Proekt A, Hudson AE. A stochastic basis for neural inertia in emergence from general anaesthesia. *Br J Anaesth* 2018; **121**: 86–94
38. Steyn-Ross ML, Steyn-Ross DA, Sleigh JW, Wilcocks LC. Toward a theory of the general-anesthetic-induced phase transition of the cerebral cortex. I. A thermodynamics analogy. *Phys Rev E Stat Nonlin Soft Matter Phys* 2001; **64**, 011917
39. Steyn-Ross DA, Steyn-Ross ML, Wilcocks LC, Sleigh JW. Toward a theory of the general-anesthetic-induced phase transition of the cerebral cortex. II. Numerical simulations, spectral entropy, and correlation times. *Phys Rev E Stat Nonlin Soft Matter Phys* 2001; **64**, 011918
40. Kim H, Moon J-Y, Mashour GA, Lee U. Mechanisms of hysteresis in human brain networks during transitions of consciousness and unconsciousness: theoretical principles and empirical evidence. *PLoS Comput Biol* 2018; **14**, e1006424
41. Warnaby CE, Sleigh JW, Hight D, Jbabdi S, Tracey I. Investigation of slow-wave activity saturation during surgical anesthesia reveals a signature of neural inertia in humans. *Anesthesiology* 2017; **127**: 645–57
42. Kuizenga MH, Colin PJ, Reyntjens KMEM, et al. Test of neural inertia in humans during general anaesthesia. *Br J Anaesth* 2018; **120**: 525–36
43. Minto CF, Schnider TW. Contributions of PK/PD modeling to intravenous anesthesia. *Clin Pharmacol Ther* 2008; **84**: 27–38
44. Gambus PL, Troconiz IF. Pharmacokinetic-pharmacodynamic modelling in anaesthesia. *Br J Clin Pharmacol* 2015; **79**: 72–84
45. Ermentrout B. Neural networks as spatio-temporal pattern-forming systems. *Rep Prog Phys* 1998; **64**: 353–430
46. Brennan C, Proekt A. A quantitative model of conserved macroscopic dynamics predicts future motor commands. *eLife* 2019; **8**, e46814
47. Nunez PL. *Electric fields of the brain: the neurophysics of EEG*. New York: Oxford University Press; 2006
48. Shortal BPBP, Reitz SLSL, Aggarwal A, et al. Development and validation of brain target controlled infusion of propofol in mice. *PLoS One* 2018; **13**, e0194949
49. Minto CF, Schnider TW, Short TG, Gregg KM, Gentilini A, Shafer SL. Response surface model for anesthetic drug interactions. *Anesthesiology* 2000; **92**: 1603–16
50. Brown EN, Lydic R, Schiff ND. General anesthesia, sleep, and coma. *N Engl J Med* 2010: 2638–50
51. Franks NP. General anaesthesia: from molecular targets to neuronal pathways of sleep and arousal. *Nat Rev Neurosci* 2008; **9**: 370–86
52. Hemmings HC. Molecular targets of general anesthetics in the nervous system. In: Hudetz A, Pearce R, editors. *Suppressing mind*. Totowa, NJ: Humana Press; 2009. p. 11–31
53. Ferron J-F, Kroeger D, Chever O, Amzica F. Cortical inhibition during burst suppression induced with isoflurane anesthesia. *J Neurosci* 2009; **29**: 9850–60
54. Colin PJ, Kuizenga MH, Vereecke HE, Struys MM. Pharmacokinetic pharmacodynamic perspective on the detection of signs of neural inertia in humans. *Anesthesiology* 2018; **129**: 373–5
55. Gutenkunst RN, Waterfall JJ, Casey FP, Brown KS, Myers CR, Sethna JP. Universally sloppy parameter sensitivities in systems biology models. *PloS Comput Biol* 2007; **3**: e189
56. Waterfall JJ, Casey FP, Gutenkunst RN, et al. Sloppy-model universality class and the vandermonde matrix. *Phys Rev Lett* 2006; **97**: 150601
57. Levinthal C. Are there pathways for protein folding? *J Chim Phys* 1968; **65**: 44–5
58. Ptitsyn OB. Structures of folding intermediates. *Curr Opin Struct Biol* 1995; **5**: 74–8
59. Alonso LM, Solovey G, Yanagawa T, Proekt A, Cecchi GA, Magnasco MO. Single-trial classification of awareness state during anesthesia by measuring critical dynamics of global brain activity. *Sci Rep* 2019; **9**: 4927
60. Solovey G, Alonso LMM, Yanagawa T, et al. Loss of consciousness is associated with stabilization of cortical activity. *J Neurosci* 2015; **35**: 10866–77
61. Alonso LM, Proekt A, Schwartz TH, Pryor KO, Cecchi GA, Magnasco MO. Dynamical criticality during induction of anesthesia in human ECoG recordings. *Front Neural Circuits* 2014; **8**: 20
62. Dyer CB, Ashton CM, Teasdale TA. Postoperative delirium: a review of 80 primary data-collection studies. *Arch Intern Med* 1995; **155**: 461–5
63. Evered L, Silbert B, Knopman DS, et al. Recommendations for the nomenclature of Cognitive change associated with anaesthesia and surgery—2018. *Anesthesiology* 2018; **129**: 872–9
64. Proekt A. Cognitive function in perioperative care emergence delirium. A new hypothesis for an old problem. In: Eckenhoff RG, Terrando N, editors. *The perioperative neurocognitive disorders*. Cambridge University Press; 2019. p. 1–10
65. Voss 1 Logan J, Guy Ludbrook, Grant Cliff, Richard Upton JWS. A comparison of pharmacokinetic/pharmacodynamic versus mass-balance measurement of brain concentrations of intravenous anesthetics in sheep. *Anesth Analg* 2007; **104**: 1440–6
66. McKinstry-Wu A, Carspecken CW, Proekt A, Kelz MB. Xenon anesthesia and CT: noninvasive measures of brain anesthetic concentration. *Methods Enzymol* 2018; **602**: 289–98
67. Box GEP. Science and statistics. *J Am Stat Assoc* 1976; **71**: 791–9

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