

Interrogating theoretical models of neural computation with deep inference
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¹ 1 Abstract

² A cornerstone of theoretical neuroscience is the circuit model: a system of equations that captures
³ a hypothesized neural mechanism. Such models are valuable when they give rise to an experimen-
⁴ tally observed phenomenon – whether behavioral or a pattern of neural activity – and thus can
⁵ offer insights into neural computation. The operation of these mechanistic circuits, like all models,
⁶ critically depends on the choices of model parameters. A key process in neuroscientific modeling
⁷ is then to identify the model parameters consistent with observed phenomena: to solve the in-
⁸ verse problem. While statistical inference has proven effective on a broad variety of neuroscientific
⁹ datasets, we clarify an important incongruity between theoretical approaches to neuroscience and
¹⁰ this probabilistic methodology. Theoretical neuroscience is focused on computational properties
¹¹ and how they emerge from biological mechanisms, rather than noisy experimental datasets and
¹² their quantified structure. In this work, we present a novel technique to directly infer circuit model
¹³ parameters producing these computational properties. This method tailors deep inference, the
¹⁴ use of deep neural networks for statistical inference, to the nature of theoretical inverse problems,
¹⁵ enabling scaling to high dimensions and considerable technical simplifications. With this method,
¹⁶ we bring deep inference to bear on important questions in theoretical neuroscience, and demon-
¹⁷ strate the broad range of insightful analyses this approach allows. First, we emphasize the general
¹⁸ applicability of this approach by inferring channel conductance parameters that produce a distinc-
¹⁹ tive spiking frequency in a biophysical model of the stomatogastric ganglion. Then, in a model
²⁰ of primary visual cortex with multiple neuron-types, where analysis becomes untenable as more

21 neuron-types are included, we use this technique to discover how noise properties govern excitatory population variability. Next, in a model of superior colliculus, we identify and characterize
22 two distinct regimes of connectivity that facilitate switching between opposite tasks throughout
23 interleaved trials. Finally, we scale inference to 1,000-dimensional parameter spaces of RNN
24 connectivity that exhibit stable, yet amplified responses. These analyses illustrate how we can further
25 leverage the power of deep learning towards solving inverse problems in theoretical neuroscience.
26

27 2 Introduction

28 The fundamental practice of theoretical neuroscience is to use a mathematical model to understand
29 neural computation, whether that computation enables perception, action, or some intermediate
30 processing. A neural circuit is systematized with a set of equations – the model – and these
31 equations are motivated by biophysics, neurophysiology, and other conceptual considerations [1,
32 2, 3, 4]. The function of this system is governed by the choice of model *parameters*, which when
33 configured in a particular way, give rise to a measurable signature of a computation. The work
34 of analyzing a model then requires solving the inverse problem: given a computation of interest,
35 how can we reason about particular parameter configurations? The inverse problem is crucial for
36 reasoning about likely parameter values, uniquenesses and degeneracies, and predictions made by
37 the model [5, 6].

38 Consider the idealized practice: one carefully designs a model and analytically derives how com-
39 putational properties determine model parameters. Seminal examples of this gold standard (which
40 often adopt approaches from statistical physics) include our field’s understanding of memory ca-
41 pacity in associative neural networks [7], chaos and autocorrelation timescales in random neural
42 networks [8], the paradoxical effect [9], and decision making [10]. Unfortunately, as circuit models
43 include more biological realism, theory via analytical derivation becomes intractable. Alternatively,
44 we can gain insight into these complex models by identifying the distribution of parameters that
45 produce a specific computational property. By solving the inverse problem in this way, scientific
46 analysis of complex biologically realistic models is made possible [11, 12, 13, 6, 14].

47 One preferred formalism for parameter identification is statistical inference, which has been used
48 to great success in neuroscience through the stipulation of statistical generative models [15, 16, 17,
49 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29] (see review, [30]). Recent work has used variational
50 autoencoders (VAEs) [31, 32] to interrogate hidden states in models of both cortical population

51 activity [33, 34, 35, 36] and animal behavior [37, 38, 39], thus expanding the domain of neural
52 data sets amenable to statistical modeling. However, most neural circuit models in theoretical
53 neuroscience are noisy systems of differential equations that can only be sampled or realized through
54 forward simulation; they lack the explicit likelihood necessary for statistical inference. Therefore,
55 the most popular approaches to theoretical inverse problems have been likelihood-free inference
56 (LFI) methods [40, 41], in which reasonable parameters are obtained via simulation and rejection.
57 A flourishing new class of techniques [42, 43, 44] use deep learning to improve upon traditional LFI
58 approaches. However, as we detail, all of these approaches require good datasets for the scientific
59 question at hand.

60 This work seeks to clarify an important incongruity between theoretical approaches to neuroscience
61 and existing statistical inference methodology. In theoretical neuroscience, we are concerned with
62 the computational properties – the *emergent phenomena* – of our models [7, 8, 9, 10], not noisy
63 observed datasets [30]. To use the aforementioned inference paradigm, scientists must shoehorn
64 such mathematical criteria into an artificial dataset compatible with existing statistical approaches.
65 Theorists are therefore barred from using the probabilistic modeling toolkit for science, unless they
66 reformulate their inverse problem to fit an evidence accumulation framework.

67 These challenges motivate the development of a novel inference framework called emergent property
68 inference (EPI). As an adaption of variational inference [45], EPI infers parameter distributions
69 that produce an emergent property: not a singular dataset, but a collection of datasets exhibiting
70 some mathematical criteria. EPI fixates on the inverse problem by constraining the predictions
71 of the inferred parameter distribution to produce the emergent property exactly. Conditioning on
72 an emergent property requires a variant of deep probabilistic inference methods, which we have
73 previously introduced [46]. By using deep probability distributions EPI flexibly captures para-
74 metric structure in mechanistic models. This technique is designed to identify the full parameter
75 space producing an emergent property and facilitate the seamless structural analysis of the inferred
76 parameter distribution. Thus, EPI provides neuroscientists with an efficient, versatile probabilistic
77 modeling toolkit designed explicitly for theoretical inverse problems.

78 Equipped with this method, we bring deep inference to bear on theoretical neuroscience to an
79 unprecedented extent. Throughout this work, we showcase the capabilities of EPI on four neural
80 circuit models across ranges of biological realism, neural system function, and network scale. First,
81 we show EPI’s ability to capture subtle, nonlinear parametric structure in a stomatogastric ganglion
82 subcircuit model [47]. In a model of primary visual cortex [48], we show how to gain insight from

multiple inferred distributions. Next, we used EPI to identify and structurally characterize multiple parametric regimes of superior colliculus activity in a model of task switching [49]. Finally, we emphasize the superior scalability of EPI compared to other LFI techniques by inferring high-dimensional distributions of RNN connectivities that exhibit amplified, yet stable responses – a hallmark of cortical sensory systems [?, 50].

Most importantly of all in this work, we present novel theories of neural computation borne from EPI analysis. We identified an unknown parametric rule of variability with respect to inhibitory neuron type in a V1 model, where analytic techniques became untenable. Furthermore, we identified multiple regimes of SC connectivity which confer rapid task switching, and used the structural analytic tools of EPI to gain a mechanistic understanding of circuit responses. These valuable theoretical insights illustrate the value of deep inference for the interrogation of neural circuit models.

3 Results

3.1 Motivating emergent property inference of theoretical models

Consideration of the typical workflow of theoretical modeling clarifies the need for emergent property inference. First, one designs or chooses an existing model that, it is hypothesized, captures the computation of interest. To ground this process in a well-known example, consider the stomatogastric ganglion (STG) of crustaceans, a small neural circuit which generates multiple rhythmic muscle activation patterns for digestion [51]. Despite full knowledge of STG connectivity and a precise characterization of its rhythmic pattern generation, biophysical models of the STG have complicated relationships between circuit parameters and neural activity [52, 12]. A subcircuit model of the STG [47] is shown schematically in Figure 1A, and note that the behavior of this model will be critically dependent on its parameterization – the choices of conductance parameters $\mathbf{z} = [g_{el}, g_{synA}]$. Specifically, the two fast neurons (f_1 and f_2) mutually inhibit one another, and oscillate at a faster frequency than the mutually inhibiting slow neurons (s_1 and s_2). The hub neuron (hub) couples with either the fast or slow population or both.

Second, once the model is selected, one defines the emergent phenomena of scientific interest. In the STG example, we are concerned with neural spiking frequency, which emerges from the dynamics of the circuit model 1B. An interesting emergent property of this stochastic model is when the hub neuron fires at an intermediate frequency between the intrinsic spiking rates of the fast and slow

113 populations. This emergent property is shown in Figure 1C at an average frequency of 0.55Hz.
 114 Third, parameter analyses ensue: brute-force parameter sweeps, ABC sampling [41], and sensitivity
 115 analyses [53] are all routinely used to reason about what parameter configurations lead to an
 116 emergent property. In this last step lies the opportunity for a precise quantification of the emergent
 117 property as a statistical feature of the model. Once we have such a methodology, we can infer a
 118 probability distribution over parameter configurations that produce this emergent property.
 119 Before presenting technical details (in the following section), let us understand emergent property
 120 inference schematically: EPI (Fig. 1D) takes, as input, the model and the specified emergent
 121 property, and as its output, produces the parameter distribution EPI (Fig. 1E). This distribution
 122 – represented for clarity as samples from the distribution – is then the most random parameter
 123 distribution producing the emergent property. In the STG model, this distribution can be specif-
 124 ically queried to reveal the prototypical parameter configuration for intermediate hub frequency
 125 (the mode; Figure 1E yellow star), and how it decays based on changes away from the mode. In-
 126 deed, samples equidistant from the mode along these EPI-identified dimensions of sensitivity (v_1)
 127 and degeneracy (v_2) (Fig. 1E, arrows) agree with error contours (Fig. 1E contours) and have
 128 diminished or preserved hub frequency, respectively (Fig. 1F activity traces) (see Section 5.2.1).

129 **3.2 A deep generative modeling approach to emergent property inference**

130 Emergent property inference (EPI) formalizes the three-step procedure of the previous section with
 131 deep probability distributions. First, we consider the model as a coupled set of differential equations
 132 [47]. In the running STG example, the model activity $\mathbf{x} = [x_{f1}, x_{f2}, x_{\text{hub}}, x_{s1}, x_{s2}]$ is the membrane
 133 potential for each neuron, which evolves according to the biophysical conductance-based equation:

$$C_m \frac{d\mathbf{x}(t)}{dt} = -h(\mathbf{x}(t); \mathbf{z}) + d\mathbf{B} \quad (1)$$

134 where $C_m=1\text{nF}$, and \mathbf{h} is a sum of the leak, calcium, potassium, hyperpolarization, electrical, and
 135 synaptic currents, all of which have their own complicated dependence on \mathbf{x} and $\mathbf{z} = [g_{\text{el}}, g_{\text{synA}}]$,
 136 and $d\mathbf{B}$ is white gaussian noise (see Section 5.2.1).

137 Second, we define the emergent property, which as above is “intermediate hub frequency” (Figure
 138 1C). Quantifying this phenomenon is straightforward: we stipulate that the hub neuron’s spiking
 139 frequency – denoted $\omega_{\text{hub}}(\mathbf{x})$ is close to a frequency of 0.55Hz. Mathematically, we achieve this

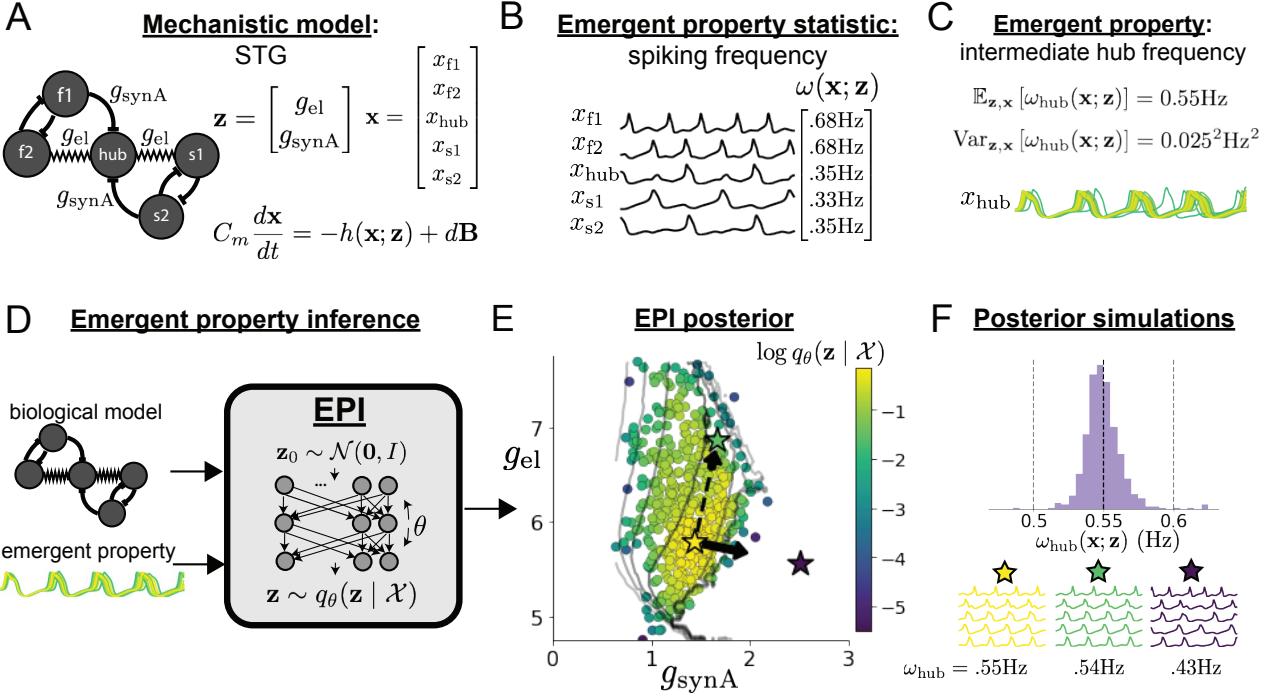


Figure 1: Emergent property inference (EPI) in the stomatogastric ganglion. **A.** Conductance-based biophysical model of the STG subcircuit. In the STG model, jagged connections indicate electrical coupling having electrical conductance g_{el} . Other connections in the diagram are inhibitory synaptic projections having strength g_{synA} onto the hub neuron, and $g_{\text{synB}} = 5\text{nS}$ for mutual inhibitory connections. Parameters are represented by the vector \mathbf{z} and membrane potentials by the vector \mathbf{x} . The evolution of this model’s activity $\mathbf{x}(t)$ is predicated by differential equations. **B.** Spiking frequency $\omega(\mathbf{x}; \mathbf{z})$ is an emergent property statistic. In this example, spiking frequency is measured from simulated activity of the STG model at parameter choices of $g_{\text{el}} = 4.5\text{nS}$ and $g_{\text{synA}} = 3\text{nS}$. **C.** The emergent property of intermediate hub frequency, in which the hub neuron fires at a rate between the fast and slow frequencies. This emergent property is defined by a mean and variance on the emergent property statistic. Simulated activity traces are colored by log probability density of their generating parameters in the EPI-inferred distribution (Panel E). **D.** For a choice of model and emergent property, emergent property inference (EPI) learns a deep probability distribution of parameters \mathbf{z} . Deep probability distributions map a simple random variable \mathbf{z}_0 through a deep neural network with weights and biases $\boldsymbol{\theta}$ to parameters $\mathbf{z} = q_{\theta}(\mathbf{z}_0)$. In EPI optimization, stochastic gradient steps in $\boldsymbol{\theta}$ are taken such that entropy is maximized, and the emergent property \mathcal{X} is produced. The EPI posterior distribution is denoted $q_{\theta}(\mathbf{z} | \mathcal{X})$. **E.** The EPI posterior producing intermediate hub frequency. Samples are colored by log probability density. Distribution contours of average hub neuron frequency from mean of .55 Hz are shown at levels of .525, .53,575 Hz (dark to light gray away from mean). Eigenvectors of the Hessian at the mode of the inferred distribution are indicated as \mathbf{v}_1 (solid) and \mathbf{v}_2 (dashed) with lengths scaled by the square root of the absolute value of their eigenvalues. **F** Simulations from parameters in E. (Top) The predictive distribution of the posterior obeys the emergent property. The black and gray dashed lines show the mean and two standard deviations according the emergent property, respectively. (Bottom) Simulations at the starred parameter values.

140 with two constraints: by setting the mean hub frequency of model generated activity to 0.55Hz.

$$\mathbb{E}_{\mathbf{z}, \mathbf{x}} [\omega_{\text{hub}}(\mathbf{x}; \mathbf{z})] = [0.55] \quad (2)$$

141 and requiring that the variance around this mean is small

$$\text{Var}_{\mathbf{z}, \mathbf{x}} [\omega_{\text{hub}}(\mathbf{x}; \mathbf{z})] = [0.025^2]. \quad (3)$$

142 This level of variance was chosen to be low enough to exclude the fast and slow frequencies of the
143 two populations, but large enough to allow structural examination of the compatible parameter
144 space. In general, an emergent property

$$\mathcal{X} : \mathbb{E}_{\mathbf{z}, \mathbf{x}} [f(\mathbf{x}; \mathbf{z})] = \boldsymbol{\mu}, \text{Var}_{\mathbf{z}, \mathbf{x}} [f(\mathbf{x}; \mathbf{z})] = \boldsymbol{\sigma}^2 \quad (4)$$

145 defines a collection of datasets with a statistic $f(\mathbf{x}; \mathbf{z})$ (which may be comprised of multiple statistics)
146 and the means $\boldsymbol{\mu}$ and variances $\boldsymbol{\sigma}^2$ of those statistics over the datasets. The choice of $\boldsymbol{\sigma}^2$
147 predicates the degree of variability in around mean $\boldsymbol{\mu}$ that is consistent with the emergent prop-
148 erty.

149 Third, we perform emergent property inference: we find a distribution over parameter configura-
150 tions \mathbf{z} , and insist that samples from this distribution produce the emergent property; in other
151 words, they obey the constraints introduced in Equation 4. This distribution will be chosen from a
152 family of probability distributions $\mathcal{Q} = \{q_{\boldsymbol{\theta}}(\mathbf{z}) : \boldsymbol{\theta} \in \Theta\}$, defined by a deep generative distribution
153 of the normalizing flow class [54, 55, 56] – neural networks which transform a simple distribution
154 into a suitably complicated distribution (as is needed here). This deep distribution is represented
155 in Figure 1D (see Section 5.1). Many distributions in \mathcal{Q} will respect the emergent property con-
156 straints, so we choose a normative selection principle imposing no additional structure beyond the
157 production of the emergent property [57, 58, 46, 59], which is the same normative principle of
158 Bayesian inference (see Section 5.1.6).

159 The probabilities of the distribution inferred from EPI are the densities of these parameters in the
160 most random distribution producing the emergent property. While existing approaches to proba-
161 bilistic structural identifiability analysis use the lens of evidence accumulation [53, 42], sensitivity
162 and robustness of parameter space dimensions with respect to emergent phenomena can be directly
163 quantified with EPI. Sensitivity quantifications are measured by the second order derivative of EPI
164 probability along the parameteric dimension of interest: to what extent is the emergent property
165 maintained or diminished along this dimension? Once an EPI distribution has been inferred, this
166 second order derivative requires trivial computation (as long as the correct architecture class is

167 chosen, see Section 5.1.2). Equipped with this method, we may examine structure in the resulting
 168 parameter distributions or make comparisons between distributions conditioned at different levels
 169 of the same emergent property statistic. In Sections 3.3 and 3.4, we prove out the value of EPI by
 170 using these techniques to investigate and produce novel scientific insight.

171 **3.3 EPI reveals how neuron-type specific noise governs variability in the stochastic
 172 stabilized supralinear network**

173 Dynamical models of excitatory (E) and inhibitory (I) populations with supralinear input-output
 174 function have succeeded in explaining a host of experimentally documented phenomena. In a
 175 regime characterized by inhibitory stabilization of strong recurrent excitation, these models give
 176 rise to paradoxical responses [9], selective amplification [60, 61], surround suppression [62] and
 177 normalization [63]. Despite their strong predictive power, E-I circuit models rely on the assumption
 178 that inhibition can be studied as an indivisible unit. However, experimental evidence shows
 179 that inhibition is composed of distinct elements – parvalbumin (P), somatostatin (S), VIP (V) –
 180 composing 80% of GABAergic interneurons in V1 [64, 65, 66], and that these inhibitory cell types
 181 follow specific connectivity patterns (Fig. 2A) [67]. Recent theoretical advances [68, 69, 70], have
 182 only started to address the consequences of this multiplicity in the dynamics of V1, strongly relying
 183 on linear theoretical tools. Here, we use EPI to analyze V1 models of greater complexity in order
 184 to characterize properties of slow noise governing circuit variability.

185 We considered the response properties of a nonlinear dynamical V1 circuit model (Fig. 2A) with
 186 a state comprised of each neuron-type population’s rate $\mathbf{x} = [x_E, x_P, x_S, x_V]^\top$. Each population
 187 receives recurrent input $W\mathbf{x}$ from synaptic projections of effective connectivity W and an external
 188 input \mathbf{h} , which determine the population rate via supralinear nonlinearity $\phi = []_+^2$. The input is
 189 also comprised of a slow noise component $\epsilon \sim OU(\tau_{noise}, \sigma)$ of time scale $\tau_{noise} > \tau$ and variance
 190 parameters σ (see Section 5.2.2)

$$\tau \frac{d\mathbf{x}}{dt} = -\mathbf{x} + \phi(W\mathbf{x} + \mathbf{h} + \epsilon). \quad (5)$$

191 This model is the stochastic stabilized supralinear network (SSSN) [71] generalized to have in-
 192 hibitory multiplicity, and introduces stochasticity to previous four neuron-type models of V1 [68].
 193 Stochasticity and inhibitory multiplicity introduce substantial complexity to mathematical deriva-
 194 tions (see Section 5.2.3) motivating the treatment of this model with EPI. Here, we consider fixed
 195 weights W and input \mathbf{h} according to a fit of the deterministic model to contrast responses [48] (Fig.

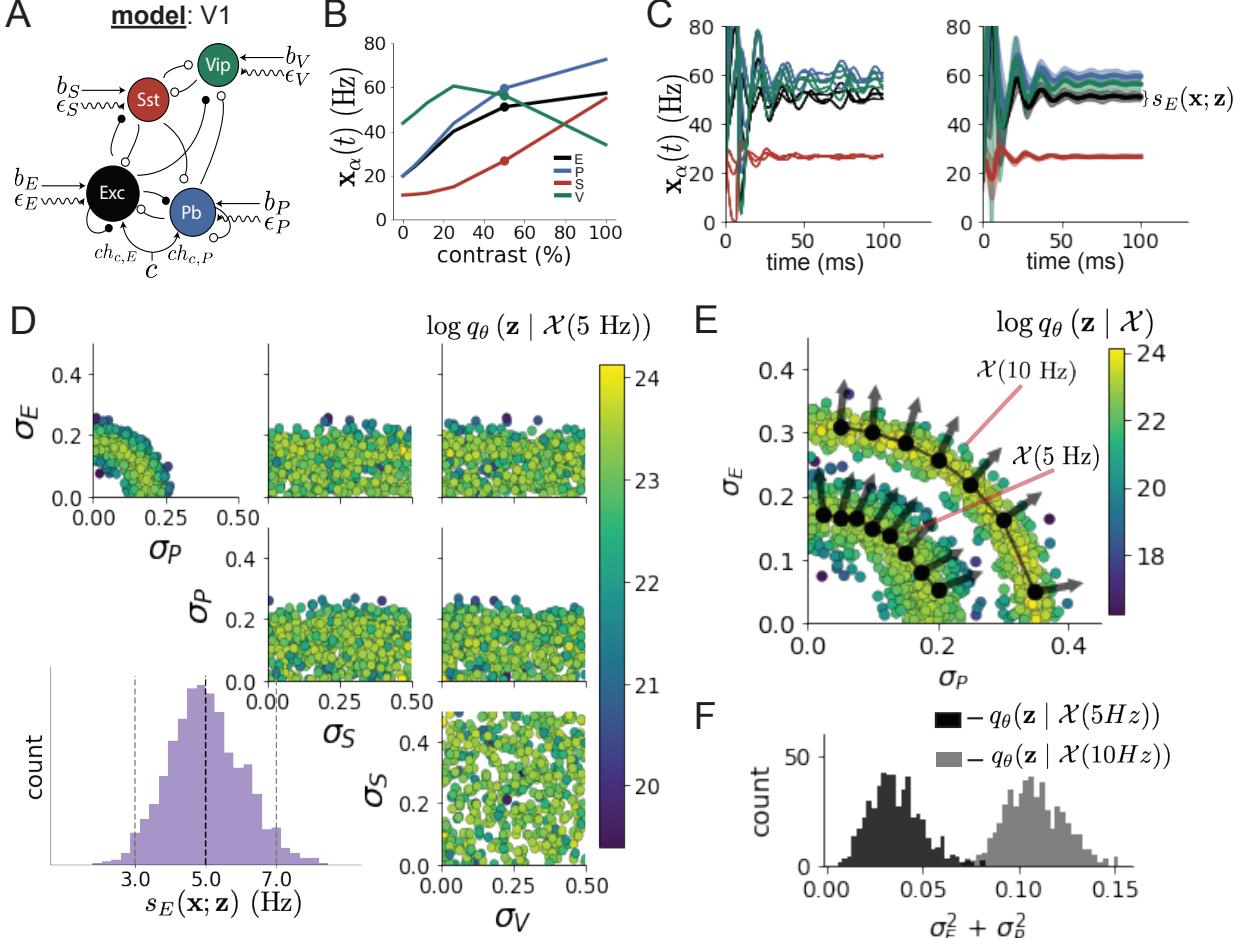


Figure 2: Emergent property inference in the stochastic stabilized supralinear network (SSSN) **A.** Four-population model of primary visual cortex with excitatory (black), parvalbumin (blue), somatostatin (red), and VIP (green) neurons (excitatory and inhibitory projections filled and unfilled, respectively). Some neuron-types largely do not form synaptic projections to others ($|W_{\alpha_1, \alpha_2}| < 0.025$). Each neural population receives a baseline input \mathbf{h}_b , and the E- and P-populations also receive a contrast-dependent input \mathbf{h}_c . Additionally, each neural population receives a slow noisy input ϵ . **B.** Steady-state responses of the SSN model (deterministic, $\sigma = \mathbf{0}$) to varying contrasts. The response at 50% contrast (dots) is the focus of our analysis. **C.** Transient network responses of the SSSN model at 50 % contrast. (Left) Traces are independent trials with varying initialization $\mathbf{x}(0)$ and noise realization. (Right) Mean (solid line) and standard deviation (shading) of responses. **D.** EPI posterior of noise parameters \mathbf{z} conditioned on E-population variability. The posterior predictive distribution of $s_E(\mathbf{x}; \mathbf{z})$ is show on the bottom-left. **E.** (Top) Enlarged visualization of the σ_E - σ_P marginal distribution of the posteriors $q_\theta(\mathbf{z} | \mathcal{X}(5 \text{ Hz}))$ and $q_\theta(\mathbf{z} | \mathcal{X}(10 \text{ Hz}))$. Each black dot shows the mode at each σ_P . The arrows show the most sensitive dimensions of the Hessian evaluated at these modes. **F.** The predictive distributions of $\sigma_E^2 + \sigma_P^2$ of each posterior $q_\theta(\mathbf{z} | \mathcal{X}(5 \text{ Hz}))$ and $q_\theta(\mathbf{z} | \mathcal{X}(10 \text{ Hz}))$.

196 2B), and study the effect of noise parameterization $\mathbf{z} = [\sigma_E, \sigma_P, \sigma_S, \sigma_V]^\top$ on fluctuations at 50%
197 contrast.

198 For this SSSN, we are interested in how noise variability across neural populations governs stochastic
199 fluctuations in the E-population. Here, we quantify different levels y of E-population variability
200 with the emergent property

$$\begin{aligned}\mathcal{X}(y) &: \mathbb{E}_{\mathbf{z}} [s_E(\mathbf{x}; \mathbf{z})] = y \\ \text{Var}_{\mathbf{z}} [s_E(\mathbf{x}; \mathbf{z})] &= 1\text{Hz}^2,\end{aligned}\tag{6}$$

201 where $s_E(\mathbf{x}; \mathbf{z})$ is the standard deviation of the stochastic E-population response about its steady
202 state (Fig. 2C).

203 We ran EPI to obtain a posterior distribution $q_{\theta}(\mathbf{z} | \mathcal{X}(5 \text{ Hz})$ producing E-population variability
204 around 5 Hz (Fig. 2D). From the marginal distribution of σ_E and σ_P (Fig. 2D, top-left), we can
205 see that $s_E(\mathbf{x}; \mathbf{z})$ is sensitive to various combinations of σ_E and σ_P . Alternatively, both σ_S and σ_V
206 are degenerate with respect to $s_E(\mathbf{x}; \mathbf{z})$ evidenced by the high variability in those dimensions of the
207 posterior (Fig. 2D, bottom-right). Together, these observations imply a parametric manifold of
208 degeneracy with respect to $s_E(\mathbf{x}; \mathbf{z})$ of 5 Hz, which is indicated by the modes along σ_P in the σ_E - σ_P
209 marginal (Fig. 2E). The dimensions of sensitivity conferred by EPI and this plain visual structure
210 suggest a quadratic relationship in the emergent property statistic $s_E(\mathbf{x}; \mathbf{z})$ and parameters \mathbf{z} , which
211 is preserved at a greater level of variability $\mathcal{X}(10 \text{ Hz})$ (Fig. 2E). Indeed, the sum of squares of σ_E
212 and σ_P is larger in $q_{\theta}(\mathbf{z} | \mathcal{X}(10 \text{ Hz})$ than $q_{\theta}(\mathbf{z} | \mathcal{X}(5 \text{ Hz})$ (Fig 2F, $p = 0$), while the sum of squares
213 of σ_S and σ_V are not significantly different in the two posteriors (Fig. 11, $p = .402$).

214 While a quadratic relationship in $s_E(\mathbf{x}; \mathbf{z})$ and \mathbf{z} is potentially derivable by extending the derivation
215 in Section 5.2.2 to the case of $\tau \neq \tau_{\text{noise}}$, the coefficients in front of each quadratic term would be
216 unruly, and likely escape comprehensible analysis. This makes EPI an attractive tool for revealing
217 the characteristics of noise governing variability and for answering other questions in this complex
218 model. Intriguingly, this circuit exhibited a paradoxical effect in the P-population, and no other
219 inhibitory types at 50% contrast (Fig. 11) implying that the E-population is P-stabilized. Future
220 work motivated by our analysis here, may uncover a relationship between the neuron-type mediating
221 stability and the factors governing circuit variability.

222 **3.4 EPI identifies multiple regimes of rapid task switching**

223 In a rapid task switching experiment [72], rats were explicitly cued on each trial to either orient
 224 towards a visual stimulus in the Pro (P) task or orient away from a visual stimulus in the Anti
 225 (A) task (Fig. 3A). Neural recordings in the midbrain superior colliculus (SC) exhibited two
 226 populations of neurons that simultaneously represented both task context (Pro or Anti) and motor
 227 response (contralateral or ipsilateral to the recorded side): the Pro/Contra and Anti/Ipsi neurons
 228 [49]. Duan et al. proposed a model of SC that, like the V1 model analyzed in the previous section, is
 229 a four-population dynamical system. We analyzed this model, where the neuron-type populations
 230 are functionally-defined as the Pro- and Anti-populations in each hemisphere (left (L) and right
 231 (R)), their connectivity is parameterized geometrically (Fig. 3B). The input-output function of
 232 this model is chosen such that the population responses $\mathbf{x} = [x_{LP}, x_{LA}, x_{RP}, x_{RA}]^\top$ are bounded
 233 from 0 to 1 as a function ϕ of a dynamically evolving internal variable \mathbf{u} . The model responds to
 234 the side with greater Pro neuron activation; e.g. the response is left if $x_{LP} > x_{RP}$ at the end of
 235 the trial. The dynamics evolve with timescale $\tau = 90\text{ms}$ governed by connectivity weights W

$$\begin{aligned} \tau \frac{d\mathbf{u}}{dt} &= -\mathbf{u} + W\mathbf{x} + \mathbf{h} + d\mathbf{B} \\ \mathbf{x} &= \phi(\mathbf{u}) \end{aligned} \tag{7}$$

236 with white noise of variance 0.2^2 . The input \mathbf{h} is comprised of a cue-dependent input to the Pro
 237 or Anti populations, a stimulus orientation input to either the Left or Right populations, and a
 238 choice-period input to the entire network (see Section 5.2.4). Here, we use EPI to determine the
 239 network connectivity $\mathbf{z} = [sW, vW, dW, hW]^\top$ that produces rapid task switching behavior.

240 We define rapid task switching behavior as accurate execution of each task. Inferred models should
 241 not exhibit fully random responses (50%), or perfect performance (100%), since perfection is never
 242 attained by even the best trained rats. We formulate rapid task switching as an emergent property
 243 by stipulating that the average accuracy in the Pro task $p_P(\mathbf{x}; \mathbf{z})$ and Anti task $p_A(\mathbf{x}; \mathbf{z})$ be 75%
 244 with variance $7.5\%^2$.

$$\begin{aligned} \mathcal{X} : \mathbb{E}_{\mathbf{z}} \begin{bmatrix} p_P(\mathbf{x}; \mathbf{z}) \\ p_A(\mathbf{x}; \mathbf{z}) \end{bmatrix} &= \begin{bmatrix} 75\% \\ 75\% \end{bmatrix} \\ \text{Var}_{\mathbf{z}} \begin{bmatrix} p_P(\mathbf{x}; \mathbf{z}) \\ p_A(\mathbf{x}; \mathbf{z}) \end{bmatrix} &= \begin{bmatrix} 7.5\%^2 \\ 7.5\%^2 \end{bmatrix} \end{aligned} \tag{8}$$

245 A variance of $7.5\%^2$ in each task will confer a posterior producing performances ranging from about
 246 60% – 90%, allowing us to examine the properties of connectivity that yield better performance in

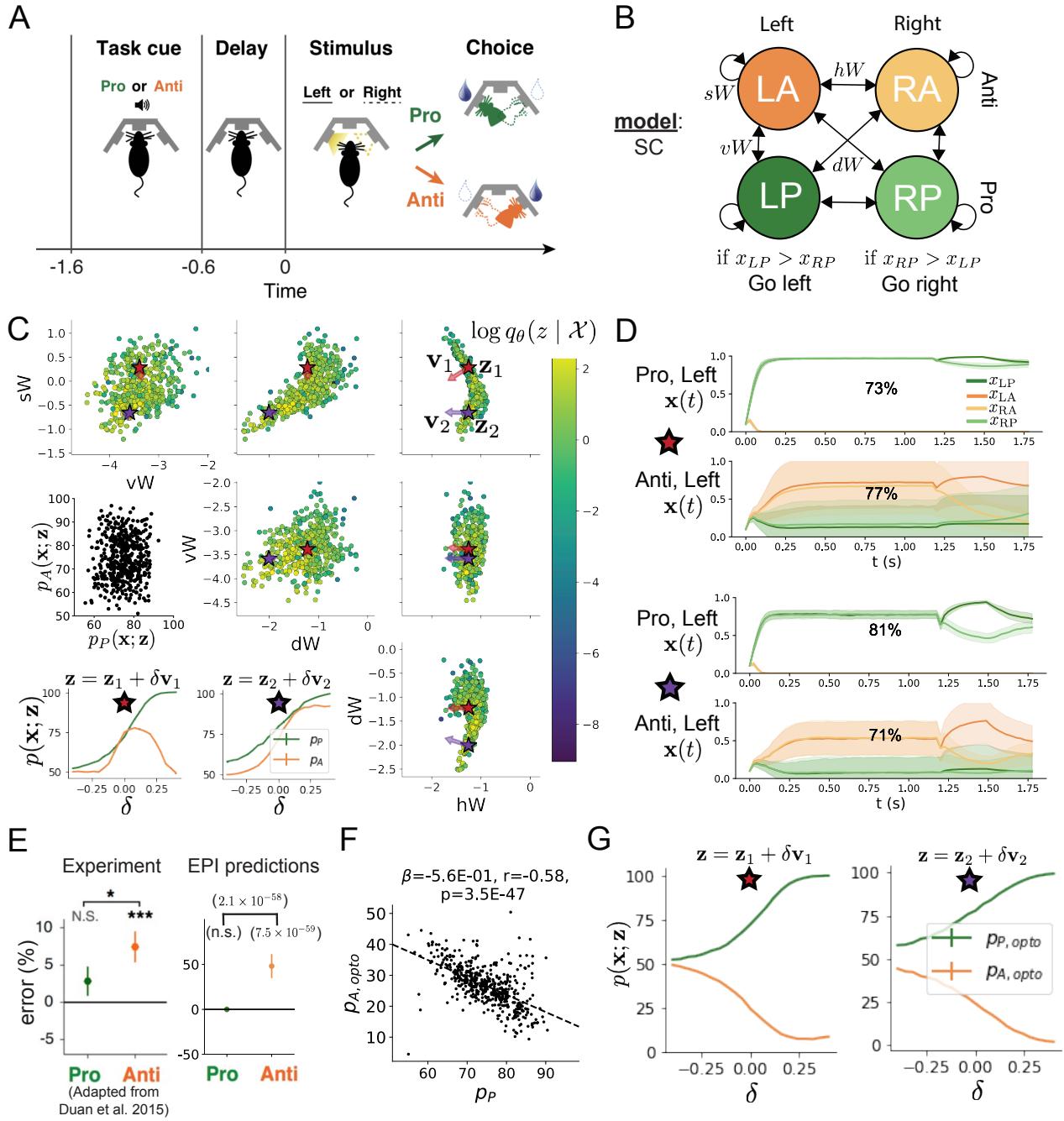


Figure 3: **A.** Rapid task switching behavioral paradigm (see text). **B.** Model of superior colliculus (SC). Neurons: LP - left pro, RP - right pro, LA - left anti, RA - right anti. Parameters: sW - self, hW - horizontal, vW - vertical, dW - diagonal weights. **C.** The EPI posterior distribution of rapid task switching networks. Red and purple stars (\mathbf{z}_1 and \mathbf{z}_2) indicate different connectivity regimes with different sensitivity vectors \mathbf{v}_1 and \mathbf{v}_2 . (Middle-left) Posterior predictive distribution of task accuracies. (Bottom-left) Task accuracy along dimensions of sensitivity in each connectivity regime. **D.** Means (solid) and standard deviations (shaded) of each population across random simulated trials. Top plots show Pro (top) and Anti (bottom) responses for connectivity \mathbf{z}_1 . Bottom rows show the same \mathbf{z}_2 . **E.** The EPI posterior predicts experimental results (left) showing no change in the Pro task, but larger error in the Anti task (right). **F.** Accuracy in the Anti task during delay period optogenetic inactivation $p_{A,\text{opto}}$ is strongly anticorrelated with accuracy in the Pro task. **G.** Accuracy with delay period inactivation along each connectivity regime's dimension of sensitivity.

247 each task. Notably, this is our first example using EPI to condition on multiple emergent property
248 statistics ($|f(\mathbf{x}; \mathbf{z})| = 2$).

249 The EPI inferred parameters (Fig. 3C) generate a distribution of task accuracies (Fig. 3C, middle-
250 left) according to our mathematical definition of rapid task switching (Equation 8). The nonlinear
251 patterns of connectivity that govern each task accuracy (Fig. 12A-B) are not fully captured by
252 linear prediction (Fig. 12C). For example, the patterns in connectivity increasing Pro accuracy
253 change dramatically after crossing a threshold of sW (Fig. 12A $sW-hW$ marginal). Not only has
254 EPI captured this complex nonlinear posterior, it offers probabilistic tools for understanding the
255 different regimes of model behavior.

256 To establish these two regimes of connectivity, we took gradient steps along $q_{\theta}(\mathbf{z} \mid \mathcal{X})$ to produce
257 modes \mathbf{z}_1 and \mathbf{z}_2 (Fig. 3C red and purple stars, Section 5.2.4). Simulations from these two regimes
258 reveal different responses in each task (Fig. 3D). We characterized these regimes by identifying
259 the dimensions of connectivity that rapid task switching is most sensitive to. The sensitivity
260 dimensions \mathbf{v}_1 and \mathbf{v}_2 (Fig. 3C, red and purple arrows) point in different directions, resulting
261 in different changes to task accuracy (Fig. 3D, bottom-left, 13). In regime 1, Anti accuracy
262 diminishes in either direction of sensitivity away from the mode, while in regime 2, Anti accuracy
263 tracks monotonic increases in Pro accuracy. These responses make intuitive sense, recognizing that
264 \mathbf{v}_1 (unlike \mathbf{v}_2) points strongly in the direction of connectivity eigenvalue λ_{diag} , which is strongly
265 anticorrelated with p_A (Fig. 14, 15, see Section 5.2.4).

266 In agreement with experimental results from Duan et al., we found optogenetic inactivation during
267 the delay period consistently decreased performance in the Anti task, but had no effect on the
268 Pro task (Fig. 3E)). This difference in resiliency across tasks to delay perturbation is a prediction
269 made by the inferred EPI distribution, rather than an emergent property that was conditioned
270 upon. Similarities across Pro and Anti trials in choice period responses following delay period
271 inactivation (Fig. 17A) suggested that connectivity patterns inducing greater Pro task accuracy
272 increase error in delay period inactivated Anti trials (Fig. 3F). The strong anticorrelation between
273 p_P and $p_{A,\text{opto}}$ across posterior connectivities led to the following hypothesis about each connectivity
274 regime: the sensitivity dimension of each regime decreases $p_{A,\text{opto}}$ irrespective of its effect on p_A ,
275 since both \mathbf{v}_1 and \mathbf{v}_2 increase p_P . Indeed, in regimes 1 and 2 where sensitivity dimensions elicit
276 different responses in p_A , $p_{A,\text{opto}}$ decreases since the connectivity changes enhancing p_P exacerbate
277 Anti trial error (Fig. 3F).

278 In summary, we used EPI to obtain the full distribution of connectivities that execute rapid task

switching. This posterior revealed multiple regimes of rapid task switching, which we characterized using the probabilistic toolkit EPI seemlessly affords. EPI allowed us to conclude that since *all* parameters of this model producing rapid task switching make an experimentally verified prediction, the model is well-chosen in that regard. Finally, we used our knowledge about how \mathbf{z} governs $p_{A,opto}$ to make accurate predictions about each identified regime of connectivity.

3.5 EPI scales well to high-dimensional parameter spaces

Transient amplification is a hallmark of neural activity throughout cortex, and is often thought to be intrinisically generated by recurrent connectivity in the responding cortical area [61, 73, 74]. It has been shown that to generate such amplified, yet stabilized responses, the connectivity of RNNs must be non-normal [60, 61], and satisfy additional constraints [50]. In theoretical neuroscience, RNNs are optimized and then examined to show how dynamical systems could execute a given computation [75, 76], but such biologically realistic constraints on connectivity are ignored during optimization for practical reasons. In general, access to distributions of connectivity adhering to theoretical criteria like stable amplification, chaotic fluctuations [8], or low tangling [77] would add great scientific value and contextualization to existing research with RNNs. Here, we use EPI to learn RNN connectivities producing stable amplification, and demonstrate the superior scalability and efficiency of EPI to alternative approaches.

We consider a rank-2 RNN with N neurons having connectivity $W = UV^\top$ and dynamics

$$\tau \dot{\mathbf{x}} = -\mathbf{x} + W\mathbf{x}, \quad (9)$$

where $U = [\mathbf{u}_1 \ \mathbf{u}_2] + g\chi^{(W)}$, $V = [\mathbf{v}_1 \ \mathbf{v}_2] + g\chi^{(V)}$, $\mathbf{u}_1, \mathbf{u}_2, \mathbf{v}_1, \mathbf{v}_2 \in [-1, 1]^N$, and $\chi_{i,j}^{(W)}, \chi_{i,j}^{(V)} \sim \mathcal{N}(0, 1)$. We infer connectivity parameterizations $\mathbf{z} = [\mathbf{u}_1^\top, \mathbf{u}_2^\top, \mathbf{v}_1^\top, \mathbf{v}_2^\top]^\top$ that produce stable amplification. Two conditions are necessary and sufficient for RNNs to exhibit stable amplification [50]: $\text{real}(\lambda_1) < 1$ and $\lambda_1^s > 1$, where λ_1 is the eigenvalue of W with greatest real part and λ^s is the maximum eigenvalue of $W^s = \frac{W+W^\top}{2}$. RNNs with $\text{real}(\lambda_1) = 0.5 \pm 0.5$ and $\lambda_1^s = 1.5 \pm 0.5$ will be stable with modest decay rate ($\text{real}(\lambda_1)$ close to its upper bound of 1) and exhibit modest amplification (λ_1^s close to its lower bound of 1). EPI can naturally condition on this emergent

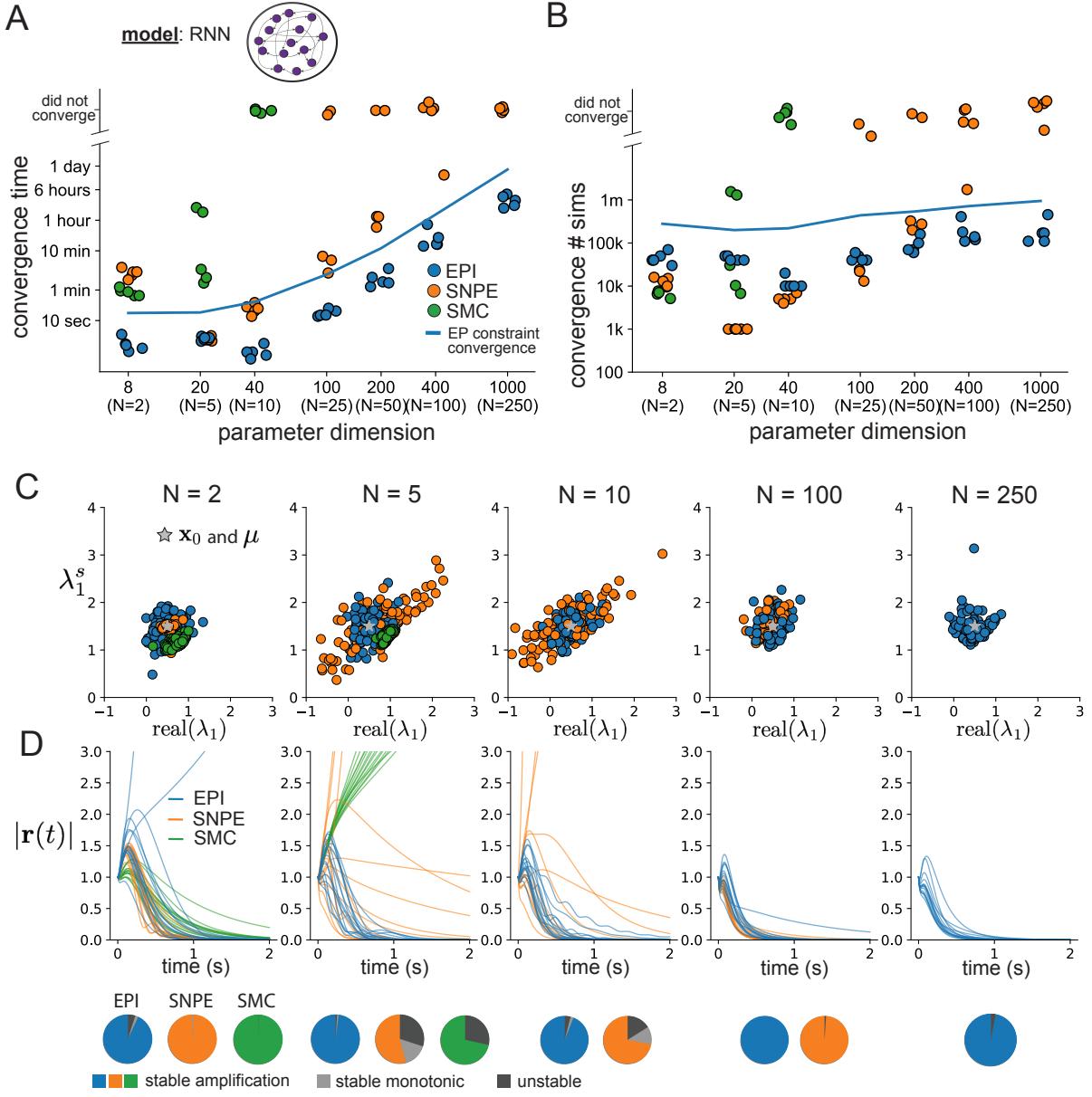


Figure 4: **A.** Wall time of EPI (blue), SNPE (orange), and SMC-ABC (green) to converge on RNN connectivities producing stable amplification. Each dot shows convergence time for an individual random seed. For reference, the mean wall time for EPI to achieve its full constraint convergence (means and variances) is shown (blue line). **B.** Simulation count of each algorithm to achieve convergence. Same conventions as A. **C.** The predictive distributions of connectivities inferred by EPI (blue), SNPE (orange), and SMC-ABC (green), with reference to $\mathbf{x}_0 = \mu$ (gray star). **D.** Simulations of networks inferred by each method ($\tau = 100ms$). Each trace (15 per algorithm) corresponds to simulation of one z . (Below) Ratio of obtained samples producing stable amplification, monotonic decay, and instability.

304 property

$$\begin{aligned} \mathcal{X} : \mathbb{E}_{\mathbf{z}, \mathbf{x}} \begin{bmatrix} \text{real}(\lambda_1) \\ \lambda_1^s \end{bmatrix} &= \begin{bmatrix} 0.5 \\ 1.5 \end{bmatrix} \\ \text{Var}_{\mathbf{z}, \mathbf{x}} \begin{bmatrix} \text{real}(\lambda_1) \\ \lambda_1^s \end{bmatrix} &= \begin{bmatrix} 0.25^2 \\ 0.25^2 \end{bmatrix}, \end{aligned} \quad (10)$$

305 under the notion that variance constraints with standard deviation 0.25 predicate that the vast
 306 majority of samples (those within two standard deviations) are within the specified ranges.

307 For comparison, we infer the parameters \mathbf{z} likely to produce stable amplification using two alter-
 308 native likelihood-free inference approaches. We ran sequential monte-carlo approximate Bayesian
 309 computation (SMC-ABC) [40] and sequential neural posterior estimation (SNPE) [42] with obser-
 310 vation $\mathbf{x}_0 = \boldsymbol{\mu}$. SMC-ABC is a rejection sampling approach that uses sophisticated techniques to
 311 improve efficiency, and SNPE approximates posteriors with deep probability distributions using a
 312 two-network architecture (see Section 5.1.1). Unlike EPI, these statistical inference techniques do
 313 not control the mean or variance of the predictive distribution, and these predictions of the inferred
 314 posteriors are typically affected by model characteristics (e.g. N and g , Fig. 18). To compare the
 315 efficiency of these different techniques, we measured the time and number of simulations necessary
 316 for the distance of the predictive mean to be less than 0.25 from $\boldsymbol{\mu} = \mathbf{x}_0$ (see Section 5.2.5).

317 As the number of neurons N in the RNN are scaled, and thus the dimension of the parameter space
 318 $\mathbf{z} \in [-1, 1]^{4N}$, we see that EPI converges at greater speed and at greater dimension than SMC-ABC
 319 and SNPE (Fig. 4A). It also becomes most efficient to use EPI in terms of simulation count at
 320 $N = 50$ (Fig. 4B). It is well known that ABC techniques struggle mightily in dimensions greater
 321 than about 30 [78], yet we were careful to assess the scalability of the more comparable approach
 322 SNPE. Between EPI and SNPE, we closely controlled the number of parameters in deep probability
 323 distributions by dimensionality (Fig. 19), and tested more aggressive SNPE hyperparameterizations
 324 when SNPE failed to converge (Fig. 20).

325 No matter the number of neurons, EPI always produces connectivity distributions with mean
 326 and variance of $\text{real}(\lambda_1)$ and λ_1^s according to \mathcal{X} (Fig. 4C, blue). For the dimensionalities in
 327 which SMC-ABC is tractable, the inferred parameters always exhibit stable amplification (Fig.
 328 4C, green), but are concentrated and offset from \mathbf{x}_0 . When using SNPE the inferred parameters
 329 are highly concentrated at some RNN sizes and widely varied in others (Fig. 4C, orange). We see
 330 these properties reflected in simulations from the inferred distributions: EPI produces a consistent
 331 variety of stable amplified activity norms $|r(t)|$, SMC produces a limited variety in responses, and the

332 changing variety of responses from SNPE emphasizes the control of EPI on parameter predictions.
333 From this analysis, we see that deep inference techniques EPI and SNPE are far more amenable to
334 high dimensional parameter distributions than rejection sampling techniques like SMC-ABC, and
335 have the additional benefit of fast sampling after optimization. EPI outperforms SNPE in high
336 dimensions by leveraging gradient information (from $\nabla_{\mathbf{z}}f(\mathbf{x}; \mathbf{z}) = \nabla_{\mathbf{z}}[\text{real}(\lambda_1), \lambda_1^s]^\top$) on each opti-
337 mization iteration and constantly adapting the approximation $q_{\theta}(\mathbf{z})$ to the parameter distribution.
338 While EPI can be used for scientific insight into RNNs, this analysis shows that when $\nabla_{\mathbf{z}}f(\mathbf{x}; \mathbf{z})$ is
339 tractable, EPI can be used to efficiently infer high dimensional parameter distributions in mechani-
340 stic models of neural computation.

341 4 Discussion

342 In neuroscience, machine learning has primarily been used to reveal structure in neural datasets
343 [30]. Such careful inference procedures are developed for these statistical models allowing precise,
344 quantitative reasoning, which clarifies the way data informs beliefs about the model parameters.
345 However, these statistical models lack resemblance to the underlying biology, making it unclear
346 how to go from the structure revealed by these methods, to the neural mechanisms giving rise
347 to it. In contrast, theoretical neuroscience has focused on careful mechanistic modeling and the
348 production of emergent properties of computation. The careful steps of *i.*) model design and
349 *ii.*) emergent property definition, are followed by *iii.*) practical inference methods resulting in an
350 opaque characterization of the way model parameters govern computation. In this work, we improve
351 upon parameter inference techniques in theoretical neuroscience with emergent property inference,
352 harnessing deep learning towards careful inference in careful models of neural computation (see
353 Section 5.1.1).

354 Specifically, approximate Bayesian computation [79, 80, 40] has been the standard approach to
355 parameter inference in neural circuit models lacking tractable likelihoods. ABC methods do not
356 confer probabilities on accepted parameters, require an acceptance threshold chosen to trade-off
357 inference quality with tractability, do not scale efficiently to high-dimensional parameter spaces, and
358 require independent techniques to analyze sensitivity for local parameter choices [78]. In contrast,
359 EPI allows probability evaluations at any point in parameter space, conditions posteriors on the
360 natural quantification of emergent properties, scales to high dimensional parameter spaces, and
361 naturally admits sensitivity quantification via fast evaluations of the posterior Hessian.

362 Technically, EPI is a maximum entropy method, which learns parameter distributions that are
363 as random as possible given that they produce the emergent property. Conceptually, maximally
364 random distributions given some constraints are useful for understanding parametric sensitivity.

365 This is well understood in Bayesian inference, where maximum entropy is the chosen normative
366 principle. This is emphasized by an innovative formalism unifying top-down maximum entropy
367 normative models with bottom-up statistical models [81]. Indeed, EPI is an adaptive variational
368 inference program, and may be considered to have a Bayesian uniform prior (see Section 5.1.6).

369 Biologically realistic models of neural circuits often prove formidable to analyze for two main rea-
370 sons. A primary challenge is that the number of parameters scales dramatically with the number of
371 neurons, limiting analysis of its parameter space. We see in Section 3.5 that EPI scales seemlessly
372 to high dimensional parameter spaces of RNN connectivities, while maintaining the production
373 of the specified emergent property. EPI strongly outperforms the standard likelihood-free infer-
374 ence technique (SMC-ABC [40]), and a recently developed deep likelihood-free inference technique
375 (SNPE [42]), most likely because of it's ability to leverage the gradient information of the emer-
376 gent property statistics and to adapt it's paramter sampling distribution at every step of gradient
377 descent.

378 A secondary challenge is that the structure of the parametric regimes governing emergent properties
379 is intricate. For example, even in low dimensional circuits, models can support more than one steady
380 state [82] and non-trivial dynamics on strange attractors [83]. With EPI, we use deep probabillity
381 distributions to capture the complex nonlinear parameter distributions governing model behavior.

382 In Section 3.3, we used EPI to reveal a curved parametric manifolds governing curcuit variability
383 in the stochastic stabilized supralinear network, and used hypothesis testing techniques to validate
384 our findings. In Section 3.4, we identified two regimes of SC connectivity resulting in rapid task
385 switching, and found that the full distribution of rapid task switching networks reproduced an
386 experimental result.

387 EPI leverages deep learning technology for neuroscientific inquiry in a categorically different way
388 than approaches focused on training neural networks to execute behavioral tasks [84]. These works
389 focus on examining optimized deep neural networks while considering the objective function, learn-
390 ing rule, and architecture used. This endeavor efficiently obtains sets of parameters that can be
391 reasoned about with respect to such considerations, but lacks the careful probabilistic treatment of
392 parameter inference in EPI. All of these approaches can be used complementarily to enhance the
393 practice of theoretical neuroscience.

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401 **Data availability statement:**

402 The datasets generated during and/or analyzed during the current study are available from the
403 corresponding author upon reasonable request.

404 **Code availability statement:**

405 All software written for the current study is available at <https://github.com/cunningham-lab/epi>.

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689 **5 Methods**

690 **5.1 Emergent property inference (EPI)**

691 Determining the combinations of model parameters that can produce observed data or a desired
 692 output is a key part of scientific practice. Solving inverse problems is especially important in
 693 neuroscience, since we require complex models to describe the complex phenomena of neural com-
 694 putations. While much machine learning research has focused on how to find latent structure
 695 in large-scale neural datasets, less has focused on inverting theoretical circuit models conditioned
 696 upon the emergent phenomena they produce. Here, we introduce a novel method for statistical
 697 inference, which finds distributions of parameter solutions that only produce the desired emer-
 698 gent property. This method seamlessly handles neural circuit models with stochastic nonlinear
 699 dynamical generative processes, which are predominant in theoretical neuroscience.

700 Consider model parameterization \mathbf{z} , which is a collection of scientifically interesting variables that
 701 govern the complex simulation of data \mathbf{x} . For example (see Section 3.1), \mathbf{z} may be the electrical
 702 conductance parameters of an STG subcircuit, and \mathbf{x} the evolving membrane potentials of the five
 703 neurons. In terms of statistical modeling, this circuit model has an intractable likelihood $p(\mathbf{x} | \mathbf{z})$,
 704 which is predicated by the stochastic differential equations that define the model. Even so, we do
 705 not scientifically reason about how \mathbf{z} governs all of \mathbf{x} , but rather specific phenomena that are a
 706 function of the data $f(\mathbf{x}; \mathbf{z})$. In the STG example, $f(\mathbf{x}; \mathbf{z})$ measures hub neuron frequency from the
 707 evolution of \mathbf{x} governed by \mathbf{z} . With EPI, we learn distributions of \mathbf{z} that results in an average and
 708 variance of $f(\mathbf{x}; \mathbf{z})$, denoted $\boldsymbol{\mu}$ and $\boldsymbol{\sigma}^2$. We refer to the collection of these statistical moments as an
 709 emergent property. Such emergent properties \mathcal{X} are defined through choice of $f(\mathbf{x}; \mathbf{z})$ (which may
 710 be one or multiple statistics), $\boldsymbol{\mu}$, and $\boldsymbol{\sigma}^2$

$$\mathcal{X} : \mathbb{E}_{\mathbf{z}, \mathbf{x}} [f(\mathbf{x}; \mathbf{z})] = \boldsymbol{\mu}, \text{Var}_{\mathbf{z}, \mathbf{x}} [f(\mathbf{x}; \mathbf{z})] = \boldsymbol{\sigma}^2. \quad (11)$$

711 Precisely, the emergent property statistics $f(\mathbf{x}; \mathbf{z})$ must have means $\boldsymbol{\mu}$ and variances $\boldsymbol{\sigma}^2$ over the
 712 EPI distribution of parameters and stochasticity of the data given the parameters.

713 In EPI, deep probability distributions are used as posterior approximations $q_{\boldsymbol{\theta}}(\mathbf{z} | \mathcal{X})$. In deep
 714 probability distributions, a simple random variable $\mathbf{z}_0 \sim q_0(\mathbf{z}_0)$ is mapped deterministically via a
 715 sequence of deep neural network layers (g_1, \dots, g_l) parameterized by weights and biases $\boldsymbol{\theta}$ to the
 716 support of the distribution of interest:

$$\mathbf{z} = g_{\boldsymbol{\theta}}(\mathbf{z}_0) = g_l(\dots g_1(\mathbf{z}_0)) \sim q_{\boldsymbol{\theta}}(\mathbf{z}). \quad (12)$$

717 Such deep probability distributions embed the posterior distribution in a deep network. Once
 718 optimized, this deep network representation has remarkably useful properties: immediate posterior
 719 sampling, and immediate probability, gradient, and Hessian evaluation at any parameter choice.
 720 Given a choice of model $p(\mathbf{x} \mid \mathbf{z})$ and emergent property of interest \mathcal{X} , $q_{\theta}(\mathbf{z})$ is optimized via
 721 the neural network parameters θ to find a maximally entropic distribution q_{θ}^* within the deep
 722 variational family \mathcal{Q} producing the emergent property \mathcal{X} :

$$q_{\theta}(\mathbf{z} \mid \mathcal{X}) = q_{\theta}^*(\mathbf{z}) = \operatorname{argmax}_{q_{\theta} \in \mathcal{Q}} H(q_{\theta}(\mathbf{z})) \quad (13)$$

s.t. $\mathcal{X} : \mathbb{E}_{\mathbf{z}, \mathbf{x}} [f(\mathbf{x}; \mathbf{z})] = \boldsymbol{\mu}, \operatorname{Var}_{\mathbf{z}, \mathbf{x}} [f(\mathbf{x}; \mathbf{z})] = \boldsymbol{\sigma}^2.$

723 Entropy is chosen as the normative selection principle, since we want the posterior to only contain
 724 structure predicated by the emergent property [57, 58]. This choice of selection principle is also
 725 that of standard Bayesian inference, and we derive an exact relation between EPI and variational
 726 inference (see Section 5.1.5). However, a key difference is that variational inference and other
 727 Bayesian methods do not constrain the predictions of their inferred posteriors. This optimization
 728 is executed using the algorithm of Maximum Entropy Flow Networks (MEFNs) [46].

729 In the remainder of Section 5.1, we will explain the finer details and motivation of the EPI method.
 730 First, we explain related approaches and what EPI introduces to this domain (Section 5.1.1). Sec-
 731 ond, we describe the special class of deep probability distributions used in EPI called normalizing
 732 flows (Section 5.1.2). Next, we explain the constrained optimization technique used to solve Equa-
 733 tion 13 (Section 5.1.3). Then, we demonstrate the details of this optimization in a toy example
 734 (Section 5.1.4). Finally, we establish the known relationship between maximum entropy distribu-
 735 tions and exponential families (Section 5.1.5), which is used to explain the relation between EPI
 736 and variational inference (Section 5.1.6).

737 5.1.1 Related approaches

738 When Bayesian inference problems lack conjugacy, scientists use approximate inference methods
 739 like variational inference (VI) [45] and Markov chain Monte Carlo (MCMC) [85, 86]. After opti-
 740 mization, variational methods return a parameterized posterior distribution, which we can analyze.
 741 Also, the variational approximating distribution class is often chosen such that it permits fast
 742 sampling. In contrast MCMC methods only produce samples from the approximated posterior dis-
 743 tribution. No parameterized distribution is estimated, and additional samples are always generated
 744 with the same sampling complexity. Inference in models defined by systems of differential has been

745 demonstrated with MCMC [87], although this approach requires tractable likelihoods. Advances
746 have leveraged structure in stochastic differential equation models to improve likelihood
747 approximations, thus expanding the domain of applicable models [88].

748 Likelihood-free (or “simulation-based”) inference (LFI) [89] is model parameter inference in the
749 absence of a tractable likelihood function. The most prevalent approach to LFI is approximate
750 Bayesian computation [79], in which satisfactory parameter samples are kept from random prior
751 sampling according to a rejection heuristic. The obtained set of parameters do not have a prob-
752 abilities, and further insight about the model must be gained from examination of the parameter
753 set and their generated activity. Methodological advances to ABC methods have come through
754 the use of Markov chain Monte Carlo (MCMC-ABC) [80] and sequential Monte Carlo (SMC-ABC)
755 [40] sampling techniques. SMC-ABC is considered state-of-the-art ABC, yet this approach still
756 struggles to scale in dimensionality (cf. Fig. 4). Furthermore, once a parameter set has been
757 obtained by SMC-ABC from a finite set of particles, the SMC-ABC algorithm must be run again
758 with a new population of initialized particles to obtain additional samples.

759 For scientific model analysis, we seek a posterior distribution exhibiting the properties of a well-
760 chosen variational approximation: a parametric form conferring analytic calculations, and trivial
761 sampling time. For this reason, ABC and MCMC techniques are unattractive, since they only
762 produce a set of parameter samples and have unchanging sampling rate. EPI executes likelihood-
763 free inference using the MEFN [46] algorithm using a deep variational posterior approximation.
764 The deep neural network of EPI defines the parametric form of the posterior approximation. Fur-
765 thermore, the EPI distribution is constrained to produce an emergent property. In other words,
766 the summary statistics of the posterior predictive distribution are fixed to have certain first and
767 second moments. EPI optimization is enabled using stochastic gradient techniques in the spirit
768 of likelihood-free variational inference [90]. The analytic relationship between EPI and variational
769 inference is explained in Secton 5.1.6.

770 We note that, during our preparation and early presentation of this work [91, 92], another work
771 has arisen with broadly similar goals: bringing statistical inference to mechanistic models of neural
772 circuits ([93, 94, 42]). We are encouraged by this general problem being recognized by others in the
773 community, and we emphasize that these works offer complementary neuroscientific contributions
774 (different theoretical models of focus) and use different technical methodologies (ours is built on
775 our prior work [46], theirs similarly [95]).

776 The method EPI differs from SNPE in some key ways. SNPE belongs to a “sequential” class of

777 recently developed LFI methods in which two neural networks are used for posterior inference.
778 This first neural network is a normalizing flow used to estimate the posterior $p(\mathbf{z} | \mathbf{x})$ (SNPE)
779 or the likelihood $p(\mathbf{x} | \mathbf{z})$ (sequential neural likelihood (SNL [43])). A recent advance uses an
780 unconstrained neural network to estimate the likelihood ratio (sequential neural ratio estimation
781 (SNRE [44])). In SNL and SNRE, MCMC sampling techniques are used to obtain samples from
782 the approximated posterior. This contrasts with EPI and SNPE, which afford a normalizing flow
783 approximation to the posterior, which facilitates immediate measurements of sample probability,
784 gradient, or Hessian for system analysis. The second neural network in this sequential class of
785 methods is the amortizer. This network maps data \mathbf{x} (or statistics $f(\mathbf{x}; \mathbf{z})$ or model parameters \mathbf{z})
786 to the weights and biases of the first neural network. These methods are optimized on a conditional
787 density (or ratio) estimation objective on a sequentially adapting finite sample-based approximation
788 to the posterior.

789 The approximating fidelity of the first neural network in sequential approaches is optimized to
790 generalize across the entire distribution it is conditioned upon. This optimization towards gen-
791 eralization of sequential methods can reduce the accuracy at the singular posterior of interest.
792 Whereas in EPI, the entire expressivity of the normalizing flow is dedicated to learning a single
793 distribution as well as possible. While amortization is not possible in EPI parameterized by the
794 mean parameter μ (due to the inverse mapping problem [96]), we have shown this two-network
795 amortization approach to be effective in exponential family distributions defined by their natural
796 parameterization [97].

797 Structural identifiability analysis involves the measurement of sensitivity and unidentifiabilities in
798 natural models. Around a point, one can measure the Jacobian. One approach that scales well is
799 EAR [98]. A popular efficient approach for systems of ODEs has been neural ODE adjoint [99] and
800 its stochastic adaptation [100]. Casting identifiability as a statistical estimation problem, the profile
801 likelihood can assess via iterated optimization while holding parameters fixed [53]. An exciting
802 recent method is capable of recovering the functional form of such unidentifiabilities away from a
803 point by following degenerate dimensions of the fisher information matrix [101]. Global structural
804 non-identifiabilities can be found for models with polynomial or rational dynamics equations using
805 DAISY [102]. With EPI, we have all the benefits given by a statistical inference method plus the
806 ability to query the gradient or Hessian of the inferred distribution at any chosen parameter value.

807 **5.1.2 Normalizing flows**

808 Deep probability distributions are comprised of multiple layers of fully connected neural networks
 809 (Equation). When each neural network layer is restricted to be a bijective function, the sample
 810 density can be calculated using the change of variables formula at each layer of the network. For
 811 $\mathbf{z}_i = g_i(\mathbf{z}_{i-1})$,

$$p(\mathbf{z}_i) = p(g_i^{-1}(\mathbf{z}_i)) \left| \det \frac{\partial g_i^{-1}(\mathbf{z}_i)}{\partial \mathbf{z}_i} \right| = p(\mathbf{z}_{i-1}) \left| \det \frac{\partial g_i(\mathbf{z}_{i-1})}{\partial \mathbf{z}_{i-1}} \right|^{-1}. \quad (14)$$

812 However, this computation has cubic complexity in dimensionality for fully connected layers. By
 813 restricting our layers to normalizing flows [54, 103] – bijective functions with fast log determinant
 814 Jacobian computations, which confer a fast calculation of the sample log probability. Fast log
 815 probability calculation confers efficient optimization of the maximum entropy objective (see Section
 816 5.1.3). We use the Real NVP [55] normalizing flow class, because its coupling architecture confers
 817 both fast sampling (forward) and fast log probability evaluation (backward). Fast probability
 818 evaluation in turn facilitates fast gradient and Hessian evaluation of log probability throughout
 819 parameter space. Glow permutations were used in between coupling stages [104]. This is in contrast
 820 to autoregressive architectures [56, 105], in which only forward or backward passes are efficient. In
 821 this work, normalizing flows are used as flexible posterior approximations $q_{\boldsymbol{\theta}}(\mathbf{z})$ having weights and
 822 biases $\boldsymbol{\theta}$. We specify the architecture used in each application by the number of Real-NVP affine
 823 coupling stages, and the number of neural network layers and units per layer of the conditioning
 824 functions.

825 **5.1.3 Augmented Lagrangian optimization**

826 To optimize $q_{\boldsymbol{\theta}}(\mathbf{z})$ in Equation 13, the constrained maximum entropy optimization is executed using
 827 the augmented Lagrangian method. The following objective is minimized:

$$L(\boldsymbol{\theta}; \boldsymbol{\eta}_{\text{opt}}, c) = -H(q_{\boldsymbol{\theta}}) + \boldsymbol{\eta}_{\text{opt}}^\top R(\boldsymbol{\theta}) + \frac{c}{2} \|R(\boldsymbol{\theta})\|^2 \quad (15)$$

828 where average constraint violations $R(\boldsymbol{\theta}) = \mathbb{E}_{\mathbf{z} \sim q_{\boldsymbol{\theta}}} [\mathbb{E}_{\mathbf{x} \sim p(\mathbf{x}|\mathbf{z})} [T(\mathbf{x}; \mathbf{z}) - \boldsymbol{\mu}_{\text{opt}}]]$, $\boldsymbol{\eta}_{\text{opt}} \in \mathbb{R}^m$ are the
 829 Lagrange multipliers where $m = |\boldsymbol{\mu}_{\text{opt}}| = |T(\mathbf{x}; \mathbf{z})| = 2|f(\mathbf{x}; \mathbf{z})|$, and c is the penalty coefficient.
 830 The sufficient statistics $T(\mathbf{x}; \mathbf{z})$ and mean parameter $\boldsymbol{\mu}_{\text{opt}}$ are determined by the means $\boldsymbol{\mu}$ and
 831 variances $\boldsymbol{\sigma}^2$ of emergent property statistics $f(\mathbf{x}; \mathbf{z})$ defined in Equation 13. Specifically, $T(\mathbf{x}; \mathbf{z})$ is
 832 a concatenation of the first and second moments, $\boldsymbol{\mu}_{\text{opt}}$ is a concatenation of $\boldsymbol{\mu}$ and $\boldsymbol{\sigma}^2$ (see section
 833 5.1.5), and the Lagrange multipliers are closely related to the natural parameters $\boldsymbol{\eta}$ of exponential

834 families (see Section 5.1.6). Weights and biases $\boldsymbol{\theta}$ of the deep probability distribution are optimized
835 according to Equation 15 using the Adam optimizer with learning rate 10^{-3} [106].

836 To take gradients with respect to the entropy $H(q_{\boldsymbol{\theta}}(\mathbf{z}))$, it can be expressed using the reparam-
837 eterization trick as an expectation of the negative log density of parameter samples \mathbf{z} over the
838 randomness in the parameterless initial distribution $q_0(\mathbf{z}_0)$:

$$H(q_{\boldsymbol{\theta}}(\mathbf{z})) = \int -q_{\boldsymbol{\theta}}(\mathbf{z}) \log(q_{\boldsymbol{\theta}}(\mathbf{z})) d\mathbf{z} = \mathbb{E}_{\mathbf{z} \sim q_{\boldsymbol{\theta}}} [-\log(q_{\boldsymbol{\theta}}(\mathbf{z}))] = \mathbb{E}_{\mathbf{z}_0 \sim q_0} [-\log(q_{\boldsymbol{\theta}}(g_{\boldsymbol{\theta}}(\mathbf{z}_0)))]. \quad (16)$$

839 Thus, the gradient of the entropy of the deep probability distribution can be estimated as an
840 average with respect to the base distribution \mathbf{z}_0 :

$$\nabla_{\boldsymbol{\theta}} H(q_{\boldsymbol{\theta}}(\mathbf{z})) = \mathbb{E}_{\mathbf{z}_0 \sim q_0} [-\nabla_{\boldsymbol{\theta}} \log(q_{\boldsymbol{\theta}}(g_{\boldsymbol{\theta}}(\mathbf{z}_0)))]. \quad (17)$$

841 The lagrangian parameters $\boldsymbol{\eta}_{\text{opt}}$ are initialized to zero and adapted following each augmented
842 Lagrangian epoch, which is a period of optimization with fixed $(\boldsymbol{\eta}_{\text{opt}}, c)$ for a given number of
843 stochastic optimization iterations. A low value of c is used initially, and conditionally increased
844 after each epoch based on constraint error reduction. The penalty coefficient is updated based
845 on the result of a hypothesis test regarding the reduction in constraint violation. The p-value of
846 $\mathbb{E}[|R(\boldsymbol{\theta}_{k+1})|] > \gamma \mathbb{E}[|R(\boldsymbol{\theta}_k)|]$ is computed, and c_{k+1} is updated to βc_k with probability $1 - p$. The
847 other update rule is $\boldsymbol{\eta}_{\text{opt},k+1} = \boldsymbol{\eta}_{\text{opt},k} + c_k \frac{1}{n} \sum_{i=1}^n (T(\mathbf{x}^{(i)}) - \boldsymbol{\mu}_{\text{opt}})$ given a batch size n . Throughout
848 the study, $\gamma = 0.25$, while β was chosen to be either 2 or 4. The batch size of EPI also varied
849 according to application.

850 The intention is that c and $\boldsymbol{\eta}_{\text{opt}}$ start at values encouraging entropic growth early in optimization.
851 With each training epoch in which the update rule for c is invoked by unsatisfactory constraint
852 error reduction, the constraint satisfaction terms are increasingly weighted, resulting in a decreased
853 entropy. This encourages the discovery of suitable regions of parameter space, and the subsequent
854 refinement of the distribution to produce the emergent property (see example in Section 5.1.4). The
855 momentum parameters of the Adam optimizer are reset at the end of each augmented Lagrangian
856 epoch.

857 Rather than starting optimization from some $\boldsymbol{\theta}$ drawn from a randomized distribution, we found
858 that initializing $q_{\boldsymbol{\theta}}(\mathbf{z})$ to approximate an isotropic Gaussian distribution conferred more stable, con-
859 sistent optimization. The parameters of the Gaussian initialization were chosen on an application-
860 specific basis. Throughout the study, we chose isotropic Gaussian initializations with mean $\boldsymbol{\mu}_{\text{init}}$
861 at the center of the distribution support and some standard deviation σ_{init} , except for one case,
862 where an initialization informed by random search was used (see Section 5.2.1).

863 To assess whether the EPI distribution $q_{\theta}(\mathbf{z})$ produces the emergent property, we assess whether
 864 each individual constraint on the means and variances of $f(\mathbf{x}; \mathbf{z})$ is satisfied. We consider the EPI
 865 to have converged when a null hypothesis test of constraint violations $R(\boldsymbol{\theta})_i$ being zero is accepted
 866 for all constraints $i \in \{1, \dots, m\}$ at a significance threshold $\alpha = 0.05$. This significance threshold is
 867 adjusted through Bonferroni correction according to the number of constraints m . The p-values for
 868 each constraint are calculated according to a two-tailed nonparametric test, where 200 estimations
 869 of the sample mean $R(\boldsymbol{\theta})^i$ are made using N_{test} samples of $\mathbf{z} \sim q_{\theta}(\mathbf{z})$ at the end of the augmented
 870 Lagrangian epoch.

871 When assessing the suitability of EPI for a particular modeling question, there are some important
 872 technical considerations. First and foremost, as in any optimization problem, the defined emergent
 873 property should always be appropriately conditioned (constraints should not have wildly different
 874 units). Furthermore, if the program is underconstrained (not enough constraints), the distribution
 875 grows (in entropy) unstably unless mapped to a finite support. If overconstrained, there is no pa-
 876 rameter set producing the emergent property, and EPI optimization will fail (appropriately). Next,
 877 one should consider the computational cost of the gradient calculations. In the best circumstance,
 878 there is a simple, closed form expression (e.g. Section 5.2.5) for the emergent property statistic
 879 given the model parameters. On the other end of the spectrum, many forward simulation iterations
 880 may be required before a high quality measurement of the emergent property statistic is available
 881 (e.g. Section 5.2.1). In such cases, backpropagating gradients through the SDE evolution will be
 882 expensive.

883 5.1.4 Example: 2D LDS

884 To gain intuition for EPI, consider a two-dimensional linear dynamical system (2D LDS) model
 885 (Fig. S1A):

$$886 \quad \tau \frac{d\mathbf{x}}{dt} = A\mathbf{x} \quad (18)$$

with

$$A = \begin{bmatrix} a_1 & a_2 \\ a_3 & a_4 \end{bmatrix}. \quad (19)$$

887 To run EPI with the dynamics matrix elements as the free parameters $\mathbf{z} = [a_1, a_2, a_3, a_4]$ (fix-
 888 ing $\tau = 1$), the emergent property statistics $T(\mathbf{x})$ were chosen to contain the first and second
 889 moments of the oscillatory frequency, $\frac{\text{imag}(\lambda_1)}{2\pi}$, and the growth/decay factor, $\text{real}(\lambda_1)$, of the oscil-
 890 lating system. λ_1 is the eigenvalue of greatest real part when the imaginary component is zero, and

alternatively of positive imaginary component when the eigenvalues are complex conjugate pairs.
 To learn the distribution of real entries of A that produce a band of oscillating systems around 1Hz, we formalized this emergent property as $\text{real}(\lambda_1)$ having mean zero with variance 0.25^2 , and the oscillation frequency $2\pi\text{imag}(\lambda_1)$ having mean $\omega = 1$ Hz with variance $(0.1\text{Hz})^2$:

$$\mathbb{E}[T(\mathbf{x})] \triangleq \mathbb{E} \begin{bmatrix} \text{real}(\lambda_1) \\ \text{imag}(\lambda_1) \\ (\text{real}(\lambda_1) - 0)^2 \\ (\text{imag}(\lambda_1) - 2\pi\omega)^2 \end{bmatrix} = \begin{bmatrix} 0.0 \\ 2\pi\omega \\ 0.25^2 \\ (2\pi 0.1)^2 \end{bmatrix} \triangleq \boldsymbol{\mu}. \quad (20)$$

895

Unlike the models we presented in the main text, this model admits an analytical form for the mean emergent property statistics given parameter \mathbf{z} , since the eigenvalues can be calculated using the quadratic formula:

$$\lambda = \frac{\left(\frac{a_1+a_4}{\tau}\right) \pm \sqrt{\left(\frac{a_1+a_4}{\tau}\right)^2 + 4\left(\frac{a_2a_3-a_1a_4}{\tau}\right)}}{2}. \quad (21)$$

Importantly, even though $\mathbb{E}_{\mathbf{x} \sim p(\mathbf{x}|\mathbf{z})}[T(\mathbf{x})]$ is calculable directly via a closed form function and does not require simulation, we cannot derive the distribution q_{θ}^* directly. This fact is due to the formally hard problem of the backward mapping: finding the natural parameters η from the mean parameters $\boldsymbol{\mu}$ of an exponential family distribution [96]. Instead, we used EPI to approximate this distribution (Fig. S1B). We used a real-NVP normalizing flow architecture with four masks, two neural network layers of 15 units per mask, with batch normalization momentum 0.99, mapped onto a support of $z_i \in [-10, 10]$. (see Section 5.1.2).

Even this relatively simple system has nontrivial (though intuitively sensible) structure in the parameter distribution. To validate our method, we analytically derived the contours of the probability density from the emergent property statistics and values. In the a_1 - a_4 plane, the black line at $\text{real}(\lambda_1) = \frac{a_1+a_4}{2} = 0$, dotted black line at the standard deviation $\text{real}(\lambda_1) = \frac{a_1+a_4}{2} \pm 0.25$, and the dotted gray line at twice the standard deviation $\text{real}(\lambda_1) = \frac{a_1+a_4}{2} \pm 0.5$ follow the contour of probability density of the samples (Fig. S2A). The distribution precisely reflects the desired statistical constraints and model degeneracy in the sum of a_1 and a_4 . Intuitively, the parameters equivalent with respect to emergent property statistic $\text{real}(\lambda_1)$ have similar log densities.

To explain the bimodality of the EPI distribution, we examined the imaginary component of λ_1 .

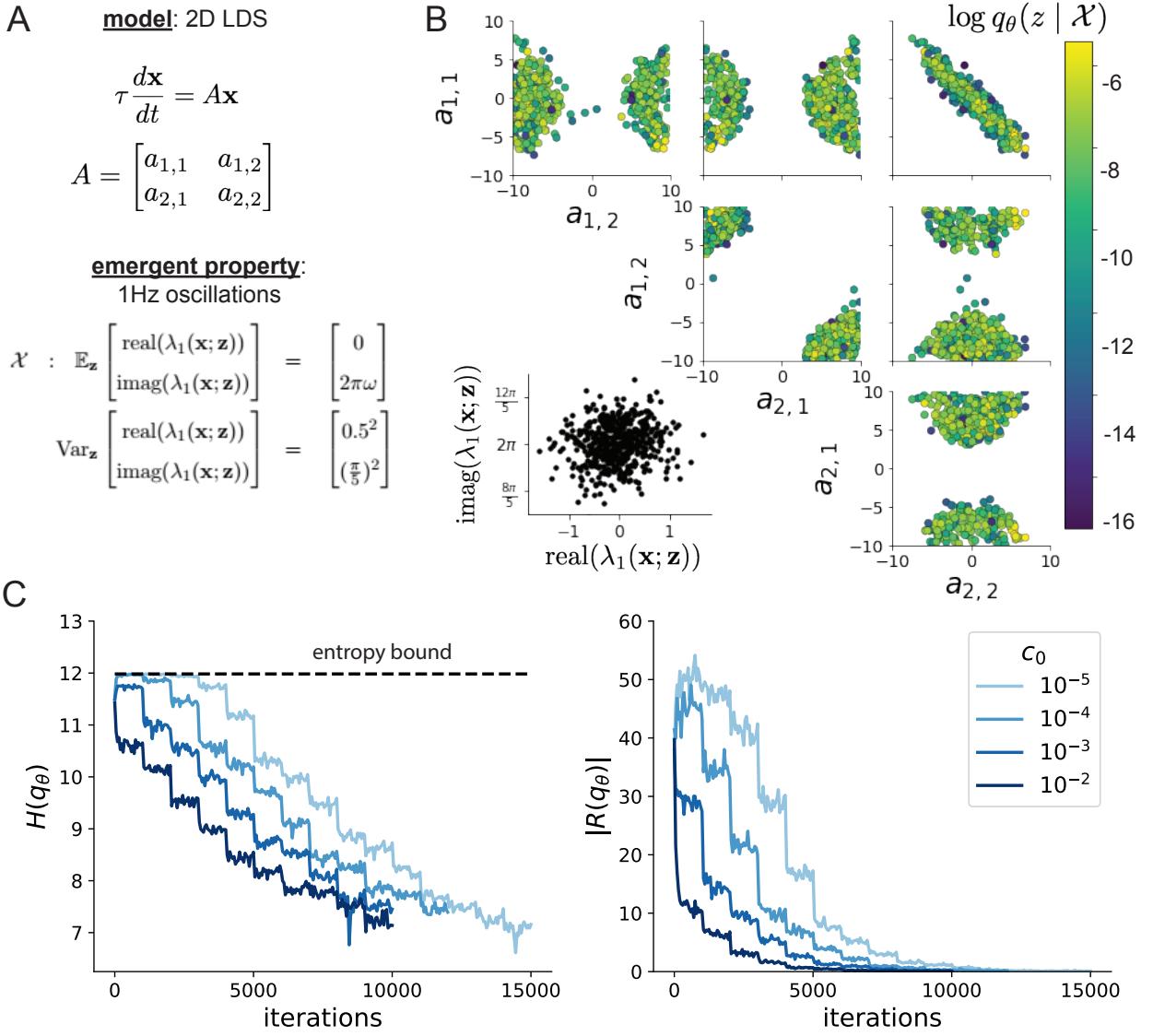


Figure 5: (LDS1): **A.** Two-dimensional linear dynamical system model, where real entries of the dynamics matrix A are the parameters. **B.** The EPI distribution for a two-dimensional linear dynamical system with $\tau = 1$ that produces an average of 1Hz oscillations with some small amount of variance. Dashed lines indicate the parameter axes. **C.** Entropy throughout the optimization. At the beginning of each augmented Lagrangian epoch (2,000 iterations), the entropy dipped due to the shifted optimization manifold where emergent property constraint satisfaction is increasingly weighted. **D.** Emergent property moments throughout optimization. At the beginning of each augmented Lagrangian epoch, the emergent property moments adjust closer to their constraints.

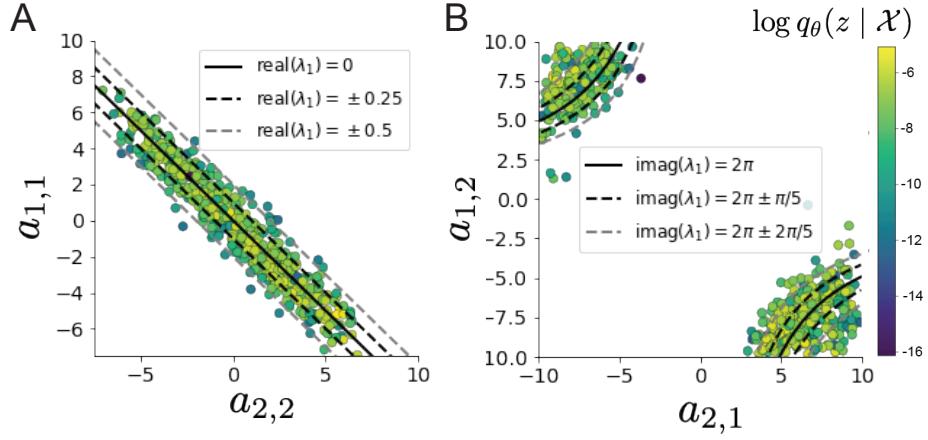


Figure 6: (LDS2): **A.** Probability contours in the a_1 - a_4 plane were derived from the relationship to emergent property statistic of growth/decay factor $\text{real}(\lambda_1)$. **B.** Probability contours in the a_2 - a_3 plane were derived from the emergent property statistic of oscillation frequency $2\pi\text{imag}(\lambda_1)$.

915 When $\text{real}(\lambda_1) = \frac{a_1+a_4}{2} = 0$, we have

$$\text{imag}(\lambda_1) = \begin{cases} \sqrt{\frac{a_1a_4 - a_2a_3}{\tau}}, & \text{if } a_1a_4 < a_2a_3 \\ 0 & \text{otherwise} \end{cases}. \quad (22)$$

916 When $\tau = 1$ and $a_1a_4 > a_2a_3$ (center of distribution above), we have the following equation for the
917 other two dimensions:

$$\text{imag}(\lambda_1)^2 = a_1a_4 - a_2a_3 \quad (23)$$

918 Since we constrained $\mathbb{E}_{z \sim q_\theta} [\text{imag}(\lambda)] = 2\pi$ (with $\omega = 1$), we can plot contours of the equation
919 $\text{imag}(\lambda_1)^2 = a_1a_4 - a_2a_3 = (2\pi)^2$ for various a_1a_4 (Fig. S2B). With $\sigma_{1,4} = \mathbb{E}_{z \sim q_\theta} [|a_1a_4 - E_{q_\theta}[a_1a_4]|]$,
920 we show the contours as $a_1a_4 = 0$ (black), $a_1a_4 = -\sigma_{1,4}$ (black dotted), and $a_1a_4 = -2\sigma_{1,4}$ (grey
921 dotted). This validates the curved structure of the inferred distribution learned through EPI. We
922 took steps in negative standard deviation of a_1a_4 (dotted and gray lines), since there are few positive
923 values a_1a_4 in the learned distribution. Subtler combinations of model and emergent property will
924 have more complexity, further motivating the use of EPI for understanding these systems. As we
925 expect, the distribution results in samples of two-dimensional linear systems oscillating near 1Hz
926 (Fig. S3).

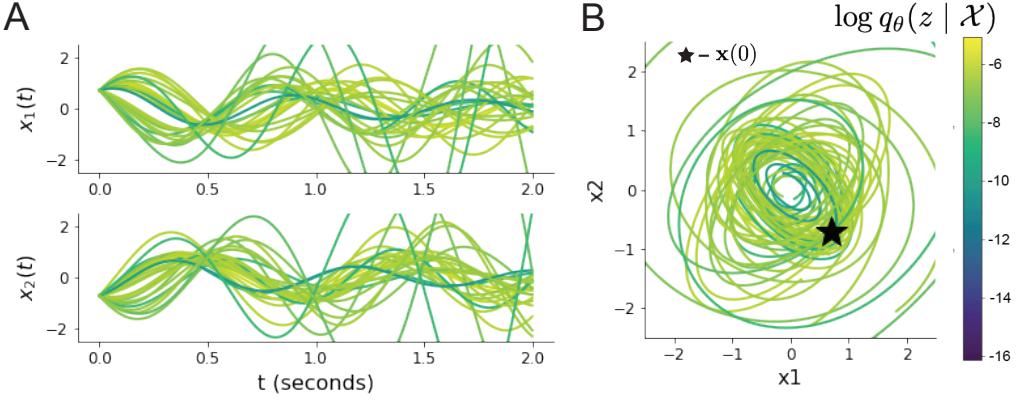


Figure 7: (LDS3): Sampled dynamical systems $\mathbf{z} \sim q_\theta(\mathbf{z})$ and their simulated activity from $\mathbf{x}(0) = [\frac{\sqrt{2}}{2}, -\frac{\sqrt{2}}{2}]$ colored by log probability. **A.** Each dimension of the simulated trajectories throughout time. **B.** The simulated trajectories in phase space.

927 5.1.5 Maximum entropy distributions and exponential families

928 Maximum entropy distributions have a fundamental link to exponential family distributions. A
929 maximum entropy distribution of form:

$$p^*(\mathbf{z}) = \underset{p \in \mathcal{P}}{\operatorname{argmax}} H(p(\mathbf{z})) \quad (24)$$

s.t. $\mathbb{E}_{\mathbf{z} \sim p}[T(\mathbf{z})] = \boldsymbol{\mu}_{\text{opt}}$.

930 will have probability density in the exponential family:

$$p^*(\mathbf{z}) \propto \exp(\boldsymbol{\eta}^\top T(\mathbf{z})). \quad (25)$$

931 The mappings between the mean parameterization $\boldsymbol{\mu}_{\text{opt}}$ and the natural parameterization $\boldsymbol{\eta}$ are
932 formally hard to identify [96].

933 In EPI, emergent properties are defined as statistics having a fixed mean and variance as in Equation
934 4

$$\mathbb{E}_{\mathbf{z}, \mathbf{x}}[f(\mathbf{x}; \mathbf{z})] = \boldsymbol{\mu}, \operatorname{Var}_{\mathbf{z}, \mathbf{x}}[f(\mathbf{x}; \mathbf{z})] = \boldsymbol{\sigma}^2. \quad (26)$$

935 The variance constraint is a second moment constraint on $f(\mathbf{x}; \mathbf{z})$

$$\operatorname{Var}_{\mathbf{z}, \mathbf{x}}[f(\mathbf{x}; \mathbf{z})] = \mathbb{E}_{\mathbf{z}, \mathbf{x}}[(f(\mathbf{x}; \mathbf{z}) - \boldsymbol{\mu})^2] \quad (27)$$

936 As a general maximum entropy distribution (Equation 24), the sufficient statistics vector contains

937 both first and second order moments of $f(\mathbf{x}; \mathbf{z})$

$$T(\mathbf{x}; \mathbf{z}) = \begin{bmatrix} f(\mathbf{x}; \mathbf{z}) \\ (f(\mathbf{x}; \mathbf{z}) - \boldsymbol{\mu})^2 \end{bmatrix}, \quad (28)$$

938 which are constrained to the chosen means and variances

$$\boldsymbol{\mu}_{\text{opt}} = \begin{bmatrix} \boldsymbol{\mu} \\ \sigma^2 \end{bmatrix}. \quad (29)$$

939 5.1.6 EPI as variational inference

940 In Bayesian inference a prior belief about model parameters \mathbf{z} is stated in a prior distribution $p(\mathbf{z})$,
 941 and the statistical model capturing the effect of \mathbf{z} on observed data points \mathbf{x} is formalized in the
 942 likelihood distribution $p(\mathbf{x} | \mathbf{z})$. In Bayesian inference, we obtain a posterior distribution $p(z | \mathbf{x})$,
 943 which captures how the data inform our knowledge of model parameters using Bayes' rule:

$$p(\mathbf{z} | \mathbf{x}) = \frac{p(\mathbf{x} | \mathbf{z})p(\mathbf{z})}{p(\mathbf{x})}. \quad (30)$$

944 The posterior distribution is analytically available when the prior is conjugate with the likelihood.
 945 However, conjugacy is rare in practice, and alternative methods, such as variational inference [107],
 946 are utilized.

947 In variational inference, a posterior approximation $q_{\boldsymbol{\theta}}^*$ is chosen from within some variational family
 948 \mathcal{Q}

$$q_{\boldsymbol{\theta}}^*(\mathbf{z}) = \underset{q_{\boldsymbol{\theta}} \in \mathcal{Q}}{\operatorname{argmin}} KL(q_{\boldsymbol{\theta}}(\mathbf{z}) || p(\mathbf{z} | \mathbf{x})). \quad (31)$$

949 The KL divergence can be written in terms of entropy of the variational approximation:

$$KL(q_{\boldsymbol{\theta}}(\mathbf{z}) || p(\mathbf{z} | \mathbf{x})) = \mathbb{E}_{\mathbf{z} \sim q_{\boldsymbol{\theta}}} [\log(q_{\boldsymbol{\theta}}(\mathbf{z}))] - \mathbb{E}_{\mathbf{z} \sim q_{\boldsymbol{\theta}}} [\log(p(\mathbf{z} | \mathbf{x}))] \quad (32)$$

$$= -H(q_{\boldsymbol{\theta}}) - \mathbb{E}_{\mathbf{z} \sim q_{\boldsymbol{\theta}}} [\log(p(\mathbf{x} | \mathbf{z})) + \log(p(\mathbf{z})) - \log(p(\mathbf{x}))] \quad (33)$$

951 Since the marginal distribution of the data $p(\mathbf{x})$ (or “evidence”) is independent of $\boldsymbol{\theta}$, variational
 952 inference is executed by optimizing the remaining expression. This is usually framed as maximizing
 953 the evidence lower bound (ELBO)

$$\underset{q_{\boldsymbol{\theta}} \in \mathcal{Q}}{\operatorname{argmin}} KL(q_{\boldsymbol{\theta}} || p(\mathbf{z} | \mathbf{x})) = \underset{q_{\boldsymbol{\theta}} \in \mathcal{Q}}{\operatorname{argmax}} H(q_{\boldsymbol{\theta}}) + \mathbb{E}_{\mathbf{z} \sim q_{\boldsymbol{\theta}}} [\log(p(\mathbf{x} | \mathbf{z})) + \log(p(\mathbf{z}))]. \quad (34)$$

954 Now, consider the setting where we have chosen a uniform prior, and stipulate a mean-field gaussian
 955 likelihood on a chosen statistic of the data $f(\mathbf{x}; \mathbf{z})$

$$p(\mathbf{x} | \mathbf{z}) = \mathcal{N}(f(\mathbf{x}; \mathbf{z}) | \boldsymbol{\mu}_f, \Sigma_f), \quad (35)$$

956 where $\Sigma_f = \text{diag}(\boldsymbol{\sigma}_f^2)$. The log likelihood is then proportional to a dot product of the natural
 957 parameter of this mean-field gaussian distribution and the first and second moment statistics.

$$\log p(\mathbf{x} | \mathbf{z}) \propto \boldsymbol{\eta}_f^\top T(\mathbf{x}, \mathbf{z}), \quad (36)$$

958 where

$$\boldsymbol{\eta}_f = \begin{bmatrix} \frac{\boldsymbol{\mu}_f}{\sigma_f^2} \\ \frac{-1}{2\sigma_f^2} \end{bmatrix}, \text{ and} \quad (37)$$

$$T(\mathbf{x}; \mathbf{z}) = \begin{bmatrix} f(\mathbf{x}; \mathbf{z}) \\ (f(\mathbf{x}; \mathbf{z}) - \boldsymbol{\mu}_f)^2 \end{bmatrix}. \quad (38)$$

960 The variational objective is then

$$\underset{q_\theta \in Q}{\operatorname{argmax}} H(q_\theta) + \boldsymbol{\eta}_f^\top \mathbb{E}_{\mathbf{z} \sim q_\theta} [T(\mathbf{x}; \mathbf{z})] \quad (39)$$

961 Comparing this to the Lagrangian objective (without augmentation) of EPI, we see they are the
 962 same

$$\begin{aligned} q_\theta^*(\mathbf{z}) &= \underset{q_\theta \in Q}{\operatorname{argmin}} -H(q_\theta) + \boldsymbol{\eta}_{\text{opt}}^\top (\mathbb{E}_{\mathbf{z}, \mathbf{x}} [T(\mathbf{x}; \mathbf{z})] - \boldsymbol{\mu}_{\text{opt}}) \\ &= \underset{q_\theta \in Q}{\operatorname{argmin}} -H(q_\theta) + \boldsymbol{\eta}_{\text{opt}}^\top \mathbb{E}_{\mathbf{z}, \mathbf{x}} [T(\mathbf{x}; \mathbf{z})]. \end{aligned} \quad (40)$$

963 where $T(\mathbf{x}; \mathbf{z})$ consists of the first and second moments of the emergent property statistic $f(\mathbf{x}; \mathbf{z})$
 964 (Equation 28). Thus, EPI is implicitly executing variational inference with a uniform prior and a
 965 mean-field gaussian likelihood on the emergent property statistics. The data \mathbf{x} used by this implicit
 966 variational inference program would be that generated by the adapting variational approximation
 967 $\mathbf{x} \sim p(\mathbf{x} | \mathbf{z})q_\theta(\mathbf{z})$, and the likelihood parameters $\boldsymbol{\eta}_f$ of EPI optimization epoch k are predicated
 968 by $\boldsymbol{\eta}_{\text{opt},k}$. However, in EPI we have not specified a prior distribution, or collected data, which can
 969 inform us about model parameters. Instead we have a mathematical specification of an emergent
 970 property, which the model must produce, and a maximum entropy selection principle. Accordingly,
 971 we replace the notation of $p(\mathbf{z} | \mathbf{x})$ with $p(\mathbf{z} | \mathcal{X})$ conceptualizing an inferred distribution that obeys
 972 emergent property \mathcal{X} (see Section 5.1).

973 5.2 Theoretical models

974 In this study, we used emergent property inference to examine several models relevant to theoretical
 975 neuroscience. Here, we provide the details of each model and the related analyses.

976 **5.2.1 Stomatogastric ganglion**

977 We analyze how the parameters $\mathbf{z} = [g_{el}, g_{synA}]$ govern the emergent phenomena of intermediate
 978 hub frequency in a model of the stomatogastric ganglion (STG) [47] shown in Figure 1A with
 979 activity $\mathbf{x} = [x_{f1}, x_{f2}, x_{hub}, x_{s1}, x_{s2}]$, using the same hyperparameter choices as Gutierrez et al.
 980 Each neuron's membrane potential $x_\alpha(t)$ for $\alpha \in \{f1, f2, hub, s1, s2\}$ is the solution of the following
 981 stochastic differential equation:

$$C_m \frac{dx_\alpha}{dt} = -[h_{leak}(\mathbf{x}; \mathbf{z}) + h_{Ca}(\mathbf{x}; \mathbf{z}) + h_K(\mathbf{x}; \mathbf{z}) + h_{hyp}(\mathbf{x}; \mathbf{z}) + h_{elec}(\mathbf{x}; \mathbf{z}) + h_{syn}(\mathbf{x}; \mathbf{z})] + dB. \quad (41)$$

982 The input current of each neuron is the sum of the leak, calcium, potassium, hyperpolarization,
 983 electrical and synaptic currents as well as gaussian noise dB . Each current component is a function
 984 of all membrane potentials and the conductance parameters \mathbf{z} .

985 The capacitance of the cell membrane was set to $C_m = 1nF$. Specifically, the currents are the
 986 difference in the neuron's membrane potential and that current type's reversal potential multiplied
 987 by a conductance:

$$h_{leak}(\mathbf{x}; \mathbf{z}) = g_{leak}(x_\alpha - V_{leak}) \quad (42)$$

$$h_{elec}(\mathbf{x}; \mathbf{z}) = g_{el}(x_\alpha^{post} - x_\alpha^{pre}) \quad (43)$$

$$h_{syn}(\mathbf{x}; \mathbf{z}) = g_{syn}S_\infty^{pre}(x_\alpha^{post} - V_{syn}) \quad (44)$$

$$h_{Ca}(\mathbf{x}; \mathbf{z}) = g_{Ca}M_\infty(x_\alpha - V_{Ca}) \quad (45)$$

$$h_K(\mathbf{x}; \mathbf{z}) = g_KN(x_\alpha - V_K) \quad (46)$$

$$h_{hyp}(\mathbf{x}; \mathbf{z}) = g_hH(x_\alpha - V_{hyp}). \quad (47)$$

993 The reversal potentials were set to $V_{leak} = -40mV$, $V_{Ca} = 100mV$, $V_K = -80mV$, $V_{hyp} = -20mV$,
 994 and $V_{syn} = -75mV$. The other conductance parameters were fixed to $g_{leak} = 1 \times 10^{-4}\mu S$. g_{Ca} ,
 995 g_K , and g_{hyp} had different values based on fast, intermediate (hub) or slow neuron. The fast
 996 conductances had values $g_{Ca} = 1.9 \times 10^{-2}$, $g_K = 3.9 \times 10^{-2}$, and $g_{hyp} = 2.5 \times 10^{-2}$. The intermediate
 997 conductances had values $g_{Ca} = 1.7 \times 10^{-2}$, $g_K = 1.9 \times 10^{-2}$, and $g_{hyp} = 8.0 \times 10^{-3}$. Finally, the
 998 slow conductances had values $g_{Ca} = 8.5 \times 10^{-3}$, $g_K = 1.5 \times 10^{-2}$, and $g_{hyp} = 1.0 \times 10^{-2}$.

999 Furthermore, the Calcium, Potassium, and hyperpolarization channels have time-dependent gating
 1000 dynamics dependent on steady-state gating variables M_∞ , N_∞ and H_∞ , respectively:

$$M_\infty = 0.5 \left(1 + \tanh \left(\frac{x_\alpha - v_1}{v_2} \right) \right) \quad (48)$$

$$\frac{dN}{dt} = \lambda_N(N_\infty - N) \quad (49)$$

$$N_\infty = 0.5 \left(1 + \tanh \left(\frac{x_\alpha - v_3}{v_4} \right) \right) \quad (50)$$

$$\lambda_N = \phi_N \cosh \left(\frac{x_\alpha - v_3}{2v_4} \right) \quad (51)$$

$$\frac{dH}{dt} = \frac{(H_\infty - H)}{\tau_h} \quad (52)$$

$$H_{\infty} = \frac{1}{1 + \exp\left(\frac{x_{\alpha} + v_5}{v_6}\right)} \quad (53)$$

$$\tau_h = 272 - \left(\frac{-1499}{1 + \exp\left(\frac{-x_\alpha + v_7}{v_8}\right)} \right). \quad (54)$$

where we set $v_1 = 0mV$, $v_2 = 20mV$, $v_3 = 0mV$, $v_4 = 15mV$, $v_5 = 78.3mV$, $v_6 = 10.5mV$,
 $v_7 = -42.2mV$, $v_8 = 87.3mV$, $v_9 = 5mV$, and $v_{th} = -25mV$.

¹⁰⁰⁹ Finally, there is a synaptic gating variable as well:

$$S_\infty = \frac{1}{1 + \exp\left(\frac{v_{th} - x_\alpha}{v_9}\right)}. \quad (55)$$

When the dynamic gating variables are considered, this is actually a 15-dimensional nonlinear dynamical system. Gaussian noise $d\mathbf{B}$ of variance $(1 \times 10^{-12})^2$ A² makes the model stochastic, and introduces variability in frequency at each parameterization \mathbf{z} .

In order to measure the frequency of the hub neuron during EPI, the STG model was simulated for $T = 300$ time steps of $dt = 25\text{ms}$. The chosen dt and T were the most computationally convenient choices yielding accurate frequency measurement. We used a basis of complex exponentials with frequencies from 0.0-1.0 Hz at 0.01Hz resolution to measure frequency from simulated time series

$$\Phi = [0.0, 0.01, \dots, 1.0]^\top .. \quad (56)$$

1017 To measure spiking frequency, we processed simulated membrane potentials with a relu (spike
1018 extraction) and low-pass filter with averaging window of size 20, then took the frequency with the
1019 maximum absolute value of the complex exponential basis coefficients of the processed time-series.
1020 The first 20 temporal samples of the simulation are ignored to account for initial transients.

1021 To differentiate through the maximum frequency identification, we used a soft-argmax Let $X_\alpha \in$
 1022 $\mathcal{C}^{|\Phi|}$ be the complex exponential filter bank dot products with the signal $x_\alpha \in \mathbb{R}^N$, where $\alpha \in$

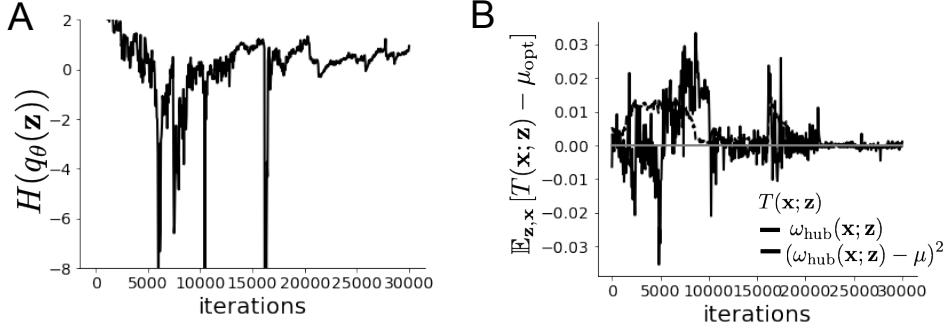


Figure 8: (STG1): EPI optimization of the STG model producing network syncing. **A.** Entropy throughout optimization. **B.** The emergent property statistic means and variances converge to their constraints at 25,000 iterations following the fifth augmented Lagrangian epoch.

1023 $\{f1, f2, \text{hub}, s1, s2\}$. The soft-argmax is then calculated using temperature parameter $\beta = 100$

$$\psi_\alpha = \text{softmax}(\beta|X_\alpha| \odot i), \quad (57)$$

1024 where $i = [0, 1, \dots, 100]$. The frequency is then calculated as

$$\omega_\alpha = 0.01\psi_\alpha \text{Hz}. \quad (58)$$

1025 Intermediate hub frequency, like all other emergent properties in this work, is defined by the mean
 1026 and variance of the emergent property statistics. In this case, we have one statistic, hub neuron
 1027 frequency, where the mean was chosen to be 0.55Hz, and variance was chosen to be $(0.025\text{Hz})^2$ to
 1028 capture variation in frequency between 0.5Hz and 0.6Hz (Equation 4). As a maximum entropy dis-
 1029 tribution, $T(\mathbf{x}, \mathbf{z})$ is comprised of both these first and second moments of the hub neuron frequency
 1030 (as in Equations 28 and 29)

$$T(\mathbf{x}; \mathbf{z}) = \begin{bmatrix} \omega_{\text{hub}}(\mathbf{x}; \mathbf{z}) \\ (\omega_{\text{hub}}(\mathbf{x}; \mathbf{z}) - 0.55)^2 \end{bmatrix}, \quad (59)$$

$$\boldsymbol{\mu}_{\text{opt}} = \begin{bmatrix} 0.55 \\ 0.025^2 \end{bmatrix}. \quad (60)$$

1031 1032 Throughout optimization, the augmented Lagrangian parameters η and c , were updated after each
 1033 epoch of 5,000 iterations(see Section 5.1.3). The optimization converged after five epochs (Fig. S4).

1034 1035 For EPI in Fig 1E, we used a real NVP architecture with three Real NVP coupling layers and two-
 layer neural networks of 25 units per layer. The normalizing flow architecture mapped $z_0 \sim \mathcal{N}(\mathbf{0}, I)$

1036 to a support of $\mathbf{z} = [g_{\text{el}}, g_{\text{synA}}] \in [4, 8] \times [0.01, 4]$, initialized to a gaussian approximation of samples
 1037 returned by a preliminary ABC search. We did not include $g_{\text{synA}} < 0.01$, for numerical stability.
 1038 EPI optimization was run using 5 different random seeds for architecture initialization $\boldsymbol{\theta}$ with an
 1039 augmented Lagrangian coefficient of $c_0 = 10^5$, a batch size $n = 400$, and $\beta = 2$. The distribution
 1040 shown is that of the architecture converging with criteria $N_{\text{test}} = 100$ at greatest entropy across
 1041 random seeds.

1042 We calculated the Hessian at the mode of the inferred EPI distribution. The Hessian of a probability
 1043 model is the second order gradient of the log probability density $\log q_{\boldsymbol{\theta}}(\mathbf{z})$ with respect to the
 1044 parameters \mathbf{z} : $\frac{\partial^2 \log q_{\boldsymbol{\theta}}(\mathbf{z})}{\partial \mathbf{z} \partial \mathbf{z}^\top}$. With EPI, we can examine the Hessian, which is analytically available
 1045 throughout distribution, to indicate the dimensions of parameter space that are sensitive (strongly
 1046 negative eigenvalue), and which are degenerate (low magnitude eigenvalue) with respect to the
 1047 emergent property produced. In Figure 1D, the eigenvectors of the Hessian v_1 (solid) and v_2
 1048 (dashed) are shown evaluated at the mode of the distribution. The length of the arrows is inversely
 1049 proportional to the square root of absolute value of their eigenvalues $\lambda_1 = -10.7$ and $\lambda_2 = -3.22$.
 1050 Since the Hessian eigenvectors have sign degeneracy, the visualized directions in 2-D parameter
 1051 space are chosen arbitrarily.

1052 5.2.2 Primary visual cortex

1053 In the stochastic stabilized supralinear network [71], population rate responses \mathbf{x} to input \mathbf{h} , recur-
 1054 rent input $W\mathbf{x}$ and slow noise $\boldsymbol{\epsilon}$ are governed by

$$\tau \frac{d\mathbf{x}}{dt} = -\mathbf{x} + \phi(W\mathbf{x} + \mathbf{h} + \boldsymbol{\epsilon}), \quad (61)$$

1055 where the noise is an Ornstein-Uhlenbeck process $\boldsymbol{\epsilon} \sim OU(\tau_{\text{noise}}, \boldsymbol{\sigma})$

$$\tau_{\text{noise}} d\epsilon_\alpha = -\epsilon_\alpha dt + \sqrt{2\tau_{\text{noise}}} \tilde{\sigma}_\alpha dB \quad (62)$$

1056 with $\tau_{\text{noise}} = 5\text{ms} > \tau = 1\text{ms}$. The noisy process is parameterized as

$$\tilde{\sigma}_\alpha = \sigma_\alpha \sqrt{1 + \frac{\tau}{\tau_{\text{noise}}}}, \quad (63)$$

1057 so that $\boldsymbol{\sigma}$ parameterizes the variance of the noisy input in the absence of recurrent connectivity
 1058 ($W = \mathbf{0}$). As contrast increases, input to the E- and P-populations increases relative to a baseline
 1059 input $\mathbf{h} = \mathbf{h}_b + c\mathbf{h}_c$. Connectivity (W_{fit}) and input ($\mathbf{h}_{b,\text{fit}}$ and $\mathbf{h}_{c,\text{fit}}$) parameters were fit using the
 1060 deterministic V1 circuit model [48]

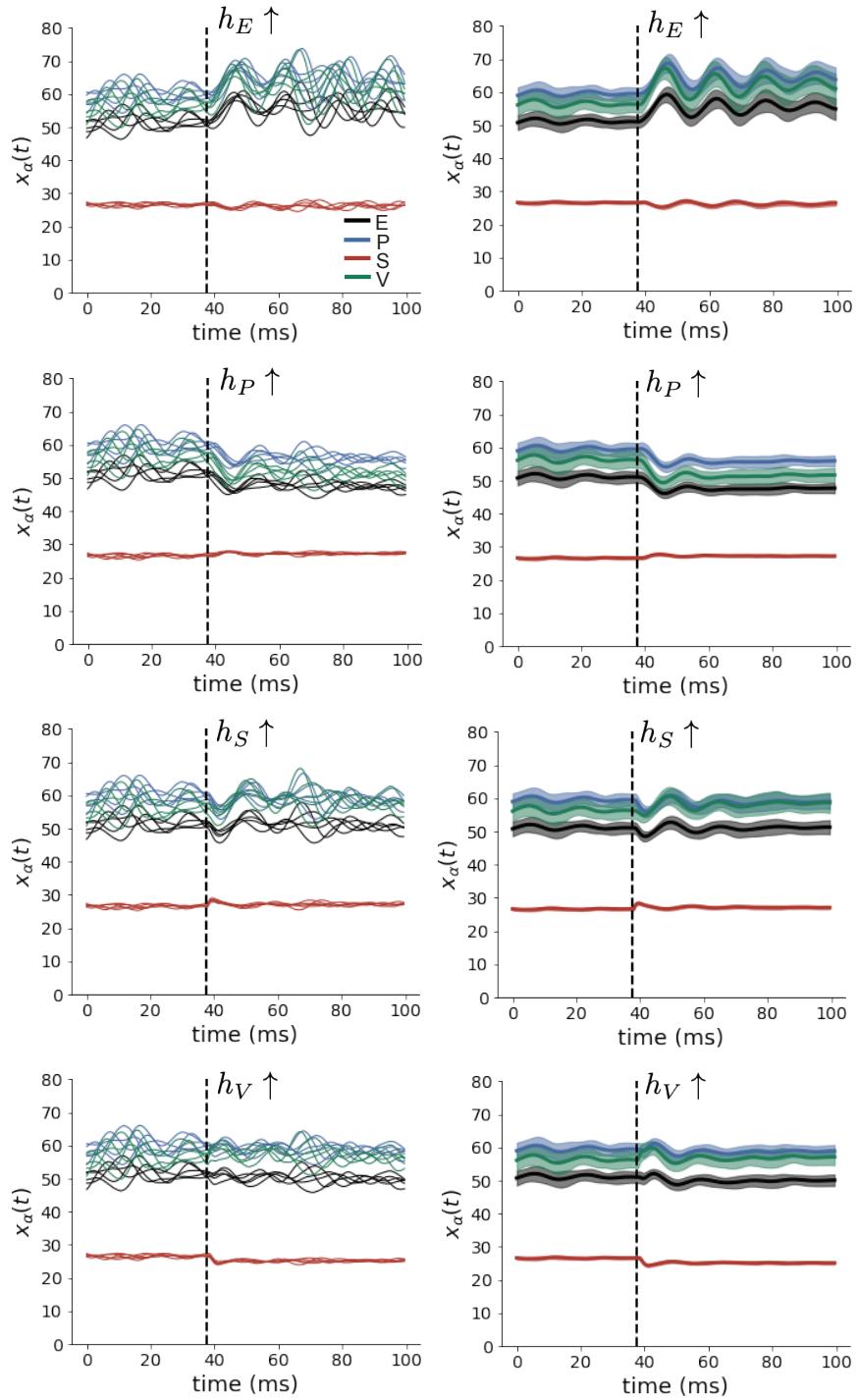


Figure 9: (V1 1) (Left) Simulations for small increases in neuron-type population input. Input magnitudes are chosen so that effect is salient (0.002 for E and P, but 0.02 for S and V). (Right) Average (solid) and standard deviation (shaded) of stochastic fluctuations of responses.

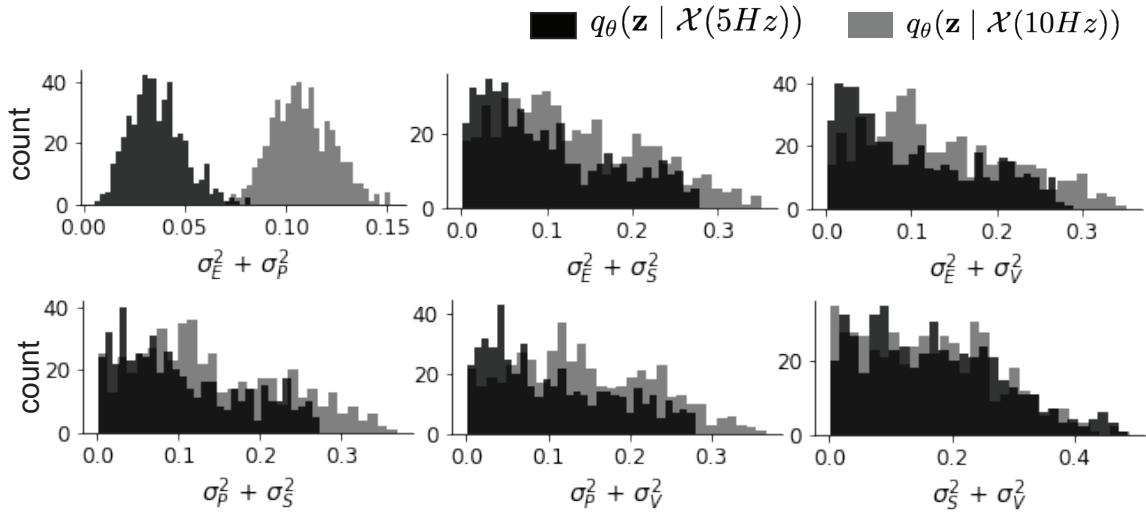


Figure 10: (V1 2) Posterior predictive distributions of the sum of squares of each pair of noise parameters.

$$W_{\text{fit}} = \begin{bmatrix} W_{EE} & W_{EP} & W_{ES} & W_{EV} \\ W_{PE} & W_{PP} & W_{PS} & W_{PV} \\ W_{SE} & W_{SP} & W_{SS} & W_{SV} \\ W_{VE} & W_{VP} & W_{VS} & W_{VV} \end{bmatrix} = \begin{bmatrix} 2.18 & -1.19 & -.594 & -.229 \\ 1.66 & -.651 & -.680 & -.242 \\ .895 & -5.22 \times 10^{-3} & -1.51 \times 10^{-4} & -.761 \\ 3.34 & -2.31 & -.254 & -2.52 \times 10^{-4} \end{bmatrix}, \quad (64)$$

$$\mathbf{h}_{b,\text{fit}} = \begin{bmatrix} .416 \\ .429 \\ .491 \\ .486 \end{bmatrix}, \quad (65)$$

¹⁰⁶¹ and

$$\mathbf{h}_{c,\text{fit}} = \begin{bmatrix} .359 \\ .403 \\ 0 \\ 0 \end{bmatrix}. \quad (66)$$

¹⁰⁶² To obtain rates on a realistic scale (100-fold greater), we map these fitted parameters to an equivalence class
¹⁰⁶³

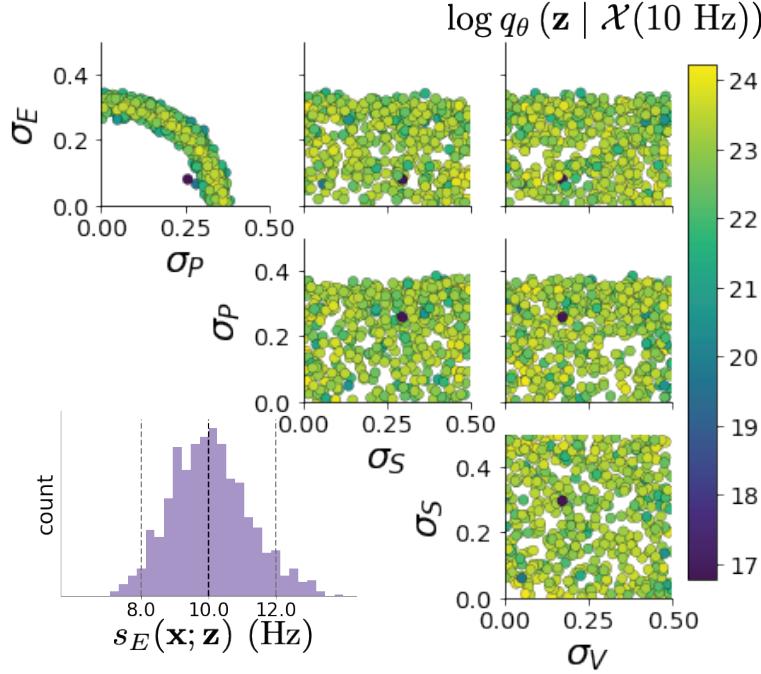


Figure 11: (V1 3) EPI posterior for $\mathcal{X}(10 \text{ Hz})$.

$$W = \begin{bmatrix} W_{EE} & W_{EP} & W_{ES} & W_{EV} \\ W_{PE} & W_{PP} & W_{PS} & W_{PV} \\ W_{SE} & W_{SP} & W_{SS} & W_{SV} \\ W_{VE} & W_{VP} & W_{VS} & W_{VV} \end{bmatrix} = \begin{bmatrix} .218 & -.119 & -.0594 & -.0229 \\ .166 & -.0651 & -.068 & -.0242 \\ .0895 & -5.22 \times 10^{-4} & -1.51 \times 10^{-5} & -.0761 \\ .334 & -.231 & -.0254 & -2.52 \times 10^{-5} \end{bmatrix}, \quad (67)$$

$$\mathbf{h}_b = \begin{bmatrix} h_{b,E} \\ h_{b,P} \\ h_{b,S} \\ h_{b,V} \end{bmatrix} = \begin{bmatrix} 4.16 \\ 4.29 \\ 4.91 \\ 4.86 \end{bmatrix}, \quad (68)$$

¹⁰⁶⁴ and

$$\mathbf{h}_c = \begin{bmatrix} h_{c,E} \\ h_{c,P} \\ h_{c,S} \\ h_{c,V} \end{bmatrix} = \begin{bmatrix} 3.59 \\ 4.03 \\ 0 \\ 0 \end{bmatrix}. \quad (69)$$

¹⁰⁶⁵ Circuit responses are simulated using $T = 200$ time steps at $dt = 0.5\text{ms}$ from an initial condition

1066 drawn from $\mathbf{x}(0) \sim U[10 \text{ Hz}, 25 \text{ Hz}]$. Standard deviation of the E-population $s_E(\mathbf{x}; \mathbf{z})$ is calculated
 1067 as the square root of the temporal variance from $t_{ss} = 75\text{ms}$ to $Tdt = 100\text{ms}$ averaged over 100
 1068 independent trials.

$$s_E(\mathbf{x}; \mathbf{z}) = \mathbb{E}_x \left[\sqrt{\mathbb{E}_{t > t_{ss}} \left[(x_E(t) - \mathbb{E}_{t > t_{ss}} [x_E(t)])^2 \right]} \right] \quad (70)$$

1069 For EPI in Fig 2D-E, we used a real NVP architecture with three Real NVP coupling layers
 1070 and two-layer neural networks of 50 units per layer. The normalizing flow architecture mapped
 1071 $z_0 \sim \mathcal{N}(\mathbf{0}, I)$ to a support of $\mathbf{z} = [\sigma_E, \sigma_P, \sigma_S, \sigma_V] \in [0.0, 0.5]^4$. EPI optimization was run using three
 1072 different random seeds for architecture initialization $\boldsymbol{\theta}$ with an augmented Lagrangian coefficient of
 1073 $c_0 = 10^{-1}$, a batch size $n = 100$, and $\beta = 2$. The distributions shown are those of the architectures
 1074 converging with criteria $N_{\text{test}} = 100$ at greatest entropy across random seeds.

1075 In Fig. 2E, we visualize the modes of $q_{\boldsymbol{\theta}}(\mathbf{z} \mid \mathcal{X})$ throughout the σ_E - σ_P marginal. Specifically, we
 1076 calculated

$$\begin{aligned} \mathbf{z}^*(\sigma_{P,\text{fixed}}) &= \underset{\mathbf{z}}{\operatorname{argmax}} \log q_{\boldsymbol{\theta}}(\mathbf{z} \mid \mathcal{X}) \\ \text{s.t. } \sigma_P &= \sigma_{P,\text{fixed}} \end{aligned} \quad (71)$$

1077 At each mode \mathbf{z}^* , we calculated the Hessian and visualized the sensitivity dimension in the direction
 1078 of positive σ_E .

1079 5.2.3 Primary visual cortex: challenges to analysis

1080 TODO Agostina and I are putting this together now.

1081 5.2.4 Superior colliculus

1082 In the model of Duan et al [49], there are four total units: two in each hemisphere corresponding to
 1083 the Pro/Contra and Anti/Ipsi populations. They are denoted as left Pro (LP), left Anti (LA), right
 1084 Pro (RP) and right Anti (RA). Each unit has an activity (x_α) and internal variable (u_α) related
 1085 by

$$x_\alpha = \phi(u_\alpha) = \left(\frac{1}{2} \tanh \left(\frac{u_\alpha - a}{b} \right) + \frac{1}{2} \right) \quad (72)$$

1086 where $\alpha \in \{LP, LA, RA, RP\}$, $a = 0.05$ and $b = 0.5$ control the position and shape of the nonlin-
 1087 earity, respectively. During periods of optogenetic inactivation, activity was decreased proportional
 1088 to the optogenetic strength γ

$$x_\alpha = (1 - \gamma)\phi(u_\alpha). \quad (73)$$

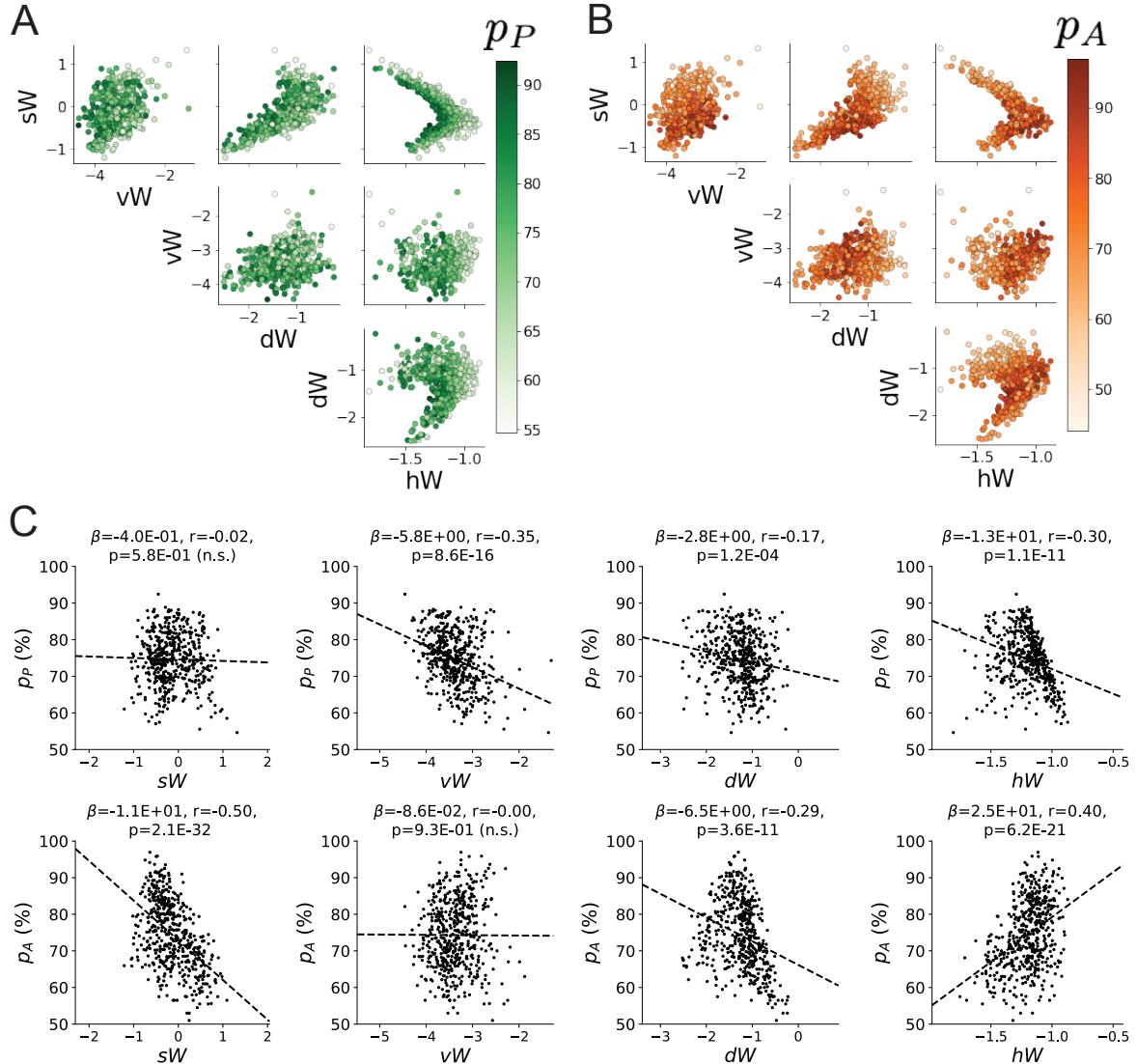


Figure 12: (SC1): **A.** Same pairplot as Fig. 3C colored by Pro task accuracy. **B.** Same as A colored by Anti task accuracy. **C.** Connectivity parameters of EPI distributions versus task accuracies. β is slope coefficient of linear regression, r is correlation, and p is the two-tailed p-value.

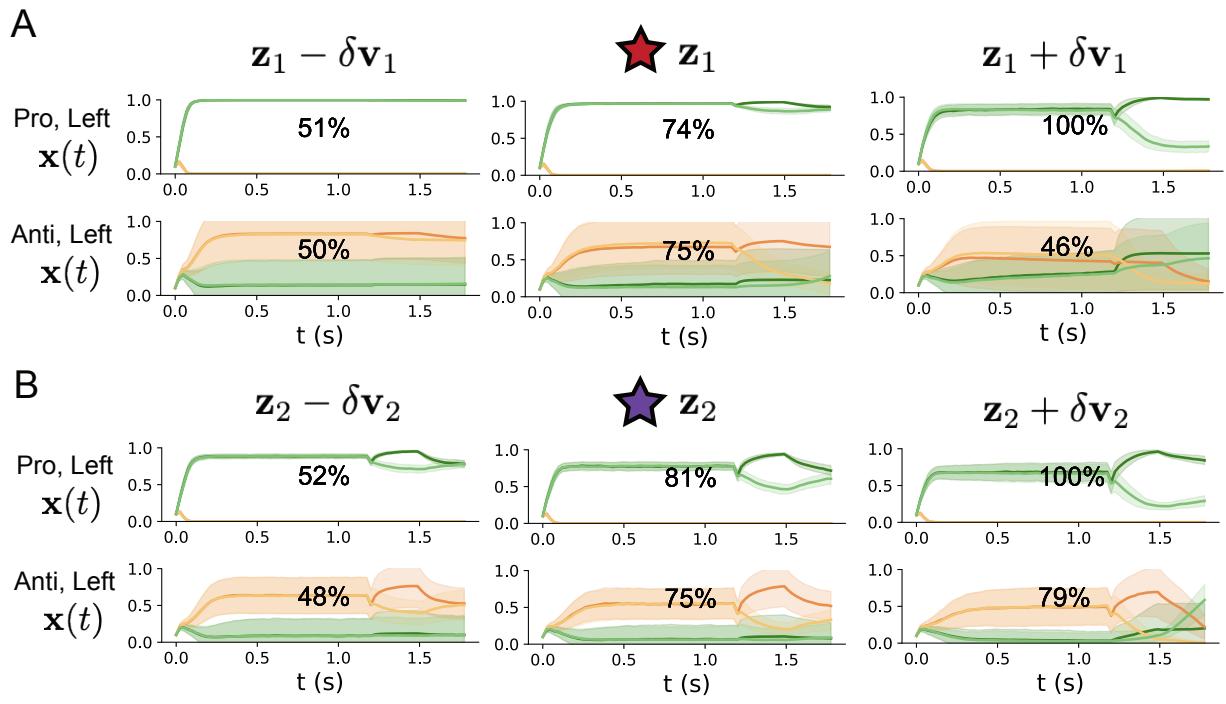


Figure 13: (SC2): **A.** Simulations in network regime \mathbf{z}_1 (center) with simulations given connectivity perturbations in the negative direction of the sensitivity vector \mathbf{v}_1 (left) and positive direction (right). **B.** Same as A for network regime \mathbf{z}_2 .

1089 We order the neural populations of x and u in the following manner

$$\mathbf{x} = \begin{bmatrix} x_{LP} \\ x_{LA} \\ x_{RP} \\ x_{RA} \end{bmatrix} \quad \mathbf{u} = \begin{bmatrix} u_{LP} \\ u_{LA} \\ u_{RP} \\ u_{RA} \end{bmatrix}, \quad (74)$$

1090 which evolve according to

$$\tau \frac{d\mathbf{u}}{dt} = -\mathbf{u} + W\mathbf{x} + \mathbf{h} + d\mathbf{B}. \quad (75)$$

1091 with time constant $\tau = 0.09s$, step size 24ms and Gaussian noise $d\mathbf{B}$ of variance 0.2^2 . The weight
1092 matrix has 4 parameters sW , vW , hW , and dW :

$$W = \begin{bmatrix} sW & vW & hW & dW \\ vW & sW & dW & hW \\ hW & dW & sW & vW \\ dW & hW & vW & sW \end{bmatrix}. \quad (76)$$

1093 The circuit receives four different inputs throughout each trial, which has a total length of 1.8s.

$$\mathbf{h} = \mathbf{h}_{\text{constant}} + \mathbf{h}_{\text{P,bias}} + \mathbf{h}_{\text{rule}} + \mathbf{h}_{\text{choice-period}} + \mathbf{h}_{\text{light}}. \quad (77)$$

1094 There is a constant input to every population,

$$\mathbf{h}_{\text{constant}} = I_{\text{constant}}[1, 1, 1, 1]^\top, \quad (78)$$

1095 a bias to the Pro populations

$$\mathbf{h}_{\text{P,bias}} = I_{\text{P,bias}}[1, 0, 1, 0]^\top, \quad (79)$$

1096 rule-based input depending on the condition

$$\mathbf{h}_{\text{P,rule}}(t) = \begin{cases} I_{\text{P,rule}}[1, 0, 1, 0]^\top, & \text{if } t \leq 1.2s \\ 0, & \text{otherwise} \end{cases} \quad (80)$$

1097

$$\mathbf{h}_{\text{A,rule}}(t) = \begin{cases} I_{\text{A,rule}}[0, 1, 0, 1]^\top, & \text{if } t \leq 1.2s \\ 0, & \text{otherwise} \end{cases}, \quad (81)$$

1098 a choice-period input

$$\mathbf{h}_{\text{choice}}(t) = \begin{cases} I_{\text{choice}}[1, 1, 1, 1]^\top, & \text{if } t > 1.2s \\ 0, & \text{otherwise} \end{cases}, \quad (82)$$

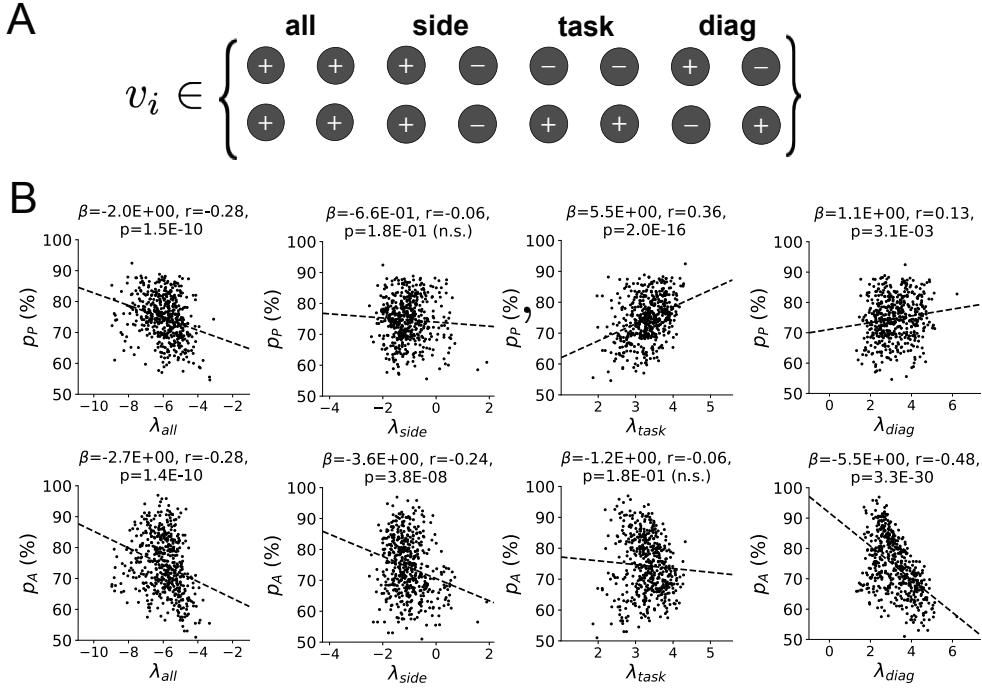


Figure 14: (SC3): **A.** Invariant eigenvectors of connectivity matrix W . **B.** Eigenvalues of connectivities of EPI distribution versus task accuracies.

1099 and an input to the right or left-side depending on where the light stimulus is delivered

$$\mathbf{h}_{\text{light}}(t) = \begin{cases} I_{\text{light}}[1, 1, 0, 0]^T, & \text{if } 1.2s < t < 1.5s \text{ and Left} \\ I_{\text{light}}[0, 0, 1, 1]^T, & \text{if } 1.2s < t < 1.5s \text{ and Right} \\ 0, & \text{otherwise} \end{cases} \quad (83)$$

1100 The input parameterization was fixed to $I_{\text{constant}} = 0.75$, $I_{P,\text{bias}} = 0.5$, $I_{P,\text{rule}} = 0.6$, $I_{A,\text{rule}} = 0.6$,
1101 $I_{\text{choice}} = 0.25$, and $I_{\text{light}} = 0.5$.

1102 The accuracies of p_P and p_A are calculated as

$$p_P(\mathbf{x}; \mathbf{z}) = \mathbb{E}_{\mathbf{x} \sim p(\mathbf{x}|\mathbf{z})} [\Theta[x_{LP}(t = 1.8s) - x_{RP}(t = 1.8s)]] \quad (84)$$

1103 and

$$p_A(\mathbf{x}; \mathbf{z}) = \mathbb{E}_{\mathbf{x} \sim p(\mathbf{x}|\mathbf{z})} [\Theta[x_{RP}(t = 1.8s) - x_{LP}(t = 1.8s)]] \quad (85)$$

1104 given that the stimulus is on the left side, where Θ is the Heaviside step function, and the accuracy
1105 is averaged over 200 independent trials. The Heaviside step function is approximated as

$$\Theta(\mathbf{x}) = \text{sigmoid}(\beta \mathbf{x}), \quad (86)$$

1106 where $\beta = 100$.

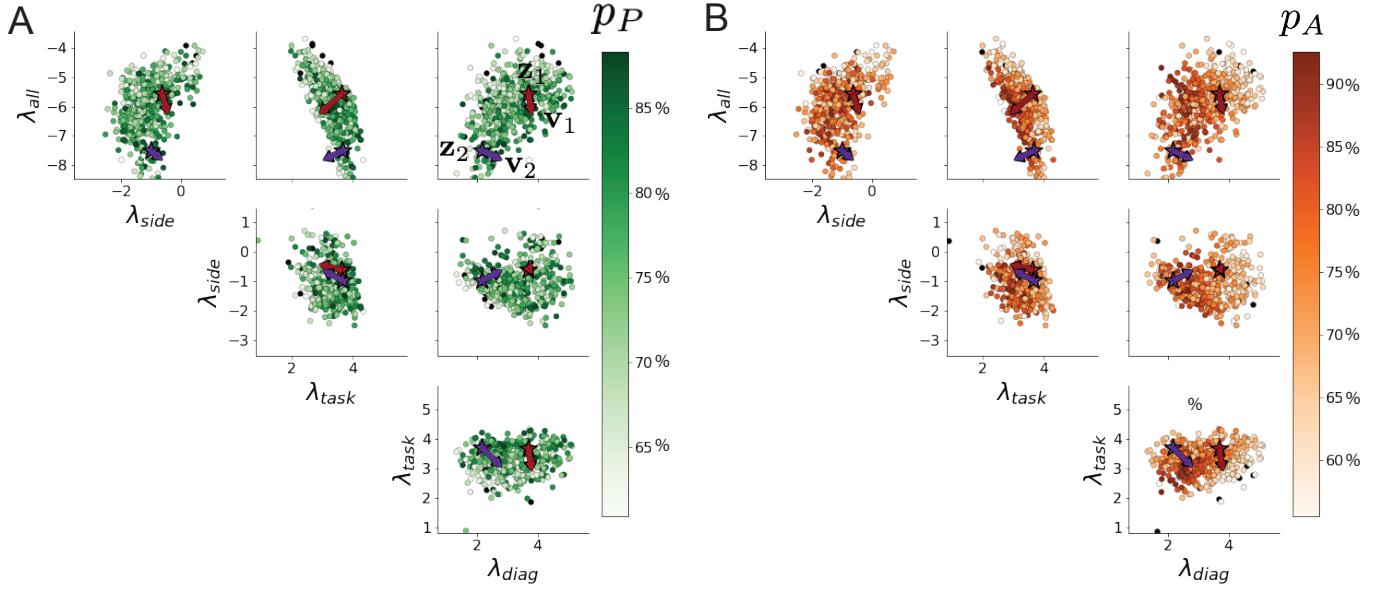


Figure 15: (SC4): **A.** Pairplots of eigenvalues of connectivity matrices in EPI distribution colored by Pro task accuracy. Red and purple stars and arrows correspond to eigenvalues and sensitivity directions \mathbf{z}_1 , \mathbf{z}_2 , \mathbf{v}_1 , and \mathbf{v}_2 . **B.** Same colored by Anti task accuracy.

1107 Writing the EPI posterior as a maximum entropy distribution, $T(\mathbf{x}; \mathbf{z})$ is comprised of both these
1108 first and second moments of the accuracy in each task (as in Equations 28 and 29)

$$T(\mathbf{x}; \mathbf{z}) = \begin{bmatrix} p(\mathbf{x}; \mathbf{z})_P \\ p(\mathbf{x}; \mathbf{z})_A \\ (p(\mathbf{x}; \mathbf{z})_P - 75\%)^2 \\ (p(\mathbf{x}; \mathbf{z})_A - 75\%)^2 \end{bmatrix}, \quad (87)$$

$$\mu_{opt} = \begin{bmatrix} 75\% \\ 75\% \\ 7.5\%^2 \\ 7.5\%^2 \end{bmatrix}. \quad (88)$$

1109 Throughout optimization, the augmented Lagrangian parameters η and c , were updated after each epoch of 2,000 iterations(see Section 5.1.3). The optimization converged after six epochs (Fig. 17).

1110 For EPI in Fig. 3C, we used a real NVP architecture with three coupling layers of affine transformations parameterized by two-layer neural networks of 50 units per layer. The initial distribution 1111 was a standard isotropic gaussian $z_0 \sim \mathcal{N}(\mathbf{0}, I)$ mapped to a support of $\mathbf{z}_i \in [-5, 5]$. We used an 1112 augmented Lagrangian coefficient of $c_0 = 10^2$, a batch size $n = 100$, and $\beta = 2$. The distribution 1113

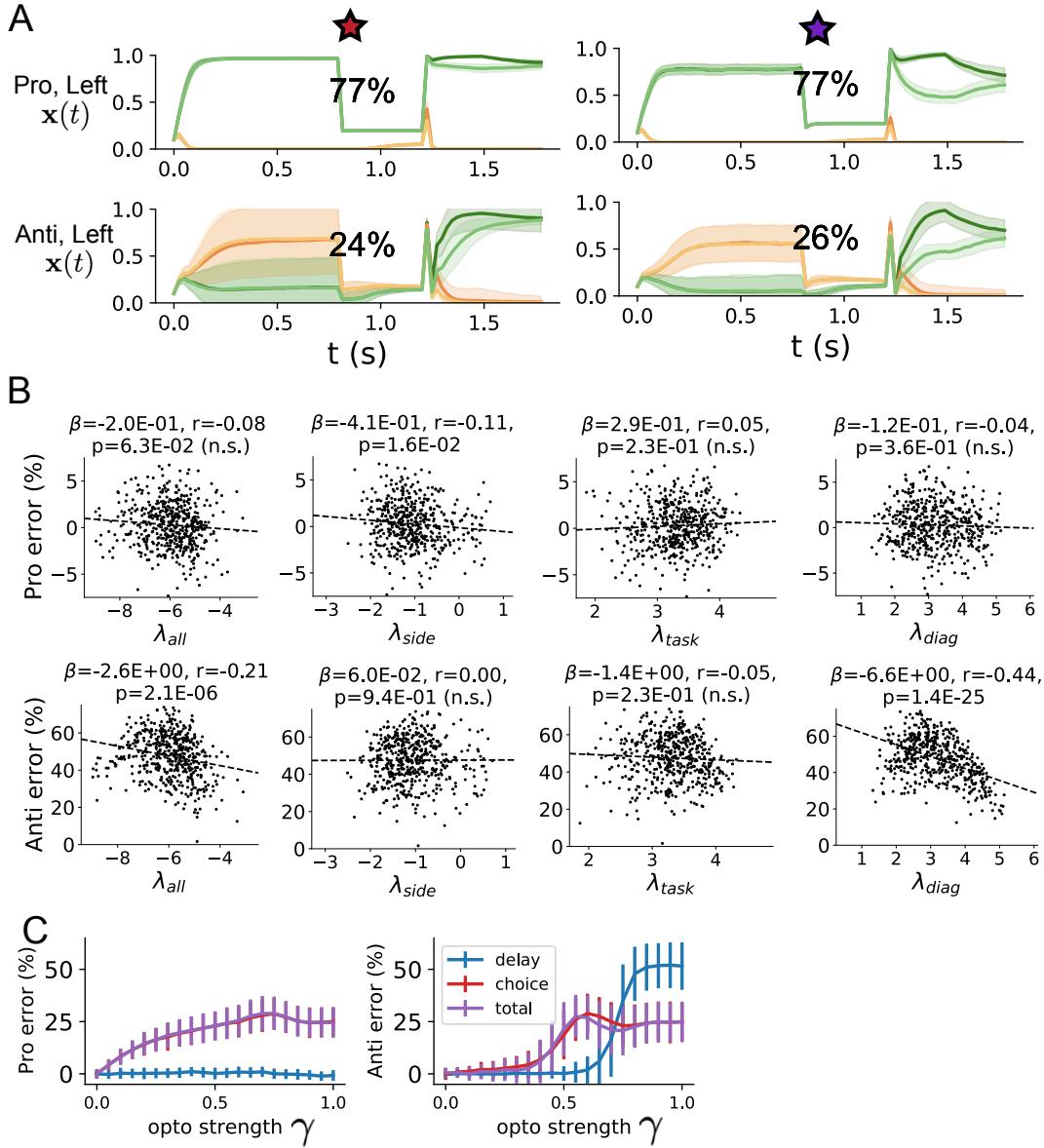


Figure 16: (SC5): **A.** Response of each parameter regime to optogenetic silencing during the delay period. **B.** Connectivity eigenvalues versus the task error induced by delay period inactivation. **C.** Error induced by delay period inactivation with increasing optogenetic strength. Means and standard deviations are calculated across the entire EPI posterior.

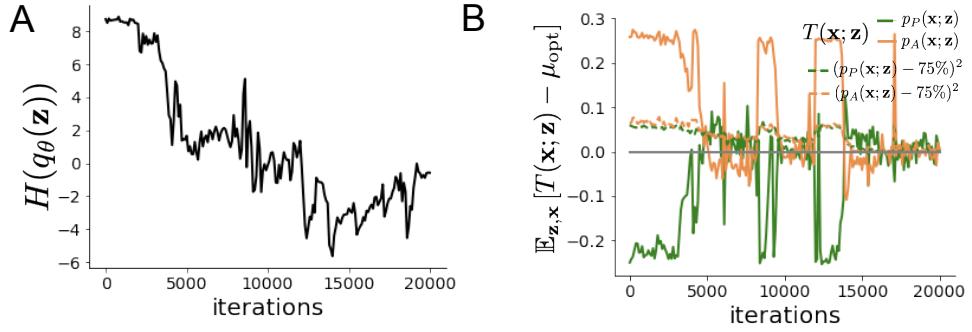


Figure 17: (SC6): **A.** Entropy throughout optimization. **B.** The emergent property statistic means and variances converge to their constraints at 20,000 iterations following the tenth augmented Lagrangian epoch.

1116 shown is that of the architecture converging with criteria $N_{\text{test}} = 25$ at greatest entropy across
1117 random seeds.

1118 To make sense of this inferred distribution, we identified two modes used to represent the two
1119 regimes of connectivity in this posterior:

$$\begin{aligned} \mathbf{z}_1 &= \underset{\mathbf{z}}{\operatorname{argmax}} \log q_\theta(\mathbf{z} \mid \mathcal{X}) \\ \text{s.t. } hw &= -1.25, sW > 0 \end{aligned} \tag{89}$$

1120 and

$$\begin{aligned} \mathbf{z}_2 &= \underset{\mathbf{z}}{\operatorname{argmax}} \log q_\theta(\mathbf{z} \mid \mathcal{X}) \\ \text{s.t. } hw &= -1.25, sW < 0 \end{aligned} \tag{90}$$

1121 To understand the connectivity mechanisms governing task accuracy, we took the eigendecomposi-
1122 tion of the symmetric connectivity matrices $W = V\Lambda V^{-1}$, which results in the same basis vectors
1123 \mathbf{v}_i for all W parameterized by \mathbf{z} (Fig. 14A). These basis vectors have intuitive roles in processing
1124 for this task, and are accordingly named the *all* mode - all neurons co-fluctuate, *side* mode - one
1125 side dominates the other, *task* mode - the Pro or Anti populations dominate the other, and *diag*
1126 mode - Pro- and Anti-populations of opposite hemispheres dominate the opposite pair. We found
1127 significant trends across the EPI posterior connectivities: the eigenvalues λ_{task} and λ_{diag} were cor-
1128 related with p_P , while λ_{all} was anticorrelated with p_P . λ_{all} , λ_{side} , and λ_{diag} were all significantly
1129 anticorrelated with p_A .

1130 Under this decomposition, we can re-visualize the posterior in eigenvalue space (Fig. 15). Fur-
1131 thermore, we can project the dimensions of sensitivity into eigenvalue space as well, giving us a
1132 more intuitive sense of how connectivity affects computation in each regime. We see that sensitivity

1133 dimensions \mathbf{v}_1 and \mathbf{v}_2 , which cause p_P to increase and a regime dependent change in p_A , both point
 1134 in the direction of increasing λ_{side} and decreasing λ_{task} . These eigenvalue changes are evident in
 1135 the simulations of connectivity perturbations away from the modes (Fig. 13). As the component
 1136 of connectivity along \mathbf{v}_1 and \mathbf{v}_2 becomes stronger (left-to-right), there is less separation between
 1137 Pro an Anti populations (lower λ_{task}) and greater separation between Left and Right populations
 1138 following stimulus presentation (greater λ_{side}). A key differentiating factor is that \mathbf{v}_1 substantially
 1139 increases λ_{diag} , while \mathbf{v}_2 does not.

1140 During optogenetic silencing simulations, activations $x_\alpha(t)$ were set to a fraction of their values $(1 -$
 1141 $\gamma)$, where γ is the optogenetic perturbation strength. We found that λ_{all} and λ_{diag} were significantly
 1142 anticorrelated with Anti error during delay period inactivation. Delay period inactivation was from
 1143 $0.8 < t < 1.2$, choice period inactivation was for $t > 1.2$ and total inactivation was for the entire
 1144 trial.

1145 5.2.5 Scaling EPI for stable amplification in RNNs

1146 We examine the scaling properties of EPI by learning connectivities of RNNs of increasing size
 1147 that exhibit stable amplification. Rank-2 RNN connectivity is modeled as $W = UV^\top$, where
 1148 $U = [\mathbf{u}_1 \ \mathbf{u}_2] + g\chi^{(W)}$, $V = [\mathbf{v}_1 \ \mathbf{v}_2] + g\chi^{(V)}$, and $\chi_{i,j}^{(W)}, \chi_{i,j}^{(V)} \sim \mathcal{N}(0, 1)$. This RNN model has
 1149 dynamics

$$\tau \dot{\mathbf{x}} = -\mathbf{x} + W\mathbf{x}. \quad (91)$$

1150 In this analysis, we infer connectivity parameterizations $\mathbf{z} = [\mathbf{u}_1^\top, \mathbf{u}_2^\top, \mathbf{v}_1^\top, \mathbf{v}_2^\top]^\top \in [-1, 1]^{(4N)}$ that
 1151 produce stable amplification using EPI, SMC-ABC [40], and SNPE [42] (see Section 5.1.1).

1152 For this RNN model to be stable, all real eigenvalues of W must be less than 1: $\text{real}(\lambda_1) < 1$,
 1153 where λ_1 denotes the greatest real eigenvalue of W . For a stable RNN to amplify at least one input
 1154 pattern, the symmetric connectivity $W^s = \frac{W+W^\top}{2}$ must have an eigenvalue greater than 1: $\lambda_1^s > 1$,
 1155 where λ^s is the maximum eigenvalue of W^s . These two conditions are necessary and sufficient for
 1156 stable amplification in RNNs [50]. We define the emergent property of stable amplification with
 1157 means of these eigenvalues (0.5 and 1.5, respectively) that satisfy these conditions. To complete
 1158 the emergent property definition, we chose variances (0.25^2) about those means such that samples
 1159 rarely violate the eigenvalue constraints. In terms of the EPI optimization variables, this is written

1160 as

$$T(\mathbf{x}; \mathbf{z}) = \begin{bmatrix} \text{real}(\lambda_1)(\mathbf{x}; \mathbf{z}) \\ \lambda_1^s(\mathbf{x}; \mathbf{z}) \\ (\text{real}(\lambda_1)(\mathbf{x}; \mathbf{z}) - 0.5)^2 \\ (\lambda_1^s(\mathbf{x}; \mathbf{z}) - 1.5)^2 \end{bmatrix}, \quad (92)$$

1161

$$\boldsymbol{\mu}_{\text{opt}} = \begin{bmatrix} 0.5 \\ 1.5 \\ 0.25^2 \\ 0.25^2 \end{bmatrix}. \quad (93)$$

1162 Gradients of maximum eigenvalues of hermitian matrices like W^s are available with modern auto-
 1163 automatic differentiation tools. To differentiate through the $\text{real}(\lambda_1)$, we solve the following equation
 1164 for eigenvalues of rank-2 matrices using the rank reduced matrix $W^r = V^\top U$

$$\lambda_{\pm} = \frac{\text{Tr}(W^r) \pm \sqrt{\text{Tr}(W^r)^2 - 4\text{Det}(W^r)}}{2}. \quad (94)$$

1165 For EPI in Fig. 4, we used a real NVP architecture with three coupling layers of affine transfor-
 1166 mations parameterized by two-layer neural networks of 100 units per layer. The initial distribution
 1167 was a standard isotropic gaussian $z_0 \sim \mathcal{N}(\mathbf{0}, I)$ mapped to the support of $\mathbf{z}_i \in [-1, 1]$. We used
 1168 an augmented Lagrangian coefficient of $c_0 = 10^3$, a batch size $n = 200$, $\beta = 4$, and chose to use
 1169 500 iterations per augmented Lagrangian epoch and emergent property constraint convergence was
 1170 evaluated at $N_{\text{test}} = 200$ (Fig. 4B blue line, and Fig. 4C-D blue).

1171 We compared EPI to two alternative likelihood-free inference (LFI) techniques, since the likelihood
 1172 of these eigenvalues given \mathbf{z} is not available. Approximate Bayesian computation (ABC) [79] is a
 1173 rejection sampling technique for obtaining sets of parameters \mathbf{z} that produce activity \mathbf{x} close to some
 1174 observed data \mathbf{x}_0 . Sequential Monte Carlo approximate Bayesian computation (SMC-ABC) is the
 1175 state-of-the-art ABC method, which leverages SMC techniques to improve sampling speed. We ran
 1176 SMC-ABC with the pyABC package [108] to infer RNNs with stable amplification: connectivities
 1177 having eigenvalues within an ϵ -defined l_2 distance of

$$x_0 = \begin{bmatrix} \text{real}(\lambda_1) \\ \lambda_1^s \end{bmatrix} = \begin{bmatrix} 0.5 \\ 1.5 \end{bmatrix}. \quad (95)$$

1178 SMC-ABC was run with a uniform prior over $\mathbf{z} \in [-1, 1]^{(4N)}$, a population size of 1,000 particles
 1179 with simulations parallelized over 32 cores, and a multivariate normal transition model.

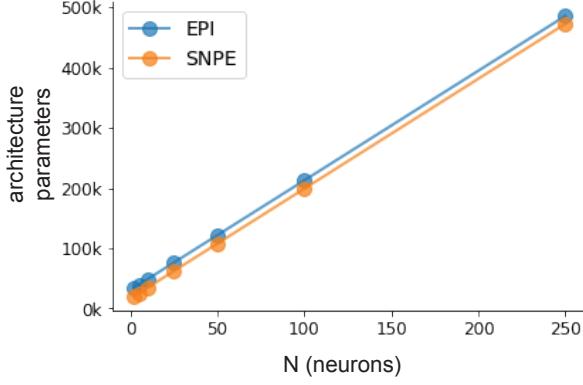


Figure 18: (RNN1): Number of parameters in deep probability distribution architectures of EPI (blue) and SNPE (orange) by RNN size (N).

1180 SNPE, the next LFI approach in our comparison, is far more similar to EPI. Like EPI, SNPE
 1181 models parameters in mechanistic models with deep probability distributions, yet their learning
 1182 algorithms are categorically different. SNPE uses a two-network architecture to approximate the
 1183 posterior distribution of the model conditioned on observed data \mathbf{x}_0 . The amortizing network maps
 1184 observations \mathbf{x}_i to the parameters of the deep probability distribution. The weights and biases of the
 1185 parameter network are optimized by sequentially augmenting the training data with additional pairs
 1186 $(\mathbf{z}_i, \mathbf{x}_i)$ based on the most recent posterior approximation. This sequential procedure is important
 1187 to get training data \mathbf{z}_i to be closer to the true posterior, and \mathbf{x}_i to be closer to the observed data.
 1188 For the deep probability distribution architecture, we chose a masked autoregressive flow with affine
 1189 couplings (the default choice), three transforms, 50 hidden units, and a normalizing flow mapping
 1190 to the support as in EPI. This architectural choice closely tracked the size of the architecture used
 1191 by EPI (Fig. 18). As in SMC-ABC, we ran SNPE with $\mathbf{x}_0 = \mu$. All SNPE optimizations were
 1192 run for a limit of 1.5 days on a Tesla V100 GPU, or until two consecutive rounds resulted in a
 1193 validation log probability lower than the maximum observed.

1194 To clarify the difference in objectives of EPI and SNPE, we show their results on RNN models
 1195 with different numbers of neurons N and random strength g . The parameters inferred by EPI
 1196 consistently produces the same mean and variance of $\text{real}(\lambda_1)$ and λ_1^s , while those inferred by
 1197 SNPE change according to the model definition (Fig. 19A). For $N = 2$ and $g = 0.01$, the SNPE
 1198 posterior has greater concentration in eigenvalues around \mathbf{x}_0 than at $g = 0.1$, where the model has
 1199 greater uncertainty (Fig. 19B top, orange). At both levels of g when $N = 2$, the posterior of SNPE
 1200 has lower entropy than EPI at convergence (Fig. 19B top). However at $N = 10$, SNPE results in

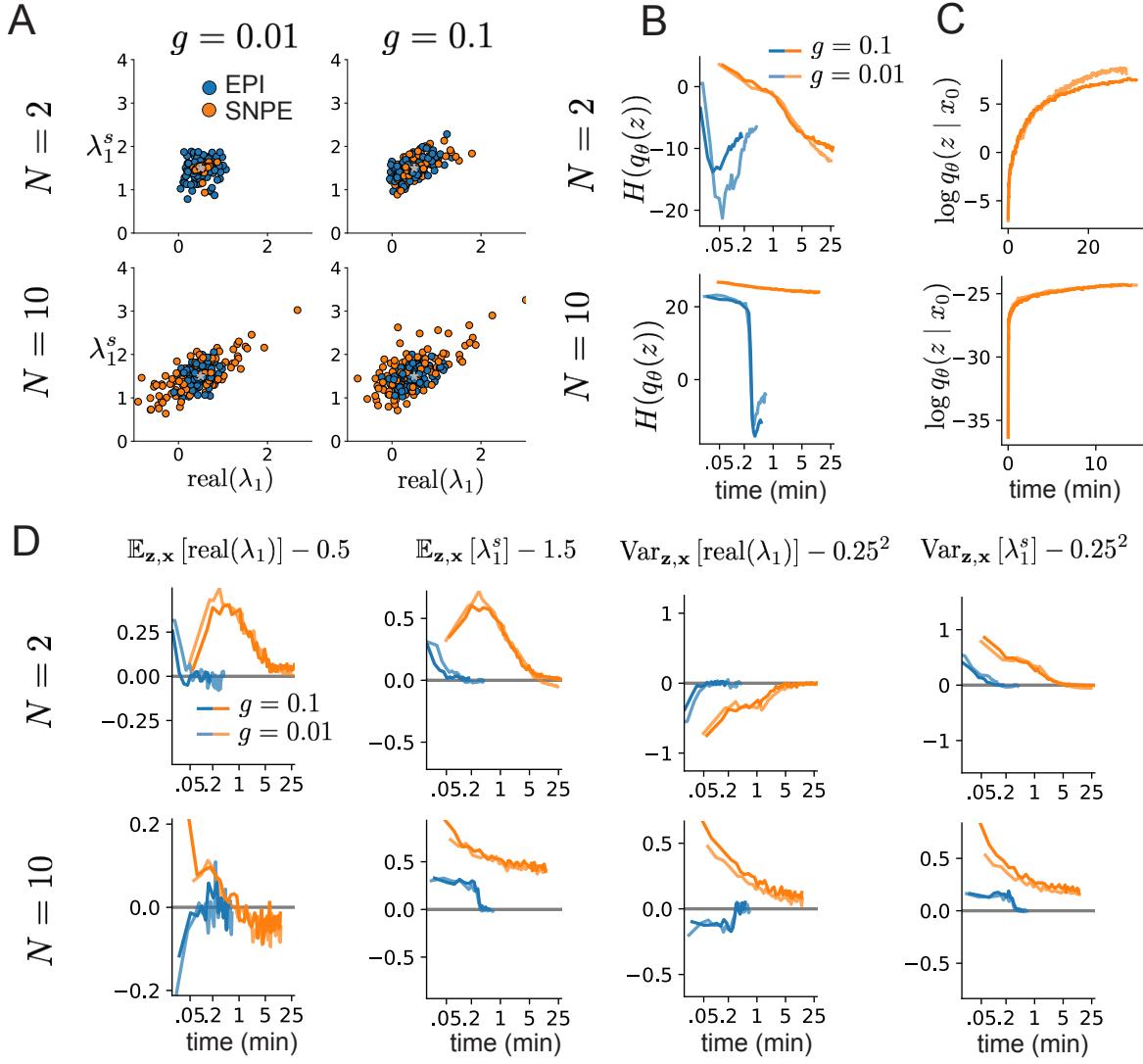


Figure 19: (RNN2): Model characteristics affect predictions of posteriors inferred by SNPE, while predictions of parameters inferred by EPI remain fixed. **A.** Predictive distribution of EPI (blue) and SNPE (orange) inferred connectivity of RNNs exhibiting stable amplification with $N = 2$ (top), $N = 10$ (bottom), $g = 0.01$ (left), and $g = 0.1$ (right). **B.** Entropy of parameter distribution approximations throughout optimization with $N = 2$ (top), $N = 10$ (bottom), $g = 0.1$ (dark shade), and $g = 0.01$ (light shade). **C.** Validation log probabilities throughout SNPE optimization. Same conventions as B. **D.** Adherence to EPI constraints. Same conventions as B.

1201 a predictive distribution of more widely dispersed eigenvalues (Fig. 19A bottom), and an inferred
1202 posterior with greater entropy than EPI (Fig. 19B bottom). We highlight these differences not
1203 to focus on an insightful trend, but to emphasize that these methods optimize different objectives
1204 with different implications.

1205 Note that SNPE converges when it's validation log probability has saturated after several rounds
1206 of optimization (Fig. 19C), and that EPI converges after several epochs of its own optimization
1207 to enforce the emergent property constraints (Fig. 19D blue). Importantly, as SNPE optimizes
1208 its posterior approximation, the predictive means change, and at convergence may be different
1209 than \mathbf{x}_0 (Fig. 19D orange, left). It is sensible to assume that predictions of a well-approximated
1210 SNPE posterior should closely reflect the data on average (especially given a uniform prior and
1211 a low degree of stochasticity), however this is not a given. Furthermore, no aspect of the SNPE
1212 optimization controls the variance of the predictions (Fig. 19D orange, right).

1213 To compare the efficiency of these algorithms for inferring RNN connectivity distributions producing
1214 stable amplification, we develop a convergence criteria that can be used across methods. While EPI
1215 has its own hypothesis testing convergence criteria for the emergent property, it would not make
1216 sense to use this criteria on SNPE and SMC-ABC which do not constrain the means and variances
1217 of their predictions. Instead, we consider EPI and SNPE to have converged after completing its
1218 most recent optimization epoch (EPI) or round (SNPE) in which the distance

$$d(q_\theta(z)) = |\mathbb{E}_{\mathbf{z}, \mathbf{x}} [f(\mathbf{x}; \mathbf{z})] - \boldsymbol{\mu}|_2 \quad (96)$$

1219 is less than 0.25. We consider SMC-ABC to have converged once the population produces samples
1220 within the $\epsilon = 0.5$ ball ensuring stable amplification.

1221 When assessing the scalability of SNPE, it is important to check that alternative hyperparameter-
1222 izations could not yield better performance. Key hyperparameters of the SNPE optimization are
1223 the number of simulations per round n_{round} , the number of atoms used in the atomic proposals of
1224 the SNPE-C algorithm [109], and the batch size n . To match EPI, we used a batch size of $n = 200$
1225 for $N \leq 25$, however we found $n = 1,000$ to be helpful for SNPE in higher dimensions. While
1226 $n_{\text{round}} = 1,000$ yielded SNPE convergence for $N \leq 25$, we found that a substantial increase to
1227 $n_{\text{round}} = 25,000$ yielded more consistent convergence at $N = 50$ (Fig. 20A). By increasing n_{round} ,
1228 we also necessarily increase the duration of each round. At $N = 100$, we tried two hyperparameter
1229 modifications. As suggested in [109], we increased n_{atom} by an order of magnitude to improve
1230 gradient quality, but this had little effect on the optimization (much overlap between same random

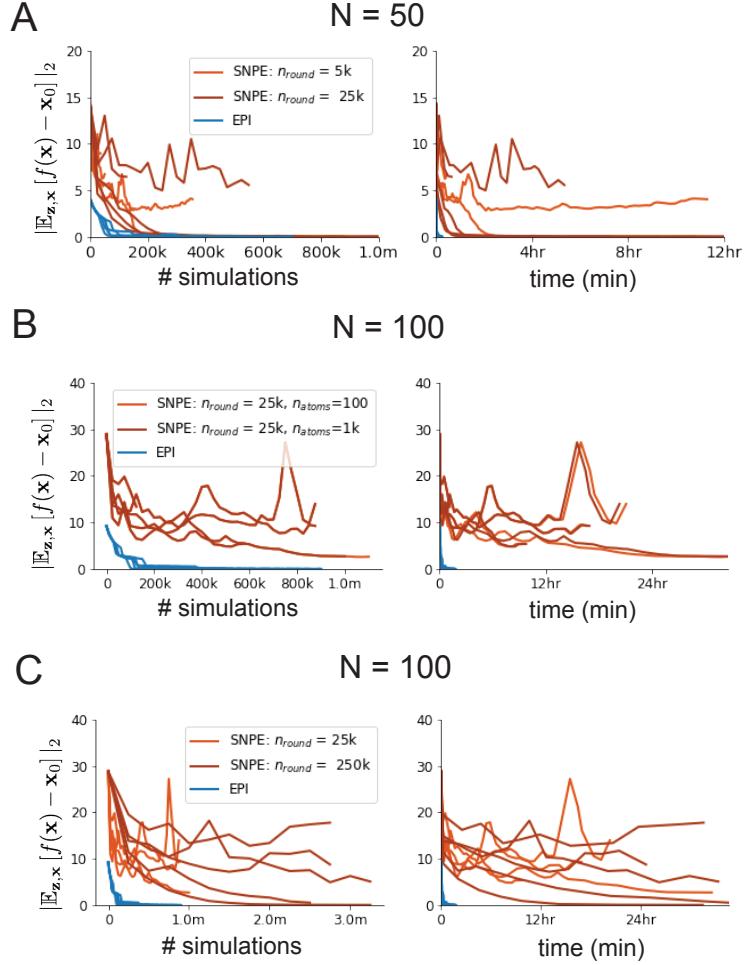


Figure 20: (RNN3): SNPE convergence was enabled by increasing n_{round} , not n_{atom} . **A.** Difference of mean predictions \mathbf{x}_0 throughout optimization at $N = 50$ with by simulation count (left) and wall time (right) of SNPE with $n_{\text{round}} = 5,000$ (light orange), SNPE with $n_{\text{round}} = 25,000$ (dark orange), and EPI (blue). Each line shows an individual random seed. **B.** Same conventions as A at $N = 100$ of SNPE with $n_{\text{atom}} = 100$ (light orange) and $n_{\text{atom}} = 1,000$ (dark orange). **C.** Same conventions as A at $N = 100$ of SNPE with $n_{\text{round}} = 25,000$ (light orange) and $n_{\text{round}} = 250,000$ (dark orange).

₁₂₃₁ seeds) (Fig. 20B). Finally we increased n_{round} by an order of magnitude, which yielded convergence
₁₂₃₂ in one case, but no others. We found no way to improve the convergence rate of SNPE without
₁₂₃₃ making more aggressive hyperparameter choices requiring high numbers of simulations.