# Supplementary Material

M. Voliotis[1,2], X. F. Li[3], K. T. O'Byrne[3], K. Tsaneva-Atanasova[1,2]

[1]Department of Mathematics and Living Systems Institute, College of Engineering, Mathematics and Physical Sciences, University of Exeter, Exeter, EX4 4QF, UK
[2]EPSRC Centre for Predictive Modelling in Healthcare, University of Exeter, Exeter, EX4 4QJ, UK.
[3]Division of Women's Health, School of Medicine, King's College London, London SE1 1UL, UK.

## 1 Derivation of the mean field model

To derive of the coarse-grained model we start by averaging Eq. 1 in the main text over all neurones (index $i$), and expressing the resulting equations in terms of the population-averaged values $\bar{D} = \frac{1}{M}\sum_i D_i$, $\bar{N} = \frac{1}{M}\sum_i N_i$, and $\bar{v} = \frac{1}{M}\sum_i v_i$:

$$\frac{d\bar{D}}{dt} = \frac{1}{M}\sum_{i=1}^{M} f_D(v_i) - d_D\bar{D}; \tag{1}$$

$$\frac{d\bar{N}}{dt} = \frac{1}{M}\sum_{i=1}^{M} f_N(v_i, D_i) - d_N\bar{N}; \tag{2}$$

$$\frac{d\bar{v}}{dt} = \frac{1}{M}\sum_{i=1}^{M} f_v\left(\{v_j, N_j\}_{j\in\text{neigh}(i)}\right) - d_v\bar{v}. \tag{3}$$

Next, we expand functions $f_D$, $f_N$, and $f_v$ around the population-averaged values $\bar{D}$, $\bar{N}$ and $\bar{v}$:

$$f_D(v_i) = f_D(\bar{v}) + (v_i - \bar{v})\frac{\partial f_D}{\partial v_i}(\bar{v}) + \ldots;$$

$$f_N(v_i, D_i) = f_D(\bar{v}, \bar{D}) + (v_i - \bar{v})\frac{\partial f_N}{\partial v_i}(\bar{v}, \bar{D}) + (D_i - \bar{D})\frac{\partial f_N}{\partial D_i}(\bar{v}, \bar{D}) + \ldots;$$

$$f_v\left(\{v_j, N_j\}_{j\in\text{neigh}(i)}\right) = f_v\left(\{\bar{v}, \bar{N}\}_{j\in\text{neigh}(i)}\right) + \sum_{j\in\text{neigh}(i)}\left[(v_i - \bar{v})\frac{\partial f_v}{\partial v_j}(\bar{v}, \bar{N}) + (N_i - \bar{N})\frac{\partial f_v}{\partial N_j}(\bar{v}, \bar{N})\right] + \ldots.$$

Replacing these expressions back into Eqs. 1-3, and assuming that deviations from the average behaviour (resulting from the random connectivity of the network) are small we obtain the equations describing the coarse grained model:

$$\frac{d\bar{D}}{dt} = f_D(\bar{v}) - d_D\bar{D}; \tag{4}$$

$$\frac{d\bar{N}}{dt} = f_N(\bar{v}, \bar{D}) - d_N\bar{N}; \tag{5}$$

$$\frac{d\bar{v}}{dt} = f_v(\bar{v}, \bar{N}) - d_v\bar{v}, \tag{6}$$

where $f_v(\bar{v}, \bar{N}) = v_0\left(\frac{2}{\exp(-I)+1} - 1\right)$ and $I = I_0 + p_v\bar{c}M\frac{\bar{N}^{n_4}}{\bar{N}^{n_4} + K_N^{n_4}}\bar{v}$.

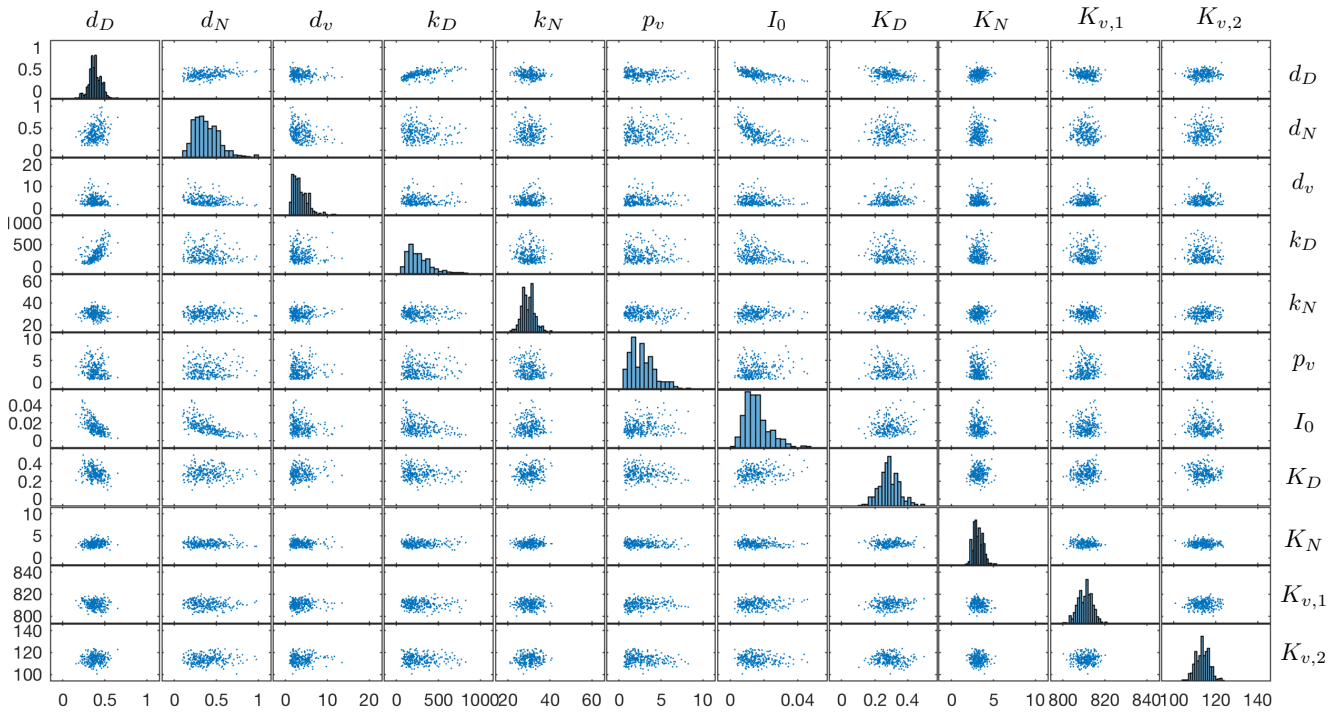


Figure A: Histograms and pairwise scatterplots from the approximated posterior distribution of parameters $d_D$, $d_N$, $d_v$, $k_d$, $k_N$, , $p_v$, , $I_0$, , $K_D$, , $K_N$, , $K_{v,1}$ and $K_{v,2}$.

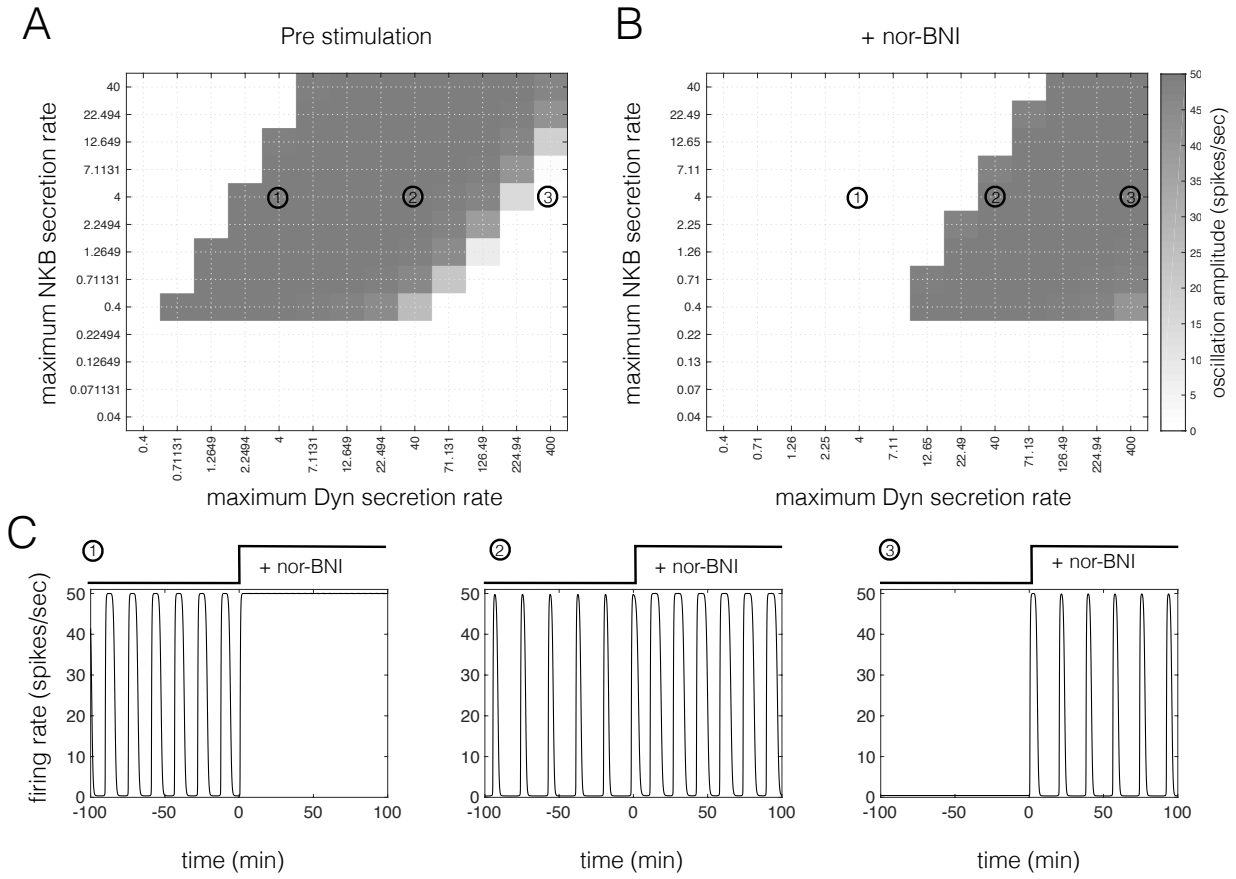


Figure B: bf The effect of neuropharmacological perturbations on the pulsatile dynamics of the KNDy population. Perturbation of the system with nor-BNI, a selective Dyn receptor antagonist, has variable effects on the pulsatile dynamics depending on the NKB and Dyn secretion rate. (A) The magnitude of oscillations (grey scale) in the unperturbed system for different levels of maximum NKB and Dyn secretion rate (parameters $k_N$ and $k_D$ in the model). (B) The magnitude of oscillations after perturbing the system with nor-BNI ($E_{nor-BNI} = 4.1$ nM). (D) Time-traces of the system activity in response to nor-BNI administration. Time-traces correspond to the $(k_N, k_D)$ combinations marked in (A) and (B). Model parameter values are given in Tbl 1 of the main text.

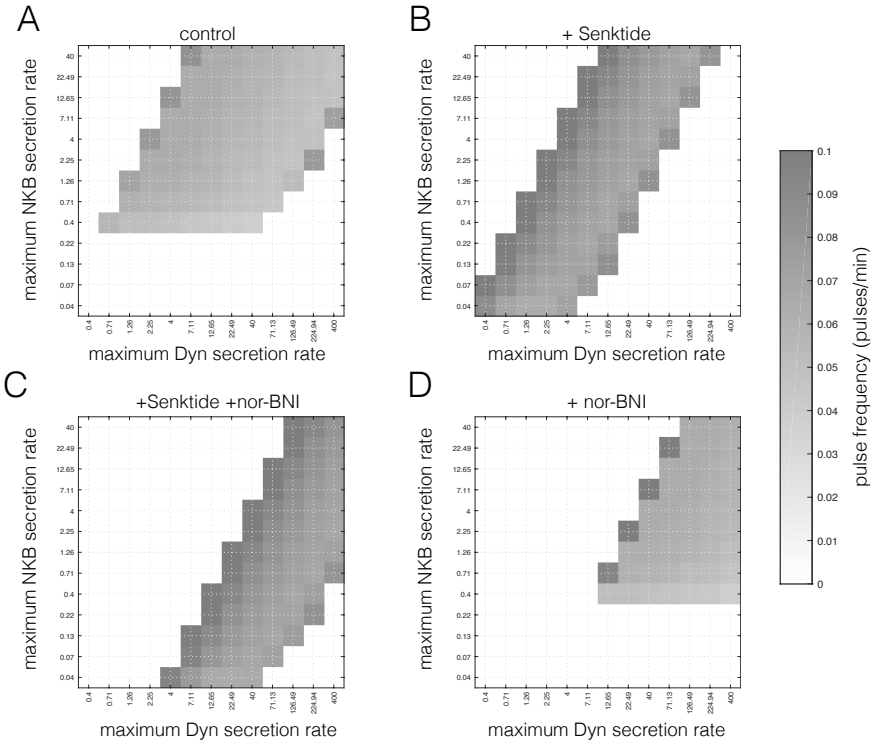


Figure C: **The effect of neuropharmacological perturbations on the frequency of the neuronal oscillator.** Perturbation of the system with two drugs—senktide, a selective NKB receptor agonist; and nor-BNI, a selective Dyn receptor antagonist—has variable effects on pulse frequency depending on the NKB and Dyn secretion rate. (A) Unperturbed system. (B) System perturbed with senktide ($E_{senktide} = 60$ pM). (C) System perturbed with senktide ($E_{senktide} = 60$ pM) and nor-BNI ($E_{nor-BNI} = 4.1$ nM). (D) System perturbed with nor-BNI ($E_{nor-BNI} = 4.1$ nM). Model parameter values are given in Tbl 1 of the main text.

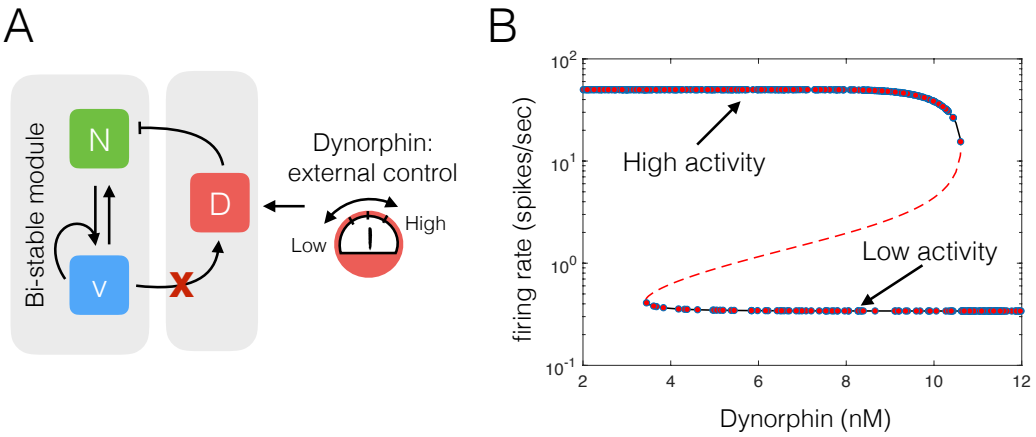


Figure D: **Disrupting the Dyn-mediated negative feedback reveals the bistability in the system.** Disrupting the negative feedback by fixing the levels of Dyn externally obliterates the oscillatory behaviour of the system. At steady stated the perturbed system relaxes in either a high or a low activity state (red dots) depending on the amplitude of the perturbation and it timing relative to the period of the oscillation. Model parameter values are given in Tbl 1 of the main text.