of capillaries were dependent on AMPA receptor activation, suggesting that the release requires activation of a postsynaptic network. ATP release could conceivably occur from presynaptic terminals within the network, from terminals activated by a retrograde messenger or even from astrocytes themselves, as an alternative to the direct release of ATP from the postsynaptic compartment.

We are now reaching a point where several cell types and signaling pathways have been shown to mediate neurovascular coupling in different experimental preparations and brain regions. It will be important to determine the relative roles of these different pathways in awake animals and to identify pathologies that affect these pathways. The findings may have importance beyond the field of neurovascular coupling. Blood oxygen level–dependent functional magnetic resonance imaging is currently the leading method for noninvasive imaging of human brain activity; however, it does not directly measure brain activity, relying instead on neurovascular coupling mechanisms. In the rat olfactory bulb[14] and in the visual cortex of anesthetized cats[15], there exists a mismatch between local neuronal activity and functional hyperemia, caused by dilating arterioles that feed a larger region of the cortex than activated. It will therefore be important to determine the relative contributions of capillary and arteriole dilations to the overall change in localized blood flow. These new findings[1,11] suggest that astrocyte processes are positioned to fine-tune the direction of blood flow and may increase the spatial specificity between brain activity and functional imaging signals.

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Many paths from state to state

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Humans and animals can collect and maintain information that guides decisions, but how neural circuits achieve this is unknown. It seems neural populations may do so by passing through diverse states in many possible sequences.

Humans and animals can actively represent and maintain information that guides decisions, but how neural circuits achieve this is unknown. The dominant notion for many years has been that neurons encode information primarily using their spike rate, which is usually hypothesized to have a static relationship with stimuli or internal state. Yet more recently there has been a resurgence of interest in the old idea that the brain might use stereotyped sequences of discrete states, switching from one activity pattern to another to maintain activity[1,2]. Each of these 'states' would be distinct enough from one another that even an imperfect realization of the activity pattern could still reliably drive the next state in the sequence. These sequences might be used explicitly as clocks[3,4], or they might be a convenient way for recurrent neural circuits to maintain information despite the short time constants of single cells[5,6]. It is challenging to perfectly tune a circuit to maintain a precise, stable state along a continuum of possibilities[7]. The idea that sequences might avoid this challenge is thus appealing and would even permit sparse activity. In this issue of *Nature Neuroscience*, Morcos and Harvey[8] present evidence that this is indeed the case, with a few wrinkles that may make the system more flexible.

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The authors began by building on previous work showing that a virtual T-maze task could evoke sequence-like activity in the posterior parietal cortex (PPC) of mice[9]. Here, as mice ran through the virtual maze, information about which way to turn was doled out over several seconds. The mice thus needed to accumulate evidence in working memory. The authors then used two-photon calcium imaging to record activity in PPC. In this task, as in previous virtual maze tasks, activity in PPC was sparse and selective for both position and intention: each neuron fired a burst of spikes at some particular point on the track—say, 50 cm from the start location—and only when the animal was within a particular context; say, planning to turn right. Interestingly, this firing was 'unreliable': a neuron would fire on only a fraction of such trials. This fickle firing naturally calls for sequences, in which neurons take up the slack for their unreliable brethren.

Here's where the authors had a crucial insight. They asked whether perhaps neurons weren't, in fact, unreliable. Instead, they postulated that there might be multiple possible sequences of neural activity for the exact same evidence and upcoming decision. But this presented a challenge: no existing analyses could detect multiple, sparse sequences in calcium imaging data. So Morcos and Harvey reasoned that there might be multiple possible sequences, but, for a neural state to be meaningful, surely the brain would visit that state on many trials. To find these repeated states for a given time window in the trial, they considered the simultaneously recorded activity of many neurons. Each trial yielded a pattern across neurons for that time window, with one spike count per neuron. They then clustered the activity patterns. While states were not necessarily repeated perfectly, each cluster revealed a state that was achieved on numerous trials. This is a remarkably flexible way to find sequences: it does not assume that activity changes smoothly or that neurons must produce the same activity for the same stimulus but can instead handle the brain jumping from one pattern of activity to a completely different pattern. Because data sets from many neural structures exhibit sparse bursts of activity, this approach can likely be employed by many experimenters in the analysis of their data.

With the states identified in PPC, the authors exploited the power of their simultaneous

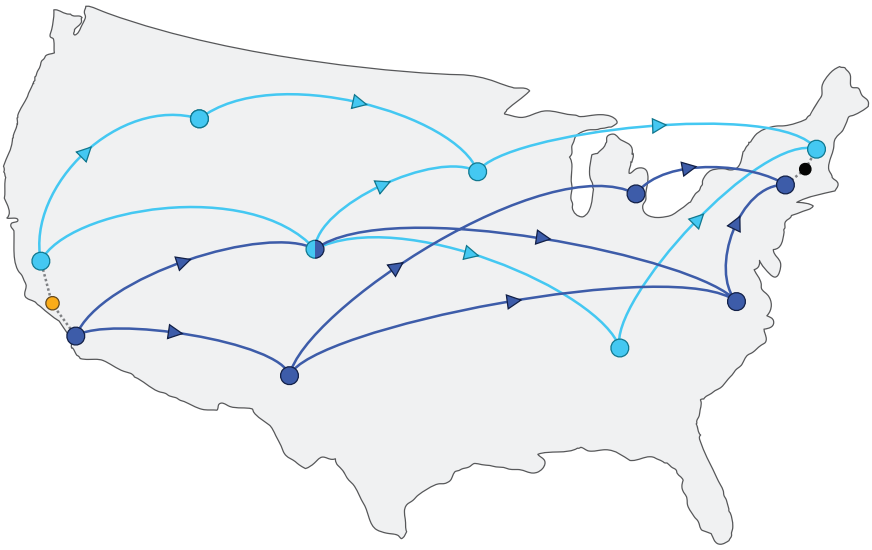

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Figure 1 Flight routes for two hypothetical airlines illustrate a key analysis. Blue lines indicate flight segments connecting Santa Barbara (orange circle) to a single destination, Hartford (black circle). Either airline (light and dark blue) can transport passengers from Santa Barbara to Hartford, visiting a number of discrete locations (airports) along the way. This naturally leads to a diversity of possible sequences, evident even at the beginning of the journey. Nonetheless, the airport occupied at any given time is informative about the limited selection of possible next airports. Indeed, the starting airport is partly predictive even of the ending airport of the journey. In PPC, neural activity likewise visits a sequence of discrete states (analogous to the airports) in advance of a single decision (say, right; leftwards decisions led to a separate set of discrete states). This sequence varies trial by trial even for decisions ending in the same outcome. This diversity of states is evident even at the very beginning and end of the trial. Despite this variability, the network state at any moment is informative about which states will subsequently be visited.

recordings to ask how sequences progressed from state to state. Reassuringly, the transitions between states were restricted: a given state would only be followed by a subset of the possible states a few moments later. Unexpectedly, these restrictions were substantial and persisted for multiple seconds (**Fig. 1**). Moreover, there was additional information embedded in which sequence was taken. For example, the brain's initial state on a trial often carried information about what had happened on the previous trial: whether the mouse chose left or right and whether he was rewarded or not. This task-irrelevant information, surprisingly, rarely biased the animals' decisions but was still latent in the neural state even seconds later: PPC would only take a subset of the possible left-choice states or right-choice states depending on what that initial state had been. Careful behavioral controls ensured that these path restrictions were not simply due to subtle behavioral differences. The upshot of this persistence was that, at decision time, the neural state depended on a number of variables beyond choice and net evidence. However, because states may be more similar to one another during some epochs than others, it is not entirely clear how these observations relate to previous work on trial-to-trial variability.

The noisiness of bursty neurons in other areas might likewise be tied to the existence of multiple sequences during what appears to be the same behavior. For example, neurons in prefrontal areas have a putative role in working memory and are notoriously noisy. Neurons in the hippocampus are likewise noisy, perhaps suggesting that the same navigational path is supported by different sequences of activity. Operationally, such variable sequences may reveal themselves in the sparse bursting of neurons combined with high trial-to-trial variability (for example, assessed via Fano factor or Variance of the Conditional Expectation, VarCE[10]). However, it is surprising that other groups recording from the same brain areas have not observed sequences[11–13]. This may indicate a unique feature of navigational tasks.

The finding of variable sequences also opens a variety of new questions. First, are there functional implications to taking one path over another? Perhaps there is a tradeoff between ignoring new information and therefore being resistant to distractors versus being receptive to unexpected opportunities. If so, then which path the brain takes might be influenced by confidence, risk-seeking, levels of background noise or distractions, or other variables that affect the tradeoff between noise robustness and information accumulation. Second, how is this complex network of states learned? Does it exist from the outset, and the brain must match an action to a preset sequence? Or is the entire network of states learned along with the required behavior? Finally, how is the sequence implemented? Is it supported by local connectivity, or are there recurrent loops between PPC and another area[14,15]?

These results are potentially transformative for our view of the 'unreliability' of neurons. Perhaps instead of neurons being noisy and unrepeatable actors, the variability we observe on the tips of our electrodes offers a glimpse of a vast network of forking paths. There may be many paths that bring the brain to its destination, but some may offer the chance to make an unexplored connection from time to time.

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