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# ***Supplementary Material:***

## **Criteria on balance, stability, and excitability in cortical networks for constraining computational models**

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### **1 BRAIN SLICES AS A SUITABLE MODEL FOR STUDYING LOCAL CIRCUIT DYNAMICS**

Since the invention of the brain slice preparation in 1957 by Henry McIlwain Collingridge (1995), it has become a widely used and powerful experimental tool in neuroscience. A vast amount of knowledge about local brain circuitry and cellular and synaptic mechanisms is obtained with this approach Dingledine et al. (1980); Andersen (1981); Steriade (2001). Methodological difficulties in minimizing tissue damage and assuring similarity of artificial cerebrospinal fluid (aCSF) in slices to in-vivo conditions have been gradually overcome Lipton (1985); Reid et al. (1988); Hájos et al. (2009); Varela et al. (2012). Optimization of brain slicing procedures combined with a proper incubation solution can substantially increase neuronal viability Richerson and Messer (1995); Moyer and Brown (1998); Ye et al. (2006); Tanaka et al. (2008); Huang and Uusisaari (2013); Buskila et al. (2014), keeping up to 60–70% of cells alive in the first 10 hours after slicing even in adult animals Buskila et al. (2014). The ionic composition and oxygenation of aCSF nowadays tend to be more carefully matched to values measured in intact brains. Realistic oxygen availability Turner et al. (2007); Hájos and Mody (2009); Hájos et al. (2009); Ivanov and Zilberter (2011) in combination with a  $K^+$  concentration matched to that measured in vivo (Table S1 on page 3) leads to the emergence of complex activity (so-called Up-Down oscillations) in organotypic and acute slices, either spontaneously Plenz and Kitai (1996); Klostermann and Wahle (1999); Sanchez-Vives and McCormick (2000); McCormick et al. (2003); Seamans et al. (2003); Shu et al. (2003); Hasenstaub et al. (2005); MacLean et al. (2005); Haider et al. (2006); Watson et al. (2008); Compte et al. (2009a); Faselow and Connors (2010); Tahvildari et al. (2012); Wester and Contreras (2012) or upon brief stimulation MacLean et al. (2005); Watson et al. (2008); Wester and Contreras (2012). This activity is characterized by periods of silence (Down states) intermingled with prolonged periods of asynchronous activity (Up states), and is in many respects similar to activity observed in sleeping Timofeev et al. (2000, 2001); Volgushev et al. (2006); Chauvette et al. (2010, 2011), anesthetized Steriade et al. (1993); Lampl et al. (1999); Timofeev et al. (2000); Kerr et al. (2005); Waters and Helmchen (2006); Sakata and Harris (2009); Chen et al. (2012); Beltramo et al. (2013), and awake attentive animals Destexhe et al. (2007).

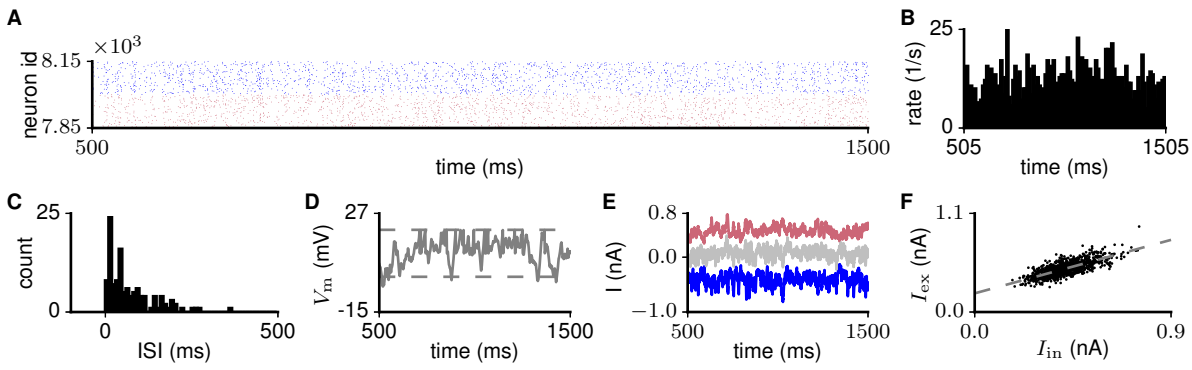
Despite differences between in-vitro and in-vivo experimental conditions, it has been shown that single-neuron and synaptic properties are well preserved in slice preparations. The relevant experiments are most easily performed in conditions of low background synaptic activity (for example during the Down state in Up-Down oscillations; Timofeev et al. (2001); Haider et al. (2006); Chauvette et al. (2010, 2011)), as this provides a greater degree of control than high-input conditions. Experiments suggest the qualitative preservation of several prominent neuronal properties: firing patterns in response to somatic current injection (in vivo: Nunez et al. (1993); Degenetais et al. (2002); Nowak et al. (2003), in vitro: Mason and Larkman (1990); Yang et al. (1996)), back-propagation of action potentials into dendrites Waters et al. (2003), I-V curves (in vivo: Degenetais et al. (2002); Waters and Helmchen (2006), in vitro: Mason and Larkman (1990); Kasper et al. (1994); Yang et al. (1996); Zaitsev et al. (2012)), f-I curves (in vivo: Nowak et al. (2003), in vitro: Mason and Larkman (1990); Chen et al. (1996); Zaitsev et al. (2012)) and NMDA-channel-evoked dendritic nonlinearities (in vivo: Palmer et al. (2014), in vitro: Schiller et al. (2000)). This suggests that the intraneuronal molecular machinery remains largely intact after the slicing and incubation procedure. Similarly, basic synaptic kinetics are largely preserved at least in the low-activity regime (in vivo: Pala and Petersen (2015), in vitro: Avermann et al. (2012)). Additionally, multiple experiments reveal high synaptic connectivity in sliced tissue Fino and Yuste (2011); Packer and Yuste (2011); Avermann et al. (2012), pointing to the preservation of local circuitry. Synaptic reliability on average is lower in in-vivo conditions, which leads to less prominent synaptic depression Borst (2010); Pala and Petersen (2015). However, these differences are well explained by higher rates of ongoing activity and the lower concentration of  $\text{Ca}^{2+}$  ions in in-vivo cerebrospinal fluid compared to the standard ionic compositions used in vitro (Table S1 on page 3; Tsodyks and Markram (1997); Dittman and Regehr (1998); Borst (2010)). Moreover, as can be seen in Table S1 on page 3, in-vivo-like (Up-state) activity has been observed in slice experiments with a wide range of ionic compositions, especially for  $[\text{K}^+]$ ,  $[\text{Mg}^{2+}]$ , and  $[\text{Ca}^{2+}]$ .

In Up states as measured in vitro, all neurons synchronously undergo large depolarization with moderate subthreshold membrane potential fluctuations, occasionally exceeding the spiking threshold and resulting in irregular spiking with a typical firing rate below 10 spikes/s in excitatory neurons Sanchez-Vives and McCormick (2000); McCormick et al. (2003); Shu et al. (2003); Hasenstaub et al. (2005); Watson et al. (2008); Fanselow and Connors (2010), resembling in-vivo activity. The main source of the prolonged neuronal depolarization is synaptic input, while non-synaptic voltage-dependent conductances contribute less, as can be concluded from the abolition of activity by blockade of glutamate receptors Sanchez-Vives and McCormick (2000); Beierlein et al. (2002); Compte et al. (2003); McCormick et al. (2003); Shu et al. (2003); Mann et al. (2009); Runfeldt et al. (2014), and the robustness of transitions between Up and Down states to neuronal hyperpolarization Sanchez-Vives and McCormick (2000); McCormick et al. (2003); Shu et al. (2003); Haider et al. (2006); Waters and Helmchen (2006). In-vivo-like activity is consistently observed in slices as long as the oxygen content is high Turner et al. (2007); Hájos and Mody (2009); Hájos et al. (2009); Ivanov and Zilberter (2011). Also, current source density analysis after electrical stimulation Kenan-Vaknin and Teylor (1994) demonstrates the preservation of the major activation pathways in vitro. Overall, we conclude that acute and organotypic cortical slices to a good approximation preserve network operation. Combined with the fact that slice activity is not confounded by input from the rest of the brain, this means that slices represent a convenient basic model of local brain circuitry.

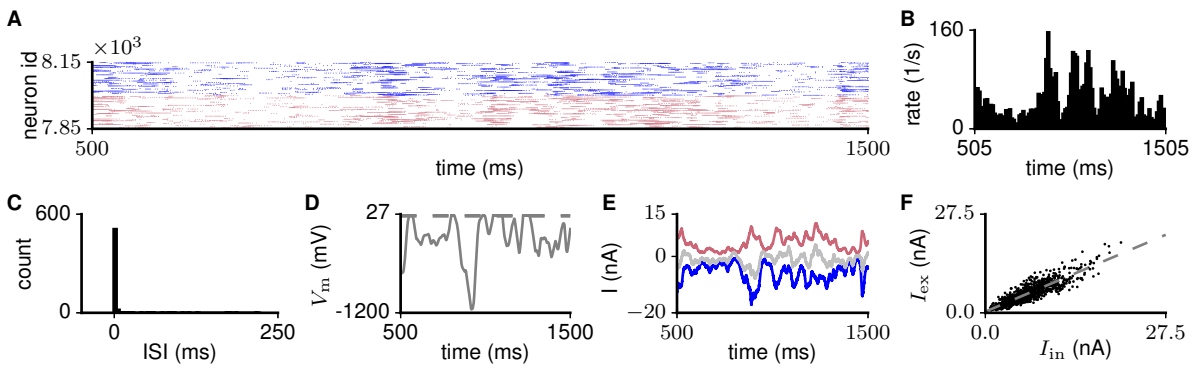
## 2 SUPPLEMENTARY TABLES AND FIGURES

|   | species        | area   | age    | [Na <sup>+</sup> ]<br>(mM) | [K <sup>+</sup> ]<br>(mM) | [Mg <sup>2+</sup> ]<br>(mM) | [Ca <sup>2+</sup> ]<br>(mM) | [Cl <sup>-</sup> ]<br>(mM) |
|---|----------------|--------|--------|----------------------------|---------------------------|-----------------------------|-----------------------------|----------------------------|
| <b>Slices with spontaneous activity or activity evoked by brief stimulation</b> |                |        |        |                            |                           |                             |                             |                            |
| Sanchez-Vives et al. (2010)   | ferret         | PFC, V | adult  | 153                        | 3.5                       | 1                           | 1; 1.2                      | 132                        |
| Compte et al. (2009b)   | ferret         | PFC, V | adult  | 151                        | 3.5                       | 1                           | 1; 1.2                      | 131                        |
| Hasenstaub et al. (2005)  | ferret         | PFC    | adult  | 153                        | 3.5                       | 1                           | 1                           | 132                        |
| McCormick et al. (2003)   | ferret         | PFC    | adult  | 153                        | 3.5                       | 1                           | 1; 1.2                      | 132                        |
| Shu et al. (2003)   | ferret         | PFC    | adult  | 153                        | 3.5                       | 1                           | 1; 1.2                      | 132                        |
| Sanchez-Vives and McCormick (2000)  | ferret         | PFC, V | adult  | 153                        | 3.5                       | 1                           | 1; 1.2                      | 132                        |
| Sippy and Yuste (2013)  | mouse          | S      | P13–35 | 150                        | 3                         | 2                           | 2                           | 130                        |
| Fanselow and Connors (2010)   | mouse          | S      | P12–17 | 153                        | 3                         | 1                           | 1                           | 129                        |
| MacLean et al. (2005); Watson et al. (2008)                                     | mouse          | S      | P14–18 | 150                        | 3                         | 2                           | 2                           | 130                        |
| Le Bon-Jego and Yuste (2007)  | mouse          | V      | P14–17 | 150                        | 3.5                       | 1                           | 1.2                         | 129                        |
| Cossart et al. (2003)   | mouse          | V      | P14–21 | 150                        | 3                         | 2                           | 2                           | 130                        |
| Case and Broberger (2013)   | rat            | S      | P21–35 | 151                        | 3.5                       | 1                           | 1                           | 129.5                      |
| Wester and Contreras (2012)   | rat            | S      | P14–23 | 152                        | 3                         | 2                           | 2                           | 133                        |
| Mann et al. (2009)  | rat            | ent    | P13–21 | 153                        | 3; 3.5                    | 2                           | 2                           | 133                        |
| Bar-Yehuda and Korngreen (2007)   | rat            | cortex | P13–15 | 141                        | 3.5                       | 1                           | 1.2                         | 132                        |
| <b>Slices without background activity</b>                                       |                |        |        |                            |                           |                             |                             |                            |
| Sanchez-Vives and McCormick (2000)  | cat;<br>ferret | V      |        | 151                        | 2.5                       | 2                           | 2                           | 130                        |
| Feldmeyer et al. (1999, 2006)   | rat            | S      | P12–15 | 151                        | 2.5                       | 1                           | 2                           | 133                        |
| Avermann et al. (2012)  | mouse          | S      | P17–22 | 151                        | 2.5                       | 1                           | 2                           | 133                        |
| <b>In-vivo measurements</b>   |                |        |        |                            |                           |                             |                             |                            |
| Somjen (2004)   | rat            | cortex |        | 152                        | 3.4                       | 1.3                         | 1.1                         |                            |
| McNay and Sherwin (2004)  | rat            | hippoc | P90    | 153.5                      | 4.3                       | 0.4                         | 0.718                       | 139.4                      |
| Jones and Keep (1988)   | rat            | cortex | P30    |                            |                           |                             | 1.2                         |                            |
| Jones and Keep (1987)   | rat            | cortex | P30    |                            | 3.3                       |                             |                             |                            |
| Moghaddam and Adams (1987)  | rat            | cortex |        |                            | 3.36                      |                             |                             |                            |
| Pumain and Heinemann (1985)   | rat            | M      | adult  |                            | 2.8                       |                             | 1.25                        |                            |
| Siemkiewicz and Hansen (1981)   | rat            | cortex | adult  |                            | 2.8                       |                             | 1.2                         |                            |
| Nicholson et al. (1977)   | rat            | cereb  |        |                            | 3                         |                             | 1.1                         |                            |
| Korytova (1977)   | rat            | cortex |        |                            | 3                         |                             |                             |                            |
| Dufour et al. (2011)  | cat            | cortex | adult  |                            | 3.25                      |                             |                             |                            |
| Amzica et al. (2002)  | cat            | cortex |        |                            | 3.2                       |                             | 1.1                         |                            |
| Massimini and Amzica (2001)   | cat            | cortex | adult  |                            |                           |                             | 1.1                         |                            |
| Nicholson et al. (1978)   | cat            | cereb  |        |                            | 3                         |                             | 1.2                         |                            |
| Moody et al. (1974)   | cat            | cortex | adult  |                            | 3.4                       |                             |                             |                            |
| Lux and Neher (1973)  | cat            | cortex |        |                            | 3.2                       |                             |                             |                            |
| Prince et al. (1973)  | cat            | cortex |        |                            | 3.25                      |                             |                             |                            |
| Sun et al. (2009)   | mouse          | CSF    | P56    |                            |                           | 0.89                        |                             |                            |
| Davson et al. (1987)  | rabbit         | CSF    |        | 149                        | 2.9                       | 1.74                        | 2.47                        | 130                        |

Table S1 Ion composition of aCSF in slice experiments with (top) and without (middle) substantial spiking activity compared to the composition of interstitial fluid and CSF in the intact brain (bottom). Columns from left to right: species, brain area, age of the animal, and concentration of Na<sup>+</sup>, K<sup>+</sup>, Mg<sup>2+</sup>, Ca<sup>2+</sup>, Cl<sup>-</sup> ions in mM. **S**, **V**, **M**, **ent**, **PFC** - somatosensory, visual, motor, entorhinal, and prefrontal cortices; **cortex** - exact cortical area is unknown; **cereb** - cerebellum; **hippoc** - hippocampus. Empty fields indicate that no data are reported. Where two values are given, both were used.



**Figure S1.** Characterization of activity in the balanced random network model with exponentially-shaped synapses and  $PSP_{e←e} = 0.2$  mV. (A) Raster plot of 150 excitatory (red) and 150 inhibitory (blue) neurons out of the total of 10000 neurons. (B) Population firing rate histogram of excitatory neurons with a bin width of 10 ms. (C–F) Dynamical properties of a typical excitatory neuron. (C) Interspike interval histograms. (D) Membrane potential traces. Dashed lines indicate the resting and threshold potentials. (E) Excitatory (red), inhibitory (blue) and summed (gray) input currents. (F) Excitatory versus inhibitory currents averaged over 10 ms bins. The dashed lines indicate linear least-squares regressions. Total simulation time 10 s. Network parameters are given in Table 1.



**Figure S2.** Characterization of activity in the balanced random network model with  $PSP_{e←e} = 0.8$  mV. Identical panel layout to that in Figure S1 on page 4. Network parameters are given in Table 2.

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