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Translational Studies

A stochastic basis for neural inertia in emergence from general anaesthesia

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Abstract

Background: Transitions into and out of the anaesthetised state exhibit resistance to state transitions known as neural inertia. As a consequence, emergence from anaesthesia occurs at a consistently lower anaesthetic concentration than induction. Motivated by stochastic switching between discrete activity patterns observed at constant anaesthetic concentration, we investigated the consequences of such switching for neural inertia.

Methods: We simulated stochastic switching in MATLAB as Brownian motion on an energy landscape or equivalently as a discrete Markov process. Effects of anaesthetics were modelled as changing stability of the awake and the anaesthetised states. Simulation results were compared with re-analysed neural inertia data from mice and *Drosophila*.

Results: Diffusion on a two-well energy landscape gives rise to hysteresis. With additive noise, hysteresis collapses. This collapse occurs over a mixing time that is independent from pharmacokinetics. The two-well potential gives rise to the leftward shift for the emergence dose-response curve. Yet, from *in vivo* data, ΔEC_{50} and Δ Hill slope are strongly negatively correlated (R^2=0.45, $P<1.7\times10^{-15}$). This correlation is not explained by a two-well potential. The extension of the diffusion model to a Markov process with 10 states (three awake, seven unconscious) reproduces both the left shift and the shallower Hill slope for emergence.

Conclusions: Stochastic state switching accounts for all known features of neural inertia. More than two states are required to explain the consistent increase observed in variability of recovery from general anaesthesia. This model predicts that hysteresis should collapse with a time scale independent of anaesthetic drug pharmacokinetics.

Keywords: anaesthesia, general; consciousness, loss of

How does the brain recover after consciousness is disrupted by general anaesthesia? The brain is a complex non-linear dynamical system, which are generically multistable. Thus, even when all parameters are fixed, the brain can exhibit multiple, qualitatively distinct behaviours depending on initial conditions.[1] It therefore is not guaranteed that, after anaesthesia, the brain will ever return to its previous, conscious state. As a consequence of resistance to state transitions, emergence from anaesthesia occurs at a consistently lower anaesthetic concentration than induction, known as neural inertia.

While sleep and anaesthesia are fundamentally distinct, there is overlap in the underlying neuronal mechanisms.[2–4]

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Editor's key points

- The dose-response curve for emergence from general anaesthesia is shifted to lower concentrations relative to induction of general anaesthesia, known as neural inertia.
- Using mathematical modelling, a bistable system can account for neural inertia, and more than two states are required to explain the variability of emergence for different anaesthetic agents and taxa.
- As a consequence of resistance to state transitions, emergence from anaesthesia occurs at a consistently lower anaesthetic concentration than induction; this is independent of pharmacokinetic factors.

Sleep and wakefulness activate mutually inhibitory sleep[5,6] and wake-active[7,8] neurone populations, respectively, suggesting that transitions between sleep and wakefulness could be thought of as a 'flip-flop' switch (Fig. 1a).[6,9] General anaesthetics inhibit wake-active and excite sleep-active neurones, biasing the flip-flop.[2,3,5,10–15] The dynamics of flip-flop networks lead to just two stable patterns of neuronal activity[16]: either the wake-active neurones are active and sleep-active neurones are silent, or vice versa (Fig. 1b). Neuronal mechanisms of anaesthesia are not limited to sleep-wake circuitry. Nevertheless, dynamics similar to the flip-flop switch arise in a broad class of neuronal systems called attractor neural networks.[17–20]

Dynamics of attractor networks are well-approximated by diffusion on an energy landscape.[21] This energy landscape typically has multiple wells representing distinct attractors (Fig. 1c). While meanfield models of anaesthesia[18,22–24] use a different formalism, their dynamics can also be thought of as diffusion on energy landscapes. These meanfield models of anaesthesia exhibit bistability—a special case of multistability where only two stable states (i.e. attractors) are observed. These stable states are typically interpreted as 'awake' or 'anaesthetised'. More complex dynamics occur when multiple bistable networks are coupled.[20]

In contrast to meanfield approaches, here we do not address how the shape of the energy landscape depends on the underlying neuronal architecture. Rather, we study the consequences of multistability for neuronal inertia.[14,25,26] That is, how does the energy landscape shift with increasing anaesthetic drug concentrations (Fig. 1d)? What are the implications of these shifts for transitions between the awake and the anaesthetised state? What is the effect of noise on neural inertia? Are just two states sufficient to explain the phenomenology of neural inertia?

Experimental evidence argues that neural inertia—the hysteresis present between dose-response curves for induction and emergence (Fig. 1e)—is ubiquitous and not explainable by pharmacokinetic factors alone. Here, we show that a bistable system such as a flip-flop switch can account for the left shift of the dose-response curve for emergence relative to induction, but more than two states are required to explain the increased variability of emergence seen across different anaesthetic agents and taxa.

Methods

Energy landscape simulations

All simulations were performed in MATLAB 2014b (MathWorks, Natick, MA, USA). To simulate transitions between two distinct states, we used a 'potential energy' function adapted from Moreno-Bote and colleagues:[21]

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

E is a function of the state of the system denoted by x. $x = r_{wake} - r_{sleep}$ where r could be thought of as the firing rate of a neuronal population in arbitrary units and a is anaesthetic concentration in arbitrary units scaled between 0 and 1.

E naturally describes an attractor network comprised of two mutually inhibitory populations of neurones. The two minima of E are located at $x \approx \pm 1$. These minima could correspond, for example, to activated wake-active neurones or sleep-active neurones. Consistent with experimental evidence, this two-well potential function assures that the two populations of neurones are not likely to be co-activated. The analogy to sleep and wake active neurones is used for illustration only. The presence of more than one well in the potential energy produces the phenomena of interest, rather than any specific features of neuronal architecture.

For the sake of mathematical convenience, anaesthetic-induced activation of sleep-active and inhibition of wake-active neurones are assumed to have the same strength. This assumption does not change any conclusions appreciably, because the Boltzmann relationship assures that the energy landscape uniquely specifies the probability distribution of the system states $\pi(x) \propto e^{-E(x,a)}$ (i.e. the probability of being awake at each anaesthetic concentration). $\pi(x)$ is the limiting distribution at steady-state in a system perturbed by noise. Without noise, the system would drift down the energy gradient and stay at the minimum indefinitely. Thus, without noise, the behaviour of the system can be computed analytically (black line in Fig. 2a). Transitions between the awake and anaesthetised states in the noiseless case only occur when the starting state of the system loses stability at some critical anaesthetic concentration. This loss of stability for the awake and the anaesthetised state occurs at different anaesthetic concentrations. This difference in concentrations is a necessary consequence of multistability—if only one stable state exists for all anaesthetic concentrations, then the system is by definition not multistable. Thus, without noise, bistable systems generically give rise to hysteresis, as predicted by meanfield models.[18,24]

Our primary interest here is the non-trivial effect of noise superimposed on the potential function. Specifically, we are concerned with the dynamics of the system at a constant anaesthetic concentration. To model the effect of noise, we use Brownian motion on an energy landscape—the change in the state of the system over time is a sum of the gradient of the energy landscape (first term) and noise ε:

$$\frac{dx}{dt} = -D\frac{\partial E(x,a)}{\partial x} + \varepsilon \quad (2)$$

Together with ε, the diffusion constant D scales the noise relative to the energy barrier separating the two stable states. For the purposes of simulation, D was held fixed while ε was varied. ε is modelled as Gaussian noise with mean 0 and variance σ. Equation (2) can be generalised to a broad class of reaction-diffusion systems which include both stochastic and deterministic components. Here, we assume the simplest model that only includes stochastic processes. For clarity we omit the normalisation constant $\sqrt{2}$ typically used to scale ε. Increasing σ makes the system more noise-driven. Simulations of Brownian motion were performed using the standard Euler method.