

# Slow oscillations of 'up' and 'down' states during general anesthesia: bi-stability in a non-linear model

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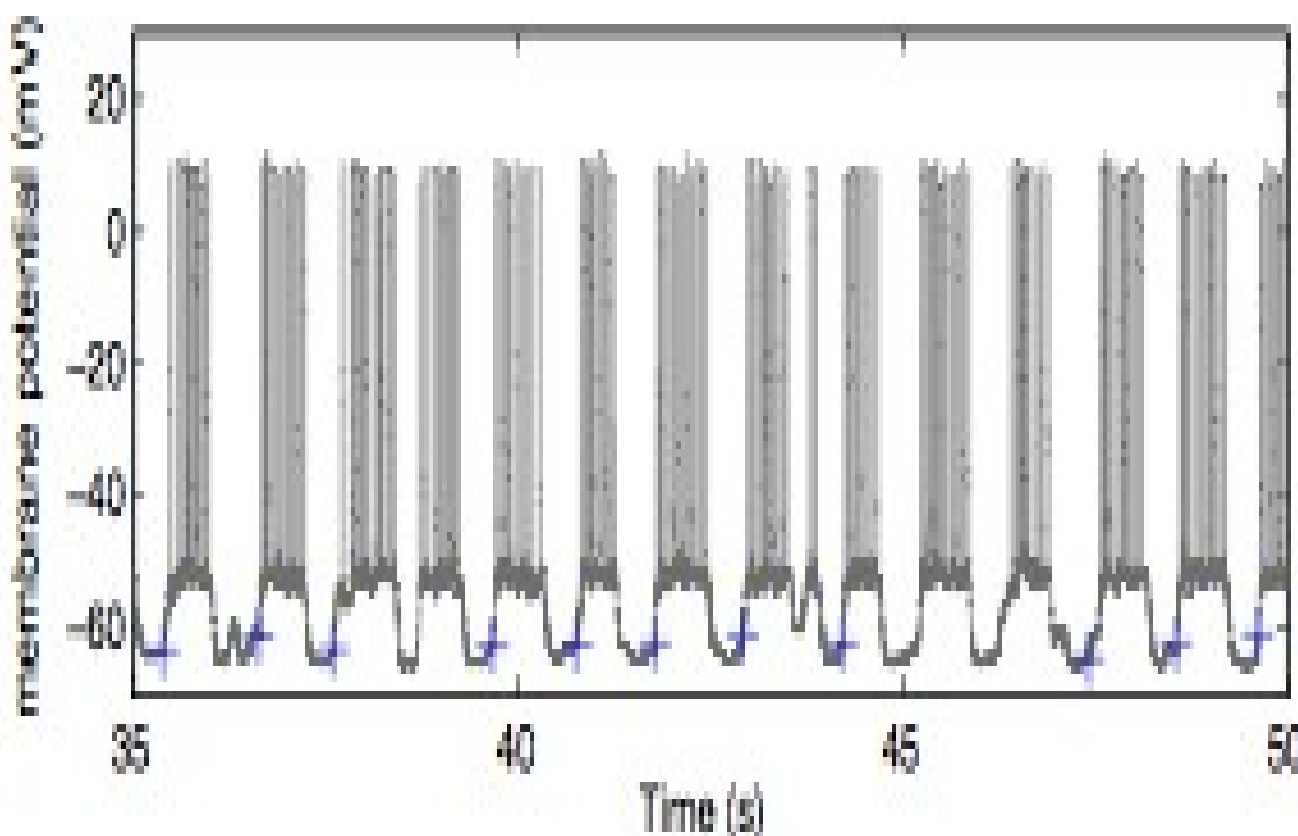
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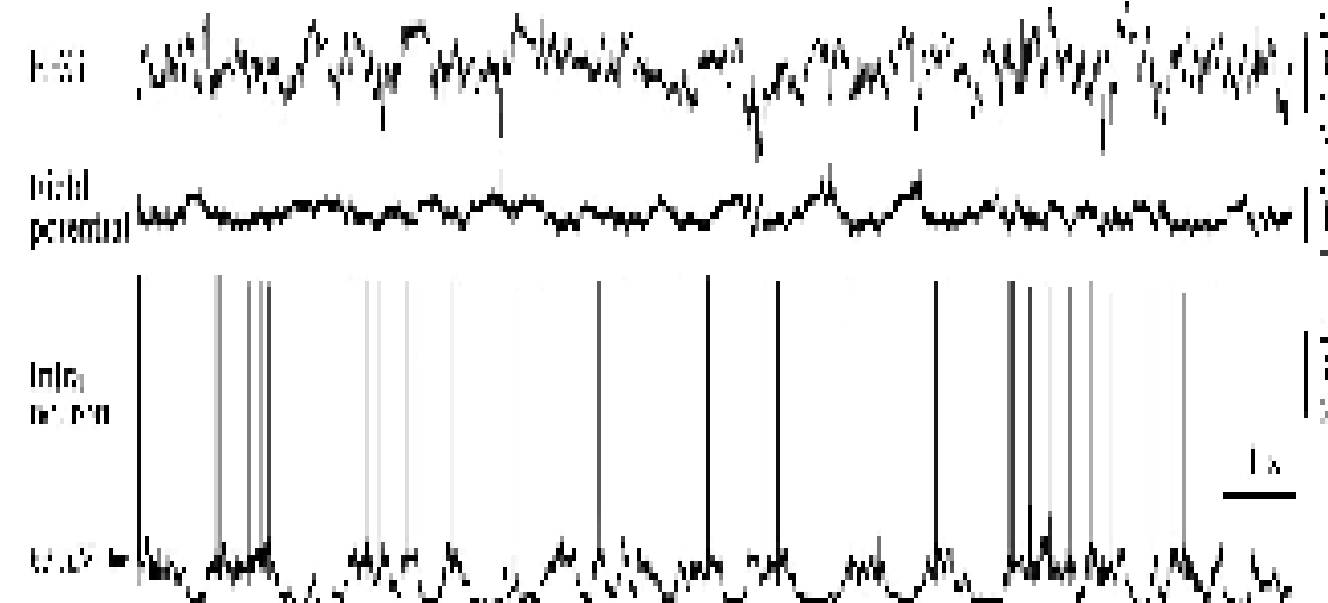
## Summary

- Sequences of alternating quiescent ('down') and bursting ('up') states in NREM sleep are found across mammalian species (Destexhe A. et al, *Trends in Neurosciences* 30: 334-342, 2007) and in neuronal recordings (LFP and EEG) of anesthetized animals (Hutt A. (ed.), Springer-Verlag, 2011).
- The dynamical principles underlying such phenomenon are unclear.
- Previous theoretical attempts to understand the neural basis of anesthesia effects suggest the existence of notable non-linearities in the behavior of the neuronal membrane potential (Steyn-Ross M. et al., *Physical Review E* 60(6): 7299-7311, 1999; Hutt A. and Longtin A., *Cognitive Neurodynamics* 4(1): 37-59, 2009).
- Noise-induced transitions between two stable branches through which the dynamics may evolve as the concentration of the anesthetic agent (AA) increases, could explain the observed alternating sequences of 'up' and 'down' states.
- Nevertheless, the mathematical tractability of these non-linear scenarios is difficult due to the 2D phase space defined by the describing variables: the excitatory and the inhibitory PSPs at excitatory cells.
- Exact solutions to these problems are only known for 1D systems and, consequently, the analysis of the existing non-linear models is typically avoided.
- In this work we undertake a first attempt to solve this task, by applying known techniques on stochastic phenomena theory (Gardiner C.W., Springer-Verlag, 2004) to the Hutt & Longtin (2009) model. We consider the time the system spends in the 'up' or 'down' states as being similar to the mean exit-time needed to escape from the corresponding attractor.

## Bistability in anesthesia



Wilson *et al.* (2010), J Biol Phys 36: 245-259



Ferron *et al.* (2009), J Neurosci 29(31): 9850-9860

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

1. Integral form:

$$V_i(t) - V_e' = \int_{-\infty}^t h_i(t-t') S_i(V_e - V_i - \theta_i) dt' + \sqrt{2}\sigma \int_{-\infty}^t h_i(t-t') dW_i(t')$$

$$V_e(t) - V_e' = \int_{-\infty}^t h_e(t-t') S_e(V_e - V_i - \theta_e) dt' + \sqrt{2}\sigma \int_{-\infty}^t h_e(t-t') dW_e(t')$$

where  $V_i$ ,  $V_e$  are the PSPs at excitatory neurons,  $V_e'$  the resting membrane potential,  $\theta_i < \theta_e$  the threshold potentials of the pre-synaptic cells,  $S_e$  and  $S_i$  are sigmoids functions  $S_k(x) = \frac{S_{max}}{1 + e^{-c_k(x-\theta_k)}}$ ,  $k \in \{i, e\}$ .  $W_k$  represent Wiener processes and  $h_k$  the mean synaptic response functions:

$$h_i(t) = a_i f(p) \frac{\beta_1 \beta_2}{\beta_2 - \beta_1} (e^{-\beta_1 t} - e^{-\beta_2 t})$$

$$h_e(t) = a_e \frac{\alpha_1 \alpha_2}{\alpha_2 - \alpha_1} (e^{-\alpha_1 t} - e^{-\alpha_2 t})$$

where  $a_k$  stand for the synaptic efficacies and  $f(p) = r^{-r/(r-1)}(rp)^{r/(rp-1)}$  mimics the inhibitory action of the propofol  $p$  level, with  $r = \beta_2/\beta_1$ ,  $\beta_1 = \beta_0/p$ .

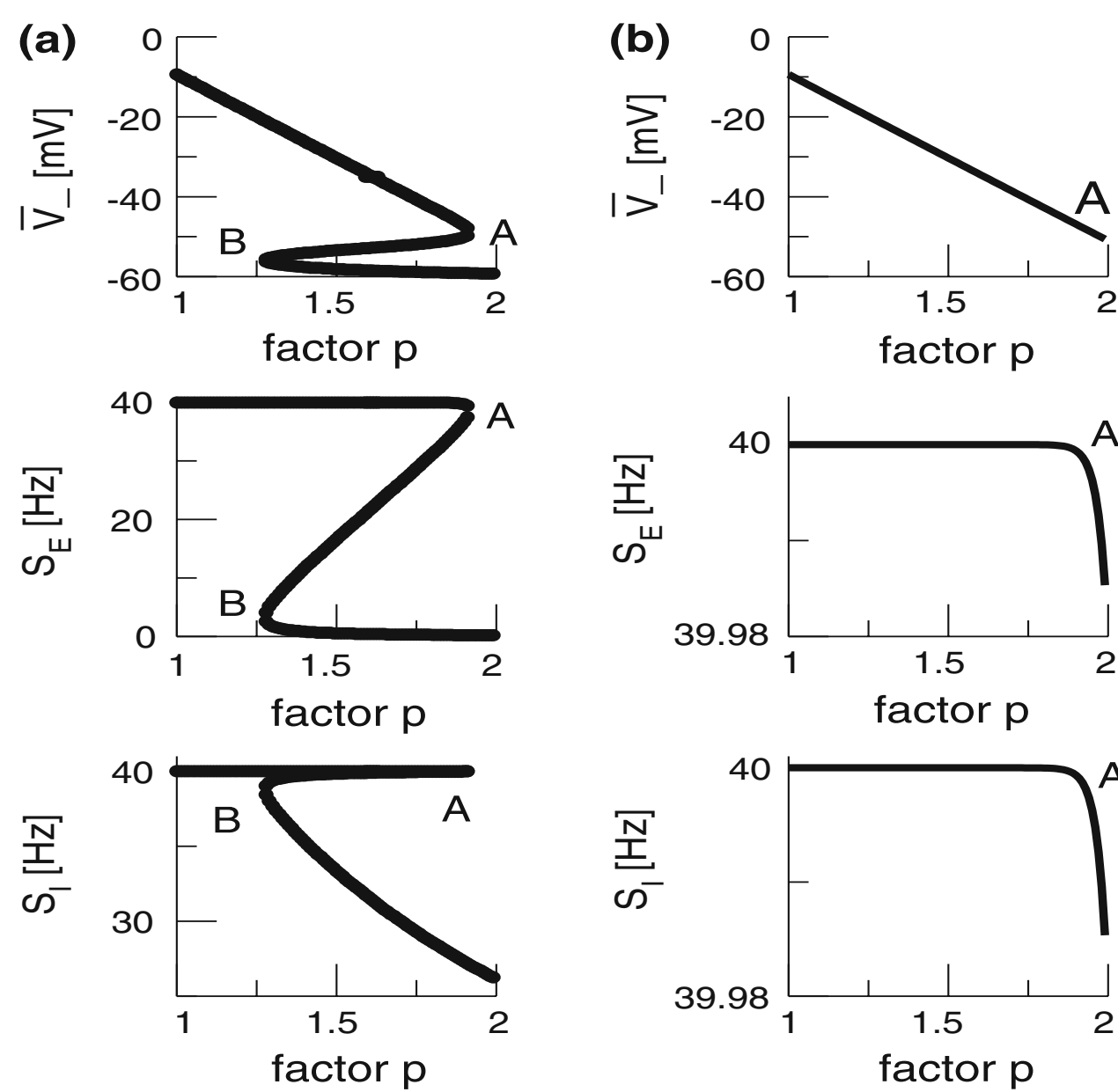
2. Differential form, using the scaled (dimensionless) time  $\tau = \sqrt{\alpha_1 \alpha_2} t$ :

$$(\partial^2/\partial \tau^2 + \gamma_i \partial/\partial \tau + \omega_i^2)(V_i - V_e') = a_i f(p) \omega_i^2 S_i(V_e - V_i - \theta_i) + \sqrt{2}\sigma \dot{W}_i$$

$$(\partial^2/\partial \tau^2 + \gamma_e \partial/\partial \tau + 1)(V_e - V_e') = a_e S_e(V_e - V_i - \theta_e) + \sqrt{2}\sigma \dot{W}_e$$

with  $\gamma_i = (\beta_1 + \beta_2)/\sqrt{\alpha_1 \alpha_2}$ ,  $\gamma_e = \sqrt{\alpha_1/\alpha_2} + \sqrt{\alpha_2/\alpha_1}$ ,  $\omega_i = \sqrt{\beta_1 \beta_2/(\alpha_1 \alpha_2)}$ .

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



(a) A triple solution case:  $\theta_E > \theta_I$ ,  $C_E = C_I$   
(b) A single solution case:  $\theta_E = \theta_I$ ,  $C_E = C_I$

( $V_- = V_e - V_i$  is the effective membrane potential)

## First-passage time (FPT) theory: obstacles to formulate the PDEs problem

- High dimensionality, *e.g.*, 2nd-order partial differential equations.
- No potentials to describe the vector field, due to the presence of the response functions  $S_k$ .
- Infinite regions given by the attraction basins.
- Oblique boundaries

## Simplifications (I)

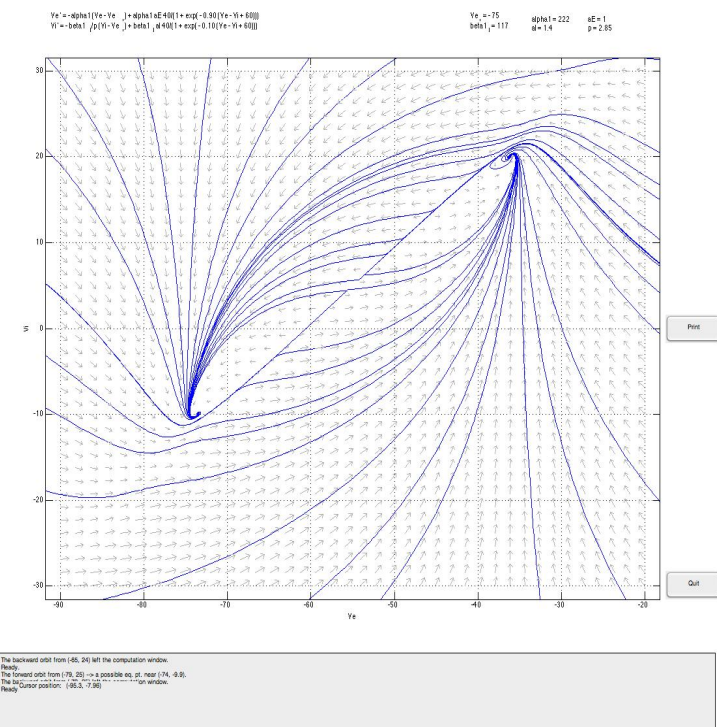
\*  $\beta_1 \ll \beta_2 \rightarrow r \gg 1 \rightarrow f(p) \approx p$  leads to 1st-order Langevin (SDE) equations:

$$\dot{V}_i = -\beta(V_i - V_e') + \beta_i a_i S_i(V_e - V_i - \theta_i) + \sqrt{2}\sigma \dot{W}_i$$

$$\dot{V}_e = -\alpha(V_e - V_e') + \alpha a_e S_e(V_e - V_i - \theta_e) + \sqrt{2}\sigma \dot{W}_e,$$

where  $\beta = \beta_1$  and  $\alpha = \alpha_1$ .

\* Replacing  $S_k$  by a Heaviside function  $S_k = \Theta(V_e - V_i - \theta_k)$ :



Phase portrait in *Sigmoid* function case

- Domain I:  $V_e < V_i + \theta_i$

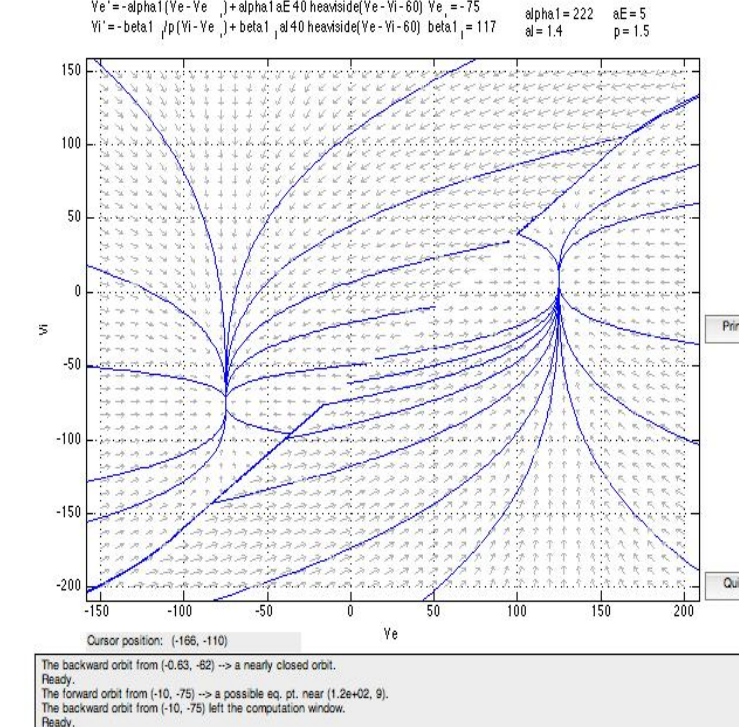
$$\dot{V}_i = -\beta(V_i - V_e') + \sqrt{2}\sigma \dot{W}_i$$

$$\dot{V}_e = -\alpha(V_e - V_e') + \sqrt{2}\sigma \dot{W}_e$$

- Domain II:  $V_e > V_i + \theta_e$

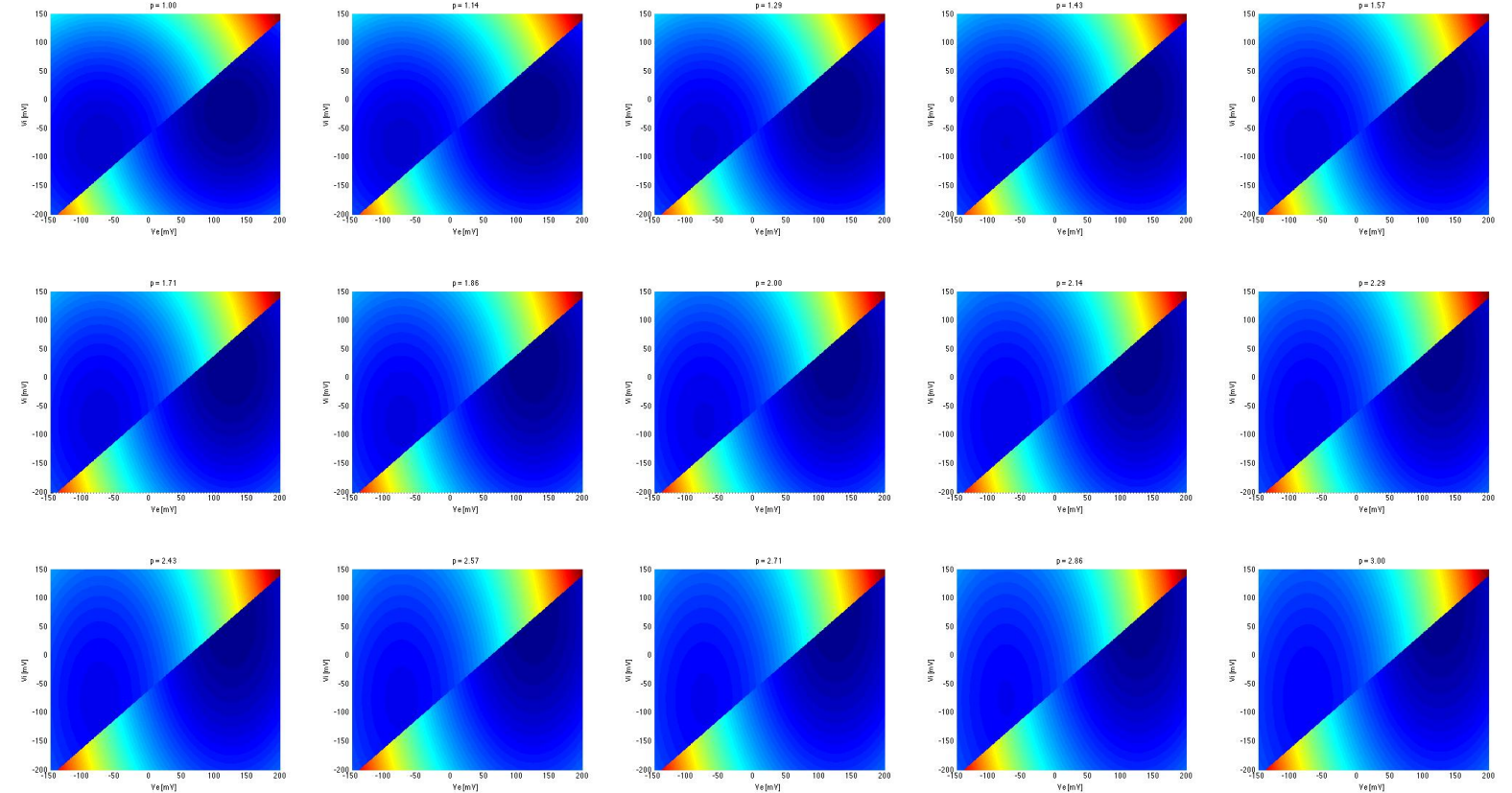
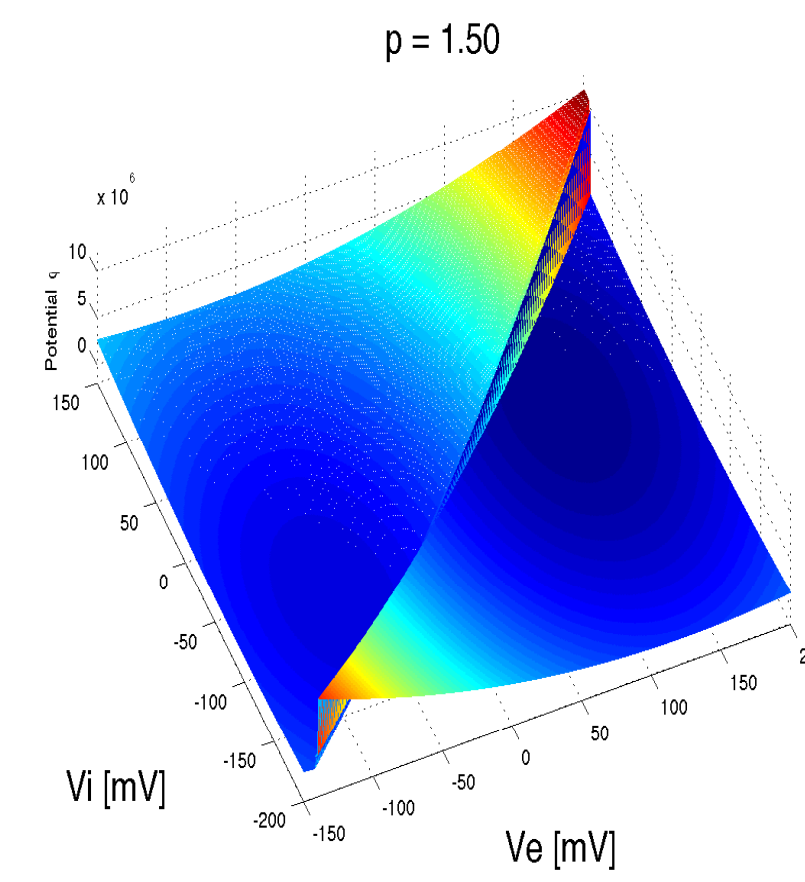
$$\dot{V}_i = -\beta(V_i - V_e') + \beta_0 a_i S_{max} + \sqrt{2}\sigma \dot{W}_i$$

$$\dot{V}_e = -\alpha(V_e - V_e') + \alpha a_e S_{max} + \sqrt{2}\sigma \dot{W}_e$$



Phase portrait in *Heaviside* function case

## Simplifications (I)...



## Simplifications (II)

\* A 45°-rotation of the ( $V_i$ ,  $V_e$ ) coordinate system about the origin:

$$\begin{bmatrix} \hat{V}_+ \\ \hat{V}_- \end{bmatrix} = \frac{1}{\sqrt{2}} \begin{bmatrix} 1 & 1 \\ -1 & 1 \end{bmatrix} \begin{bmatrix} V_i \\ V_e \end{bmatrix} = \frac{1}{\sqrt{2}} \begin{bmatrix} V_+ \\ V_- \end{bmatrix}$$

- Domain I:  $\hat{V}_- < \theta_i/\sqrt{2}$

$$\frac{d}{dt} \begin{bmatrix} \hat{V}_+ \\ \hat{V}_- \end{bmatrix} = \frac{1}{2} \begin{bmatrix} -(\beta + \alpha) & \beta - \alpha \\ \beta - \alpha & -(\beta + \alpha) \end{bmatrix} \begin{bmatrix} \hat{V}_+ \\ \hat{V}_- \end{bmatrix} + \frac{V_e'}{\sqrt{2}} \begin{bmatrix} \beta + \alpha \\ -(\beta + \alpha) \end{bmatrix} + 2\sigma \begin{bmatrix} \hat{\eta}_+ \\ \hat{\eta}_- \end{bmatrix}$$

where  $\eta_{i,+,-}$  are Wiener processes.

- Domain II:  $\hat{V}_- > \theta_e/\sqrt{2}$

$$\frac{d}{dt} \begin{bmatrix} \hat{V}_+ \\ \hat{V}_- \end{bmatrix} = \frac{1}{2} \begin{bmatrix} -(\beta + \alpha) & \beta - \alpha \\ \beta - \alpha & -(\beta + \alpha) \end{bmatrix} \begin{bmatrix} \hat{V}_+ \\ \hat{V}_- \end{bmatrix} + \frac{1}{\sqrt{2}} \begin{bmatrix} (\beta + \alpha) V_e' + (\beta_0 a_i + \alpha a_e) S_{max} \\ -(\beta - \alpha) V_e' + (-\beta_0 a_i + \alpha a_e) S_{max} \end{bmatrix} + 2\sigma \begin{bmatrix} \hat{\eta}_+ \\ \hat{\eta}_- \end{bmatrix}$$

\* A non-linear transformation:  $X_+ = \tanh \hat{V}_+$ ,  $X_- = \tanh \hat{V}_-$ . New Langevin equations are obtained with Ito's calculus :

$$\frac{dX_+}{dt} = (1 - X_+^2)[C_+ - (2\sigma)^2 X_+] + 2\sigma(1 - X_+^2)\hat{\eta}_+$$

$$\frac{dX_-}{dt} = (1 - X_-^2)[C_- - (2\sigma)^2 X_-] + 2\sigma(1 - X_-^2)\hat{\eta}_-$$

where

$$C_+ = \frac{-\beta + \alpha}{4} \ln\left(\frac{1 + X_+}{1 - X_+}\right) + \frac{\beta - \alpha}{4} \ln\left(\frac{1 + X_-}{1 - X_-}\right) + \frac{\beta + \alpha}{\sqrt{2}} V_e' + \frac{\beta_0 a_i + \alpha a_e}{\sqrt{2}} S_{max}$$

$$C_- = \frac{\beta - \alpha}{4} \ln\left(\frac{1 + X_+}{1 - X_+}\right) - \frac{\beta + \alpha}{4} \ln\left(\frac{1 + X_-}{1 - X_-}\right) + \frac{-\beta + \alpha}{\sqrt{2}} V_e' + \frac{-\beta_0 a_i + \alpha a_e}{\sqrt{2}} S_{max}$$

## Fokker-Planck equation and FPT theory

*Fokker-Planck equation:*

$$\frac{\partial P}{\partial t} = -\frac{\partial}{\partial X_+} [A_+ P] - \frac{\partial}{\partial X_-} [A_- P] + \frac{B_{++}}{2} \frac{\partial^2 P}{\partial X_+^2} + \frac{B_{--}}{2} \frac{\partial^2 P}{\partial X_-^2}$$

where  $P = P(X_+, X_-, t|X_+(0), X_-(0), 0)$  is the conditional probability, and

$$A_s = (1 - X_s^2)[C_s - (2\sigma)^2 X_s]$$

$$B_{ss} = [2\sigma(1 - X_s^2)]^2$$

are the drift and diffusion coefficients, respectively, with  $s \in \{+, -\}$ .

*Partial differential equations of FPT theory:*

$$\left[ A_+ \frac{\partial}{\partial X_+} + A_- \frac{\partial}{\partial X_-} + \frac{1}{2} B_{++} \frac{\partial^2}{\partial X_+^2} + \frac{1}{2} B_{--} \frac{\partial^2}{\partial X_-^2} \right] T(X_+, X_-) = -1$$

$$\left[ A_+ \frac{\partial}{\partial X_+} + A_- \frac{\partial}{\partial X_-} + \frac{1}{2} B_{++} \frac{\partial^2}{\partial X_+^2} + \frac{1}{2} B_{--} \frac{\partial^2}{\partial X_-^2} \right] [\pi(X_+, X_-, a_+, a_-) T(X_+, X_-, a_+, a_-)] = -\pi(a_+, a_-)$$

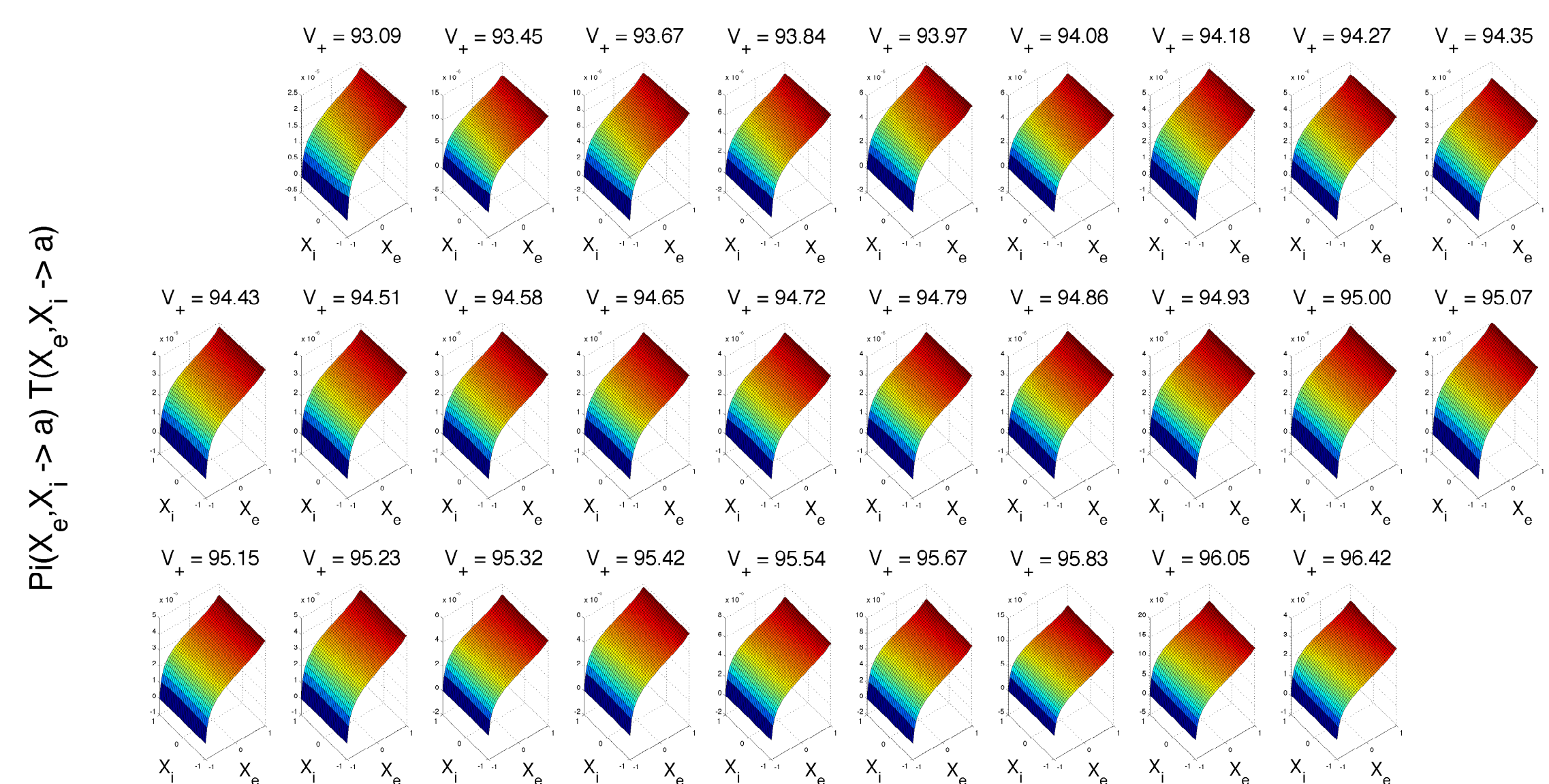
$$\left[ A_+ \frac{\partial}{\partial X_+} + A_- \frac{\partial}{\partial X_-} + \frac{1}{2} B_{++} \frac{\partial^2}{\partial X_+^2} + \frac{1}{2} B_{--} \frac{\partial^2}{\partial X_-^2} \right] \pi(X_+, X_-, a_+, a_-) = 0$$

where  $T(X_+, X_-)$  stands for the mean FPT when the escape occurs through any point in the saddles line  $V_e - V_i - \theta_k = 0$ , while  $T(X_+, X_-, a_+, a_-)$  is the exit time when it happens through a specific point  $(a_+, a_-)$ .  $\pi(a_+, a_-)$  is the corresponding exit probability. The formulation of the problem is completed with the following boundary conditions (BCs):

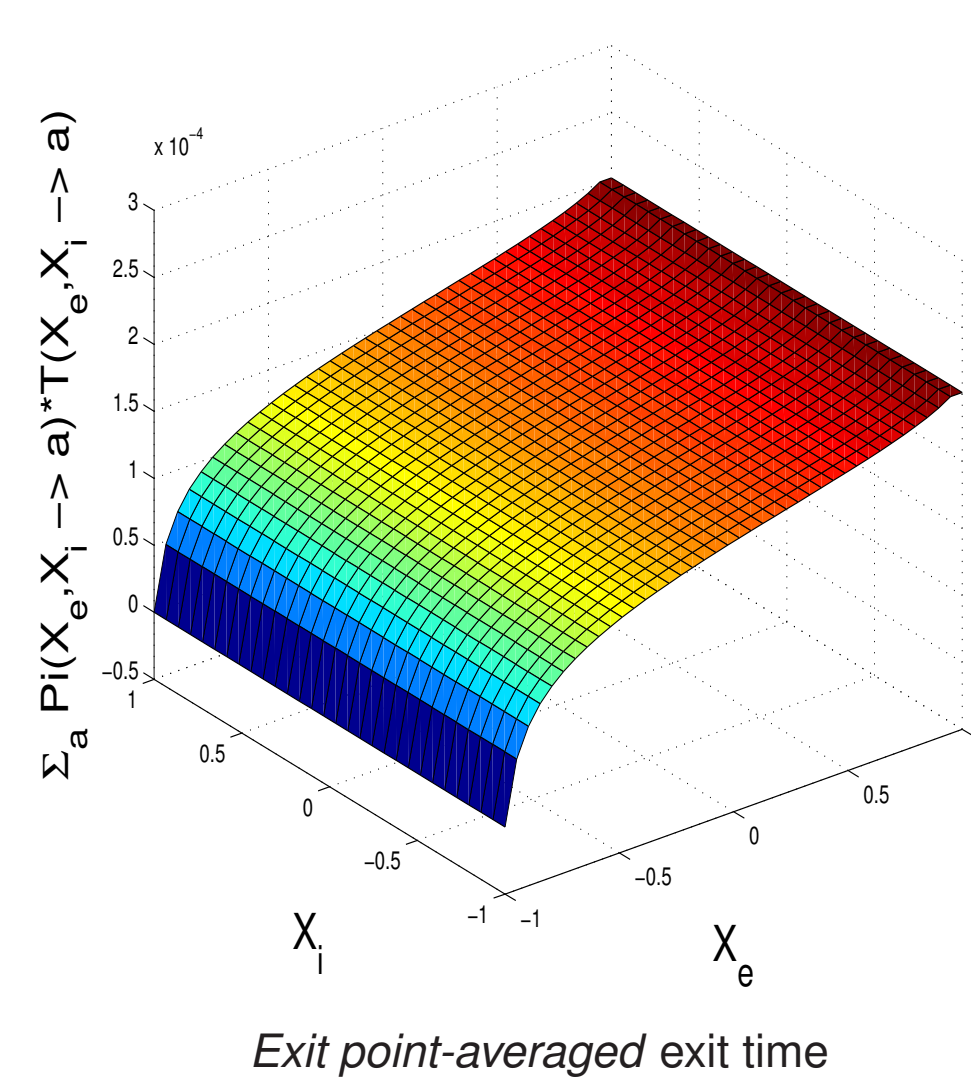
. Dirichlet BCs at the saddles line:  $T(X_+, X_-) = 0$ ,  $T(X_+, X_-, a_+, a_-) = 0$  and  $\pi(X_+, X_-, a_+, a_-) = 0$  (absorbing boundary)

. Neumann BCs at the remainder boundaries:  $\frac{\partial}{\partial X_e} T(X_+, X_-) = 0$ ,  $\frac{\partial}{\partial X_e} T(X_+, X_-, a_+, a_-) = 0$  and  $\frac{\partial}{\partial X_e} \pi(X_+, X_-, a_+, a_-) = 0$  (reflecting barriers).

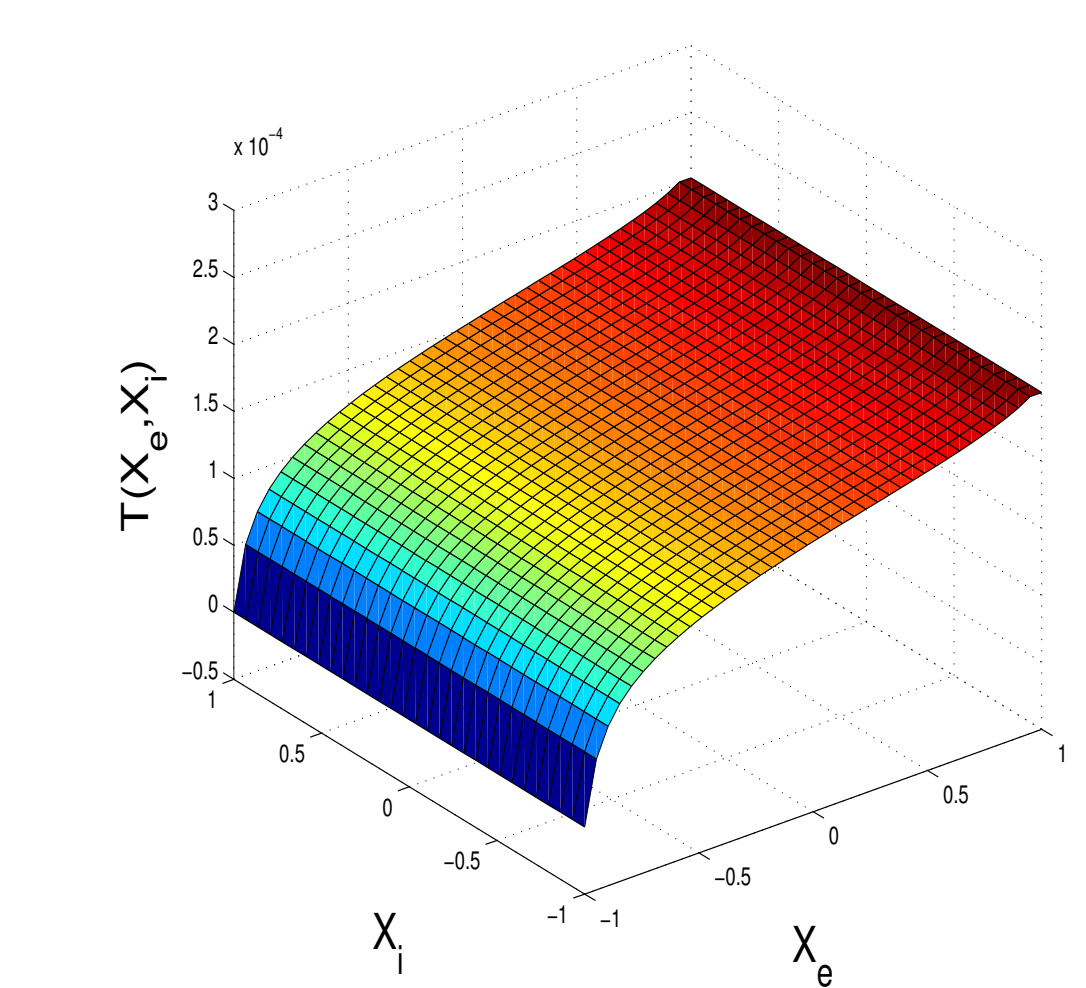
## Modelling results(I): exit through a specific point $a = X_i$ (or $V_+$ [mV]) at the boundary $X_e = -1$



## Modelling results (II): the mean exit time from the attraction basin



Exit point-averaged exit time



Mean time for exit through the boundary

## Conclusions

- FPT theory is applicable to the Hutt & Longtin (2009) model for anesthesia, where a bistable (noise-driven) regime is considered to underlie the observed sequences of 'up' and 'down' states.
- The dimensionality of the system can be reduced to a pair of 1st-order differential equations.
- Neuronal response functions can be described with a Heaviside function instead of a Sigmoid, with no essential modifications of the phase-portraits.
- Infinite basins of attractions and oblique boundaries can be avoided by appropriate coordinates changes.