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# Bursting suppression in propofol-induced general anesthesia as bi-stability in a non-linear neural mass model

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## SUMMARY

- Bursting activity suppression, a phenomenon characterized by sequences of alternating quiescent ('down') and bursting ('up') states, is ubiquitously present during deep sedation in general anesthesia and can be observed in LFPs and in EEG recordings as well [1, 2]. However, the dynamical principles underlying such phenomena are unclear.
- Prevailing theoretical approaches to this problem suggest that such bi-stable dynamics could be explained by the existence of notable non-linearities in the neuronal membrane potential as a function of the anesthetic agent, with frequent noise-induced transitions between two stable (attracting) branches.
- Nevertheless, the mathematical tractability of those models is rather limited due to the dimensionality (2D) of the phase-space.
- It has been shown for a neural-mass version of the model proposed in [3], that the 2D-trajectory likely escapes to the other attractor through a limited section of the saddle-line separating the attractors basins [4].
- This prediction is here supported by numerical simulations, permitting the simplification of the dynamics to a simpler two-state trace.
- Relevant statistics can then be extracted, including histograms of the duration of the visit in each state that may support future analytical calculations of the EEG power spectrum following renewal theory [5].

## Hutt & Longtin (2009) model with no delay nor spatial dimension: a neural mass model

Differential form, using the scaled (dimensionless) time  $\tau = \sqrt{\alpha_1 \alpha_2}$ :

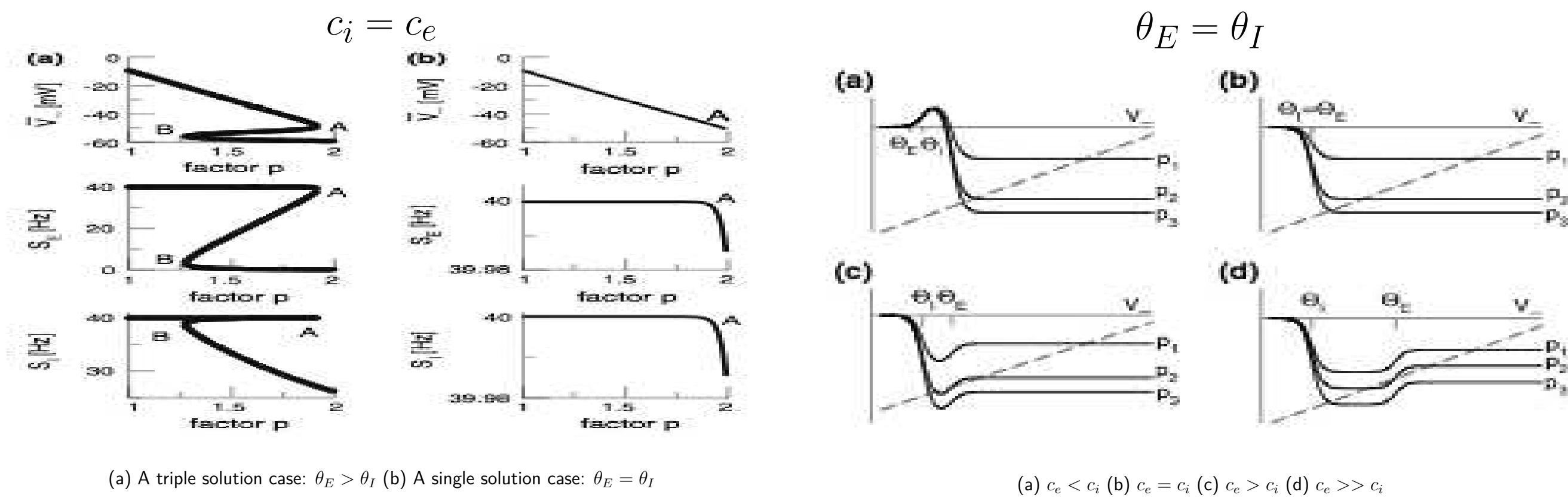
$$\begin{aligned} (\partial_t / \partial \tau^2 + \gamma_1 \partial_t / \partial \tau + \omega_1^2)(V_1 - V_1^c) &= a_1 f(p) \alpha_1 S_1(V_1 - V_1^c) + \sqrt{2\sigma} W_1 \\ (\partial_t / \partial \tau^2 + \gamma_2 \partial_t / \partial \tau + \omega_2^2)(V_2 - V_2^c) &= a_2 S_2(V_2 - V_2^c) + \sqrt{2\sigma} W_2 \end{aligned}$$

with  $\gamma_i = (\beta_i + \beta_2) / \sqrt{\alpha_1 \alpha_2}$ ,  $\omega_i = \sqrt{\alpha_1 \alpha_2}$ ,  $\omega_i = \sqrt{\beta_1 \beta_2 / (\alpha_1 \alpha_2)}$ ,  $V_i, V_i^c$  are the PSPs at excitatory neurons,  $V_i^c$  the resting membrane potential,  $\theta_i < \theta_c$  the threshold potentials of the pre-synaptic cells,  $S_1$  and  $S_2$  are sigmoid functions  $S_i(x) = \frac{1}{1 + e^{-\beta_i(x - \theta_i)}}$ ,  $\beta_i \in [1, \epsilon]$  and  $\alpha_i$  stand for the synaptic efficacies.  $W_i$  represent Wiener processes.  $\alpha_1, \beta_1, \alpha_2, \beta_2$  define the mean synaptic response functions  $h_i$ :

$$\begin{aligned} h_1(t) &= a_1 f(p) \frac{\beta_1 \beta_2}{\beta_1 - \beta_2} (e^{-\beta_1 t} - e^{-\beta_2 t}) \\ h_2(t) &= a_2 \frac{\alpha_1 \alpha_2}{\alpha_2 - \alpha_1} (e^{-\alpha_1 t} - e^{-\alpha_2 t}) \end{aligned}$$

Finally,  $f(p) = r^{-1/(r-1)}(rp)^{r/(r-1)}$  mimics the inhibitory action of the propofol  $p$  level, with  $r = \beta_2/\beta_1$ ,  $\beta_1 = \beta_2/p$

## Bifurcation diagrams of Hutt & Longtin (2009) model



Adapted from Hutt A. and Longtin A., *Cognitive Neurodyn.* 4(1): 37-59, 2009.

## Complexity reduction: a first-order system and a Heaviside rate function

$\alpha_1 \ll \alpha_2$  and  $\beta_1 \ll \beta_2 \rightarrow r \gg 1 \rightarrow f(p) \approx p$ , leads to 1st-order Langevin (SDE) equations. Besides, replacing  $S_i$  by a Heaviside function  $S_i = \Theta(V_i - V_i^c)$ , the system's equations read:

$$\begin{aligned} \dot{V}_1 &= -\beta(V_1 - V_1^c) + \beta a_1 p S_{max} \Theta(V_1 - V_1^c) + \sqrt{2\sigma} W_1 \\ \dot{V}_2 &= -\alpha(V_2 - V_2^c) + \alpha a_2 S_{max} \Theta(V_2 - V_2^c) + \sqrt{2\sigma} W_2 \end{aligned}$$

where  $\beta = \beta_1$  and  $\alpha = \alpha_1$ . The equation can also be split in three domains with a linear dynamics:

• Domain I:  $V_1 < V_1^c + \theta_1$

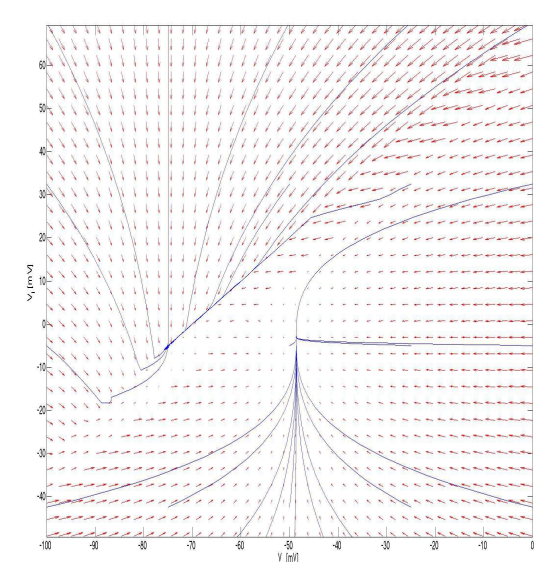
$$\begin{aligned} \dot{V}_1 &= -\beta(V_1 - V_1^c) + \sqrt{2\sigma} W_1 \\ \dot{V}_2 &= -\alpha(V_2 - V_2^c) + \sqrt{2\sigma} W_2 \end{aligned}$$

• Domain II:  $V_1 > V_1^c + \theta_1$

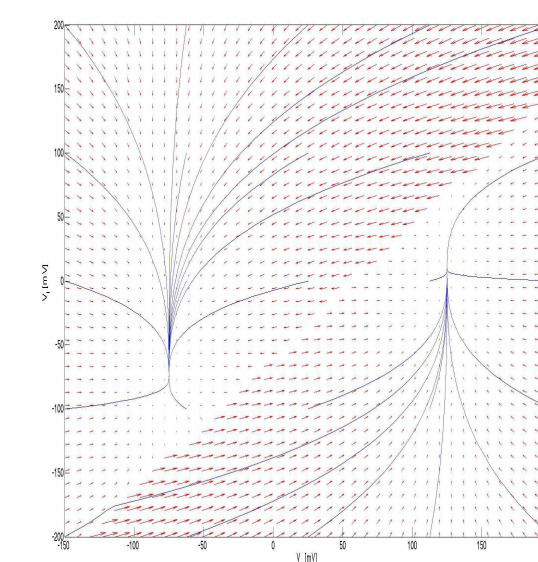
$$\begin{aligned} \dot{V}_1 &= -\beta(V_1 - V_1^c) + \beta a_1 p S_{max} + \sqrt{2\sigma} W_1 \\ \dot{V}_2 &= -\alpha(V_2 - V_2^c) + \alpha a_2 S_{max} + \sqrt{2\sigma} W_2 \end{aligned}$$

• Domain III:  $V_1 < V_1^c + \theta_1$  and  $V_2 > V_2^c + \theta_2$

$$\begin{aligned} \dot{V}_1 &= -\beta(V_1 - V_1^c) + \beta a_1 p S_{max} + \sqrt{2\sigma} W_1 \\ \dot{V}_2 &= -\alpha(V_2 - V_2^c) + \sqrt{2\sigma} W_2 \end{aligned}$$



Phase portrait in Heaviside functions case:  $\theta_e > \theta_i$



Phase portrait in Heaviside functions case:  $\theta_e = \theta_i$

## Heaviside variant of the model: ranges of bi-stability

Heaviside functions case:  $\theta_e = \theta_i = \theta$

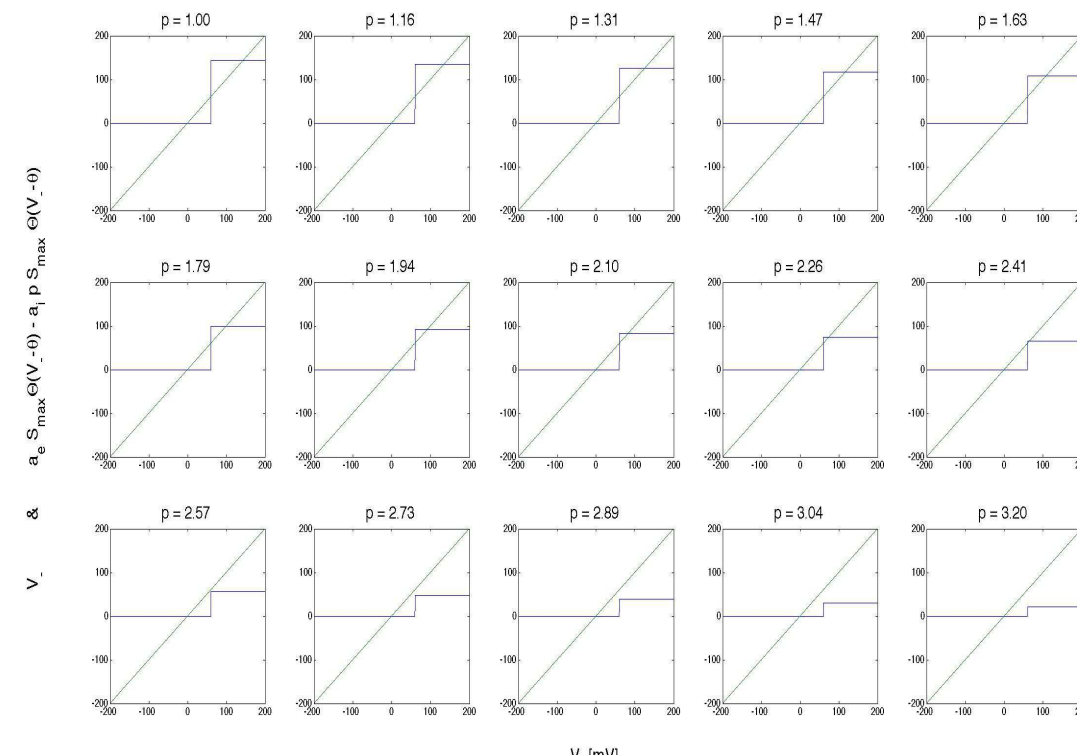
In order to determine the ranges of bi-stability in this variant of the model, it is needed to consider the following equation:

$$\bar{V}_- = a_1 S_{max} \Theta(\bar{V}_- - \theta) - a_2 p S_{max} \Theta(\bar{V}_- - \theta)$$

A first graphical analysis reveals that multiple intersections of the l.h.s. term, the straight line  $f(\bar{V}_-) = \bar{V}_-$ , with the difference of the two scaled Heaviside functions on the r.h.s., are only possible in case of positive  $p$  values for (unrealistic) values of  $\theta > 0$ . In such a case the  $\bar{V}_-$  coordinates of the fixed points are

$$\begin{aligned} \bar{V}_-^{(up)} &= (a_1 - a_2 p) S_{max} \\ \bar{V}_-^{(middle)} &= \theta \\ \bar{V}_-^{(down)} &= 0 \end{aligned}$$

and this simultaneous presence of two attractors occurs for  $p$  values below a critical one  $p_c$ :  $p < p_c = \frac{a_1 S_{max} - \theta}{a_2 S_{max}}$ . This does not exclude also unrealistic negative values for  $p$ .

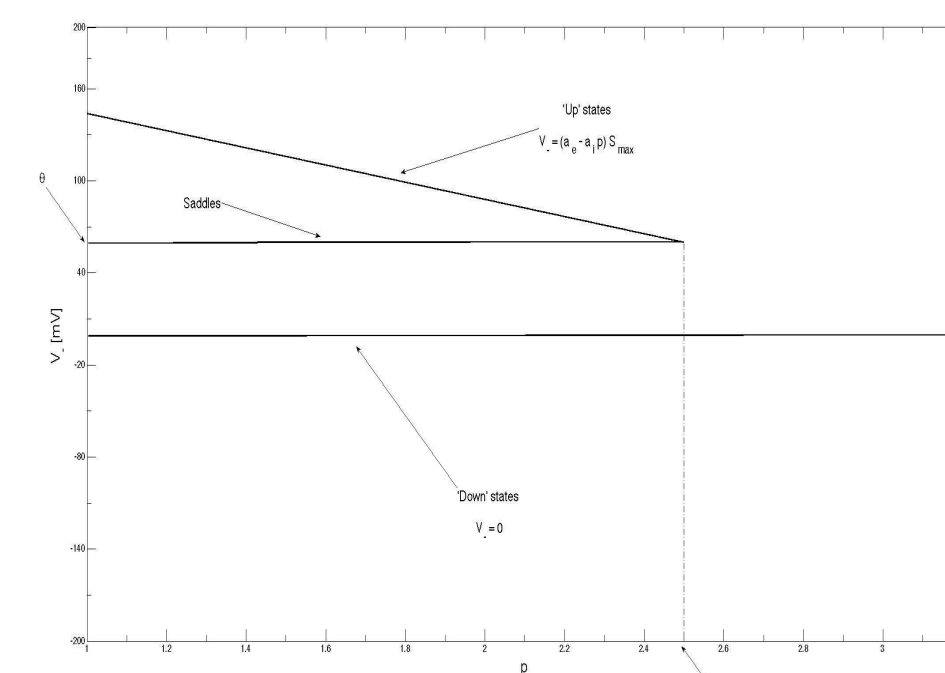


Heaviside functions case:  $\theta_e > \theta_i$

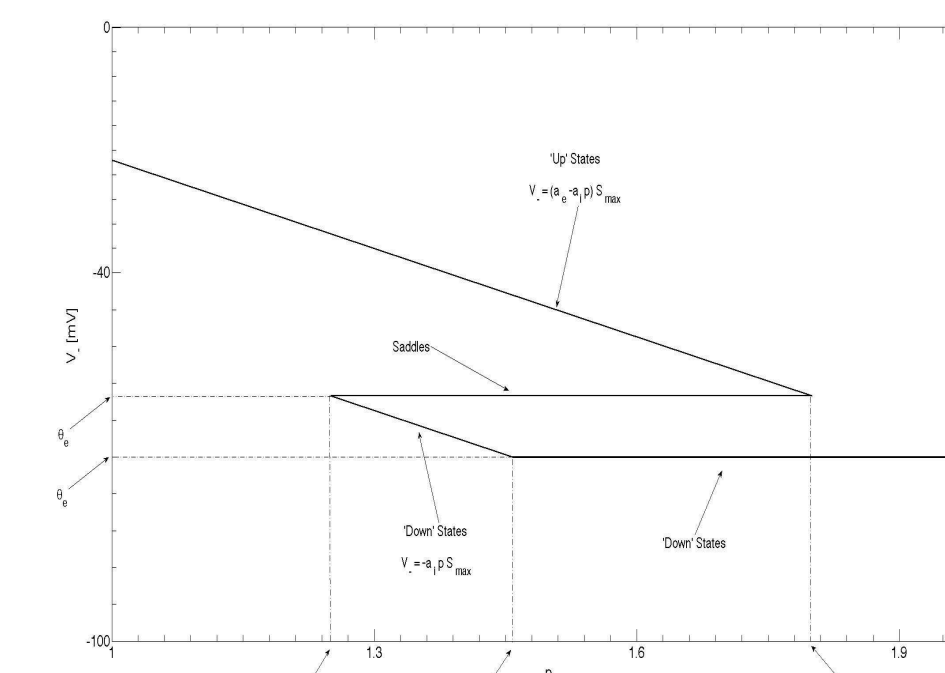
In this case, for low values of  $p$ , the r.h.s. and the l.h.s. of the fixed points equation presented above always encounter in, at least, one ('up') attractor  $\bar{V}_- > \theta_e$ , located at the upper branch of the difference between the two scaled Heaviside functions (the r.h.s.).

$$\bar{V}_-^{(up)} = (a_1 - a_2 p) S_{max}$$

## Heaviside case: bifurcation diagrams

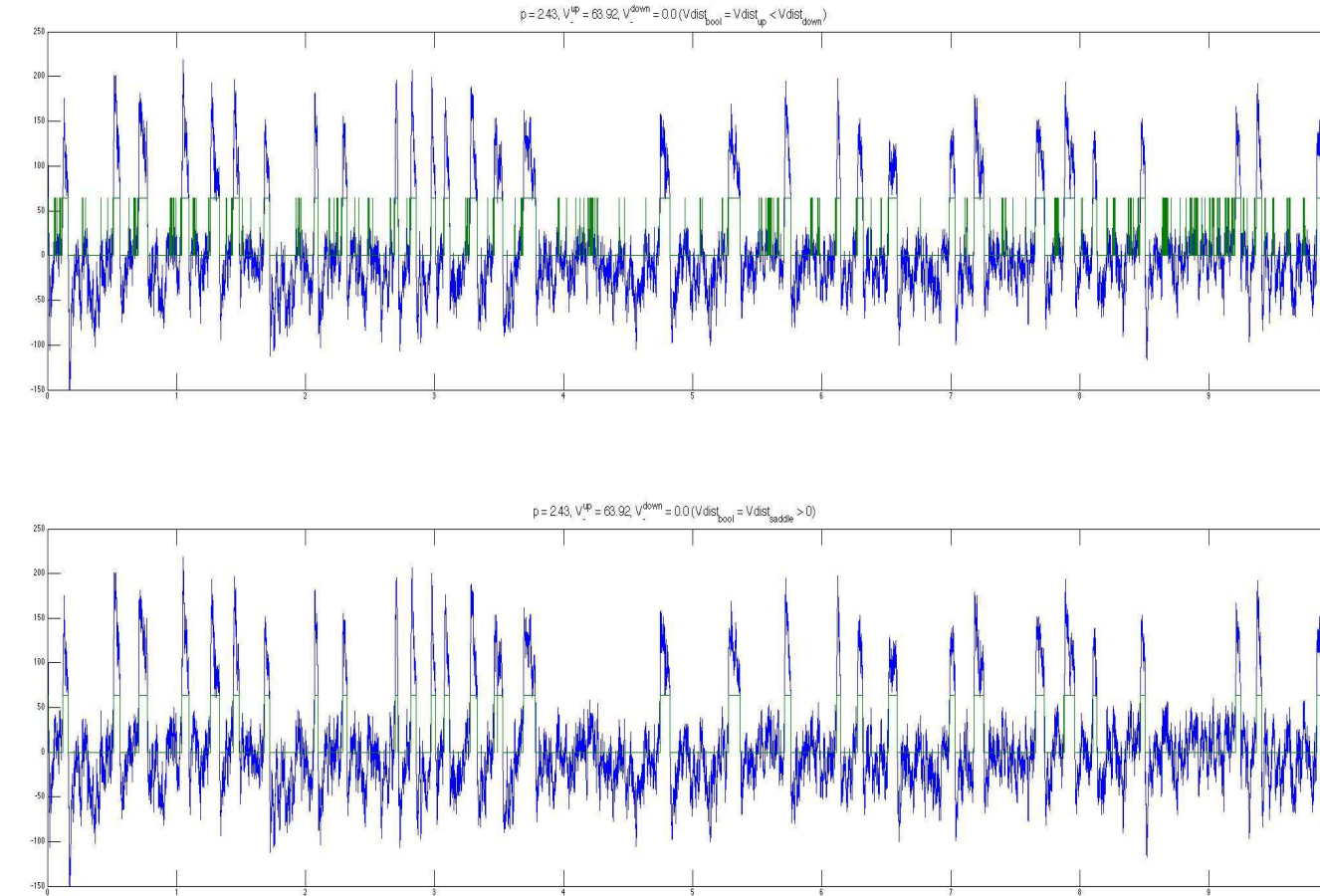


Heaviside case:  $\theta_e = \theta_i = \theta$



Heaviside case:  $\theta_e > \theta_i$

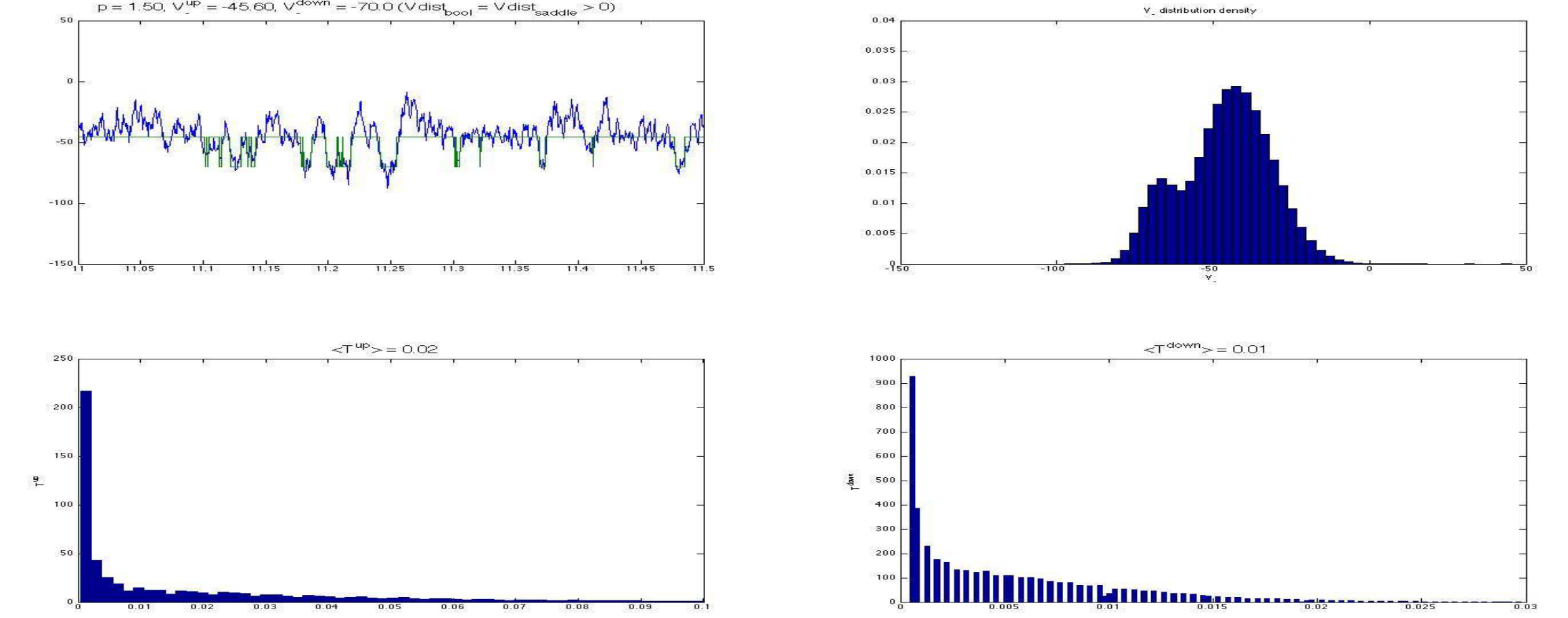
## Computational simulations (I)



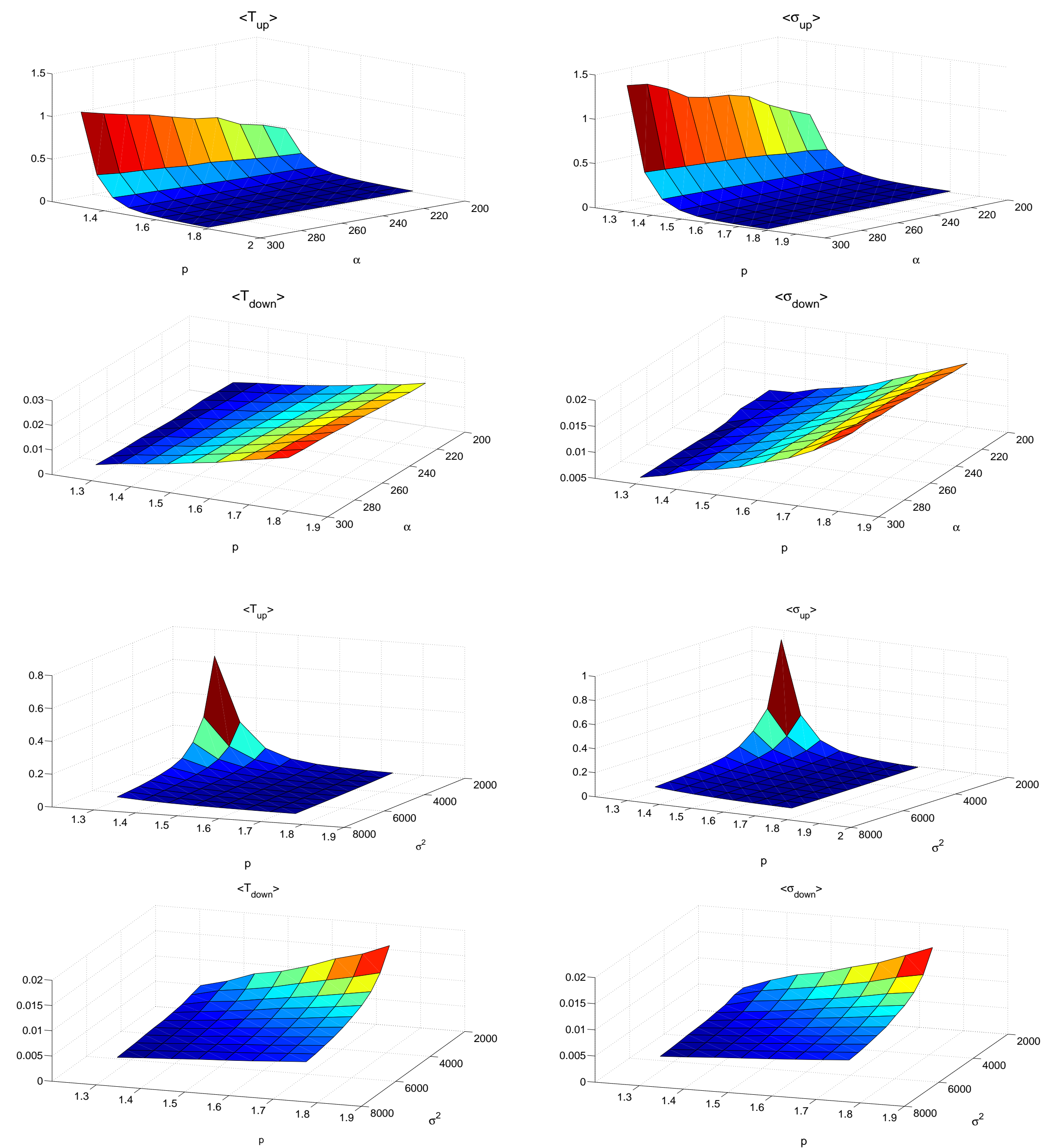
$$\begin{aligned} V_{dist}^{(up)} &= |V_- - \bar{V}_-^{(up)}| \\ V_{dist}^{(down)} &= |V_- - \bar{V}_-^{(down)}| \end{aligned}$$

$$V_{dist}^{(bool)} = \begin{cases} V_{dist}^{(up)} & \text{if } V_{dist}^{(up)} < V_{dist}^{(down)} \\ V_{dist}^{(down)} & \text{if } V_{dist}^{(down)} < V_{dist}^{(up)} \end{cases}$$

$$\begin{aligned} V_{dist}^{(saddle)} &= V_- - \bar{V}_-^{(saddle)} \\ V_{dist}^{(bool)} &= \begin{cases} V_{dist}^{(saddle)} & \text{if } V_{dist}^{(saddle)} > 0 \end{cases} \end{aligned}$$



## Computational simulations (II)



Base parameters set:  $\theta_e = -60$  mV,  $\theta_i = -70$  mV,  $S_{max} = 40$  Hz,  $V_1^c = -75$  mV,  $a_1 = 0.66$  mV/s,  $a_2 = 1.2$  mV/s,  $\beta_0 = 117$  Hz,  $\alpha = 222$  Hz and  $\sigma^2 = 2.24 \times 10^7$

## CONCLUSIONS

- The coefficient of variation  $C_v = \frac{\sigma^2}{\mu^2} \approx 1$  across the planes  $(p, \alpha)$  and  $(p, \sigma)$ , what might point to an intermediate-variance distribution, i.e., an exponential-like function.
- In simultaneous variations of  $p$  and  $\alpha$ , it is found a clear decreasing trend in the mean waiting time  $\langle T_{up} \rangle$  for the 'up' state when  $p$  increases. The contrary holds for the competing state. Conversely, none of them shows a considerable dependence on the  $\alpha$  parameter.
- The average waiting time in the 'up' states is a non-linear decreasing function of  $p$ , differently to the residence time in the 'down' state that behaves mostly linearly in both  $p$  and in the synaptic time-scale  $(1/\alpha)$  direction.
- In simultaneous variations of  $p$  and  $\sigma$ , the 'up' state is more sensitive to  $p$  changes than to  $\sigma$  variations, in comparison with the behaviour observed for the 'down' states, which 'feels' more the variations in  $\sigma$ .

## References

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