Theoretical & computational Neuroscience:

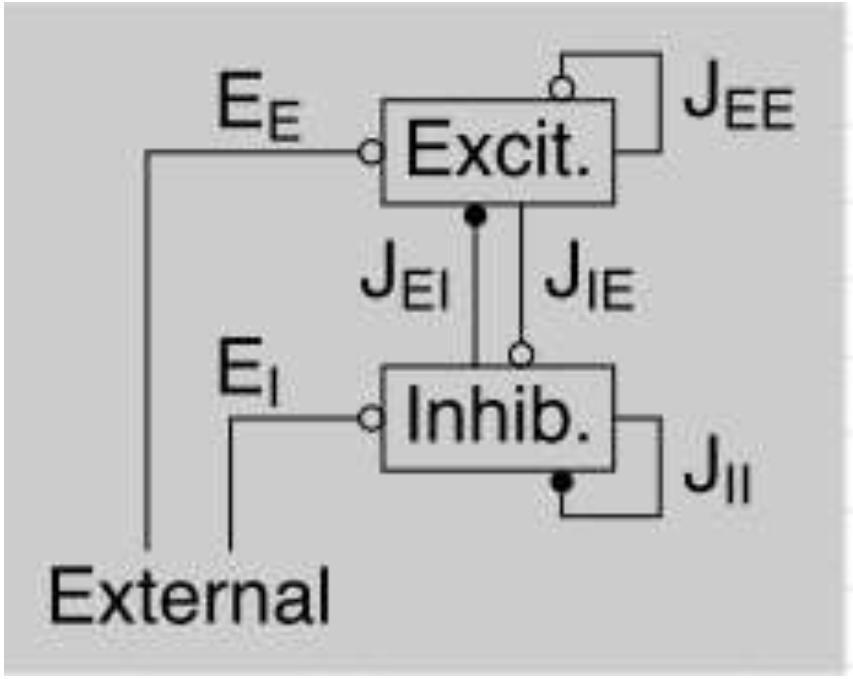
Programming the Brain

(BM 6140)

2-credit

Network dynamics

Coupled Excitatory-Inhibitory network



$$I_s = \sum_{b=1}^{N_u} w_b \int_{-\infty}^{t} d\tau \, K_s(t-\tau)\rho_b(\tau) \, . \tag{7.2}$$

As discussed previously, the critical step in the construction of a firing-rate model is the replacement of the neural response function $\rho_b(\tau)$ in equation 7.2 by the firing rate of neuron b, namely $u_b(\tau)$, so that we write

$$I_s = \sum_{b=1}^{N_u} w_b \int_{-\infty}^{t} d\tau \, K_s(t-\tau)u_b(\tau) \, . \tag{7.3}$$

The synaptic kernel most frequently used in firing-rate models is an exponential, $K_s(t) = \exp(-t/\tau_r)/\tau_r$. With this kernel, we can describe I_s by a differential equation if we take the derivative of equation 7.3 with respect to t,

$$\tau_s \frac{dI_s}{dt} = -I_s + \sum_{b=1}^{N_u} w_b u_b = -I_s + \mathbf{w} \cdot \mathbf{u} \, . \tag{7.4}$$

$$v_\infty = F(\mathbf{w} \cdot \mathbf{u}) . \tag{7.5}$$

The steady-state firing rate tells us how a neuron responds to constant current, but not to a current that changes with time. To model time-dependent inputs, we need to know the firing rate in response to a time-dependent synaptic current $I_s(t)$. The simplest assumption is that this is still given by the activation function, so $v = F(I_s(t))$ even when the total synaptic current varies with time. This leads to a firing-rate model in which all the dynamics arise exclusively from equation 7.4,

$$\tau_s \frac{dI_s}{dt} = -I_s + \mathbf{w} \cdot \mathbf{u} \quad \text{with} \quad v = F(I_s) . \tag{7.6}$$

An alternative formulation of a firing-rate model can be constructed by assuming that the firing rate does not follow changes in the total synaptic current instantaneously, as was assumed for the model of equation 7.6. Action potentials are generated by the synaptic current through its effect on the membrane potential of the neuron. Due to the membrane capacitance and resistance, the membrane potential is, roughly speaking, a low-pass filtered version of I_s (see the Mathematical Appendix). For this reason, the time-dependent firing rate is often modeled as a low-pass filtered version of the steady-state firing rate,

$$\tau_r \frac{dv}{dt} = -v + F(I_s(t)) . \tag{7.7}$$

$$\tau_r \frac{dv}{dt} = -v + F(\mathbf{w} \cdot \mathbf{u}) .$$

Wilson-Cowan model for networks

- Assume that E and I networks fire at a mean rate of $r_e and\ r_i$
- The network may be captured by its state (r_e, r_i)
- The equations representing the system are
- $\tau_e \frac{dr_e}{dt} = -r_e + J_{EE} r_e \ - J_{EI} r_i + U_E = \ -r_e + \phi_e(r_e, r_i)$
- $\tau_i \frac{dr_i}{dt} \ = -r_i + J_{IE} r_e \ - J_{II} r_i + U_I \ = \ -r_I + \phi_i(r_e, r_i)$

- ϕ can be thought of as a gain function or the feedback of the network

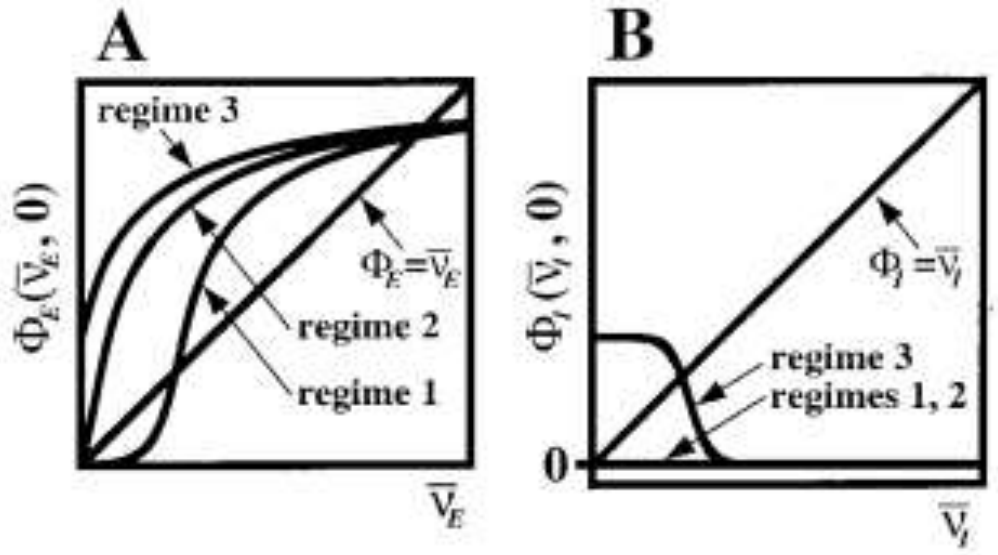
- Fixed points on r_e, r_i plane are equilibrium firing rates of the network

Examining network equilibria analytically

- Equilibrium states may be obtained by
  - Solve to get fixed points
  - Linearize using the Jacobian and examine stability of f.ps
  - Need an analytical expression for ϕ

Graphical method: Gain function

- At high firing rates
  - Gain functions are stereotypical and sigmoidal
  - Independent of neuron and network properties
  - Inhibitory gain has negative slope
- At low firing rates
  - Gain is sensitive to single neuron properties
  - Several regimes can be identified
    1. No cell fires in response to single EPSP
    2. Some cells fire in response to single EPSP
    3. Some cell spontaneously fire even at RMP



$\phi_e(r_e, c\ \ ) \ vs\ r_e$
For $r_i = c$

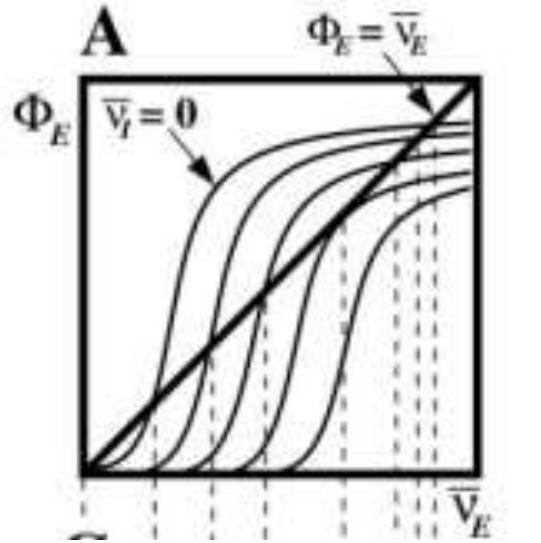
$\phi_i(r_e, k\ \ ) \ vs\ r_i$
For r_e =k

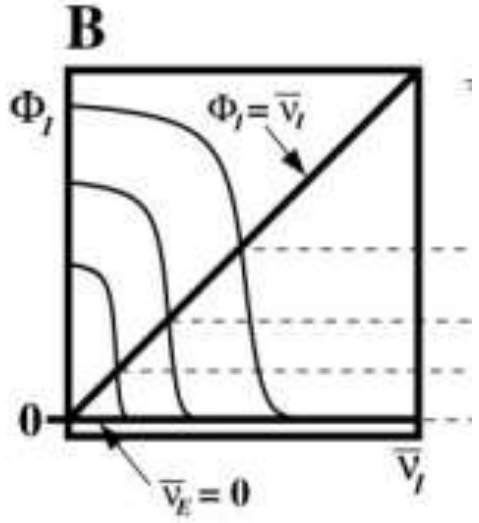
Latham, 2000

Graphical method for examining equilibria at low firing rates

- For various values of $r_i = \mathrm{c}_1, \mathrm{c}_2 \ldots$. plot $\phi(r_e, c_x) vs\ r_e$
  - Intersection of these curves with the 45 degree line are points on the r_e nullcline

- Similarly for various values of $r_e = k_1, \mathrm{k}_2 \ldots$. plot $\phi(r_e, k_x) vs\ r_i$
  - Intersection of these curves with the 45 degree line are points on the r_i nullcline

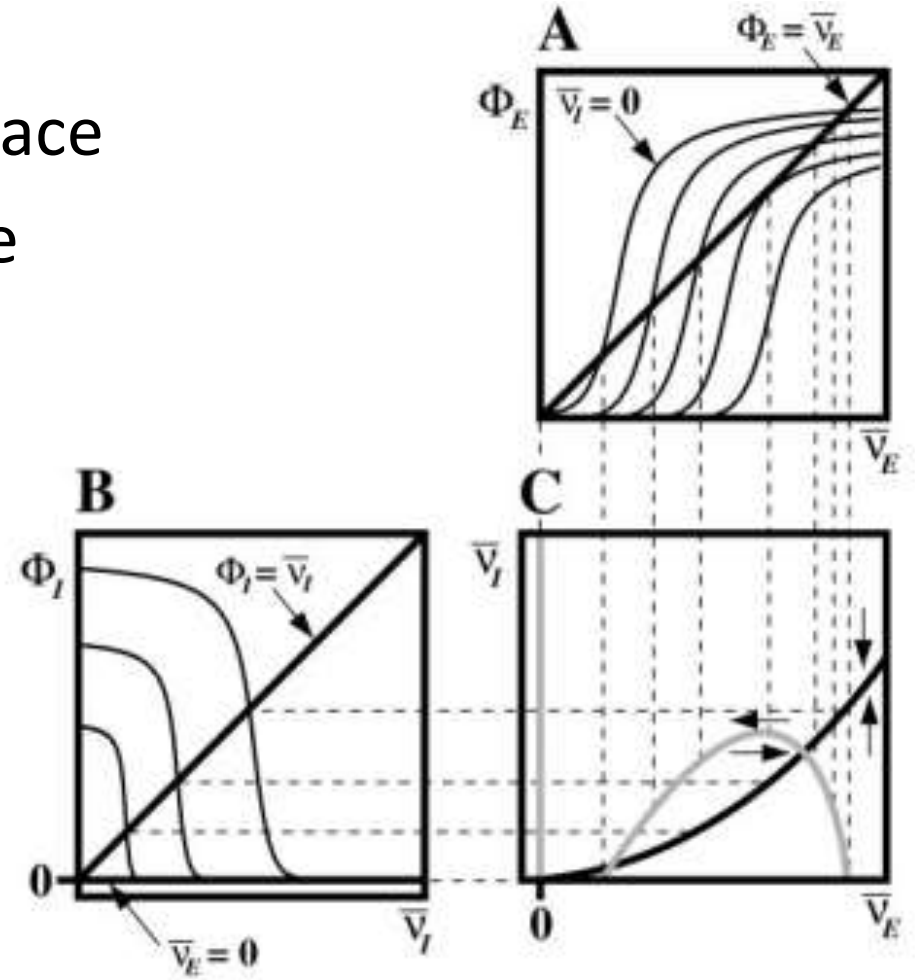




Latham, 2000

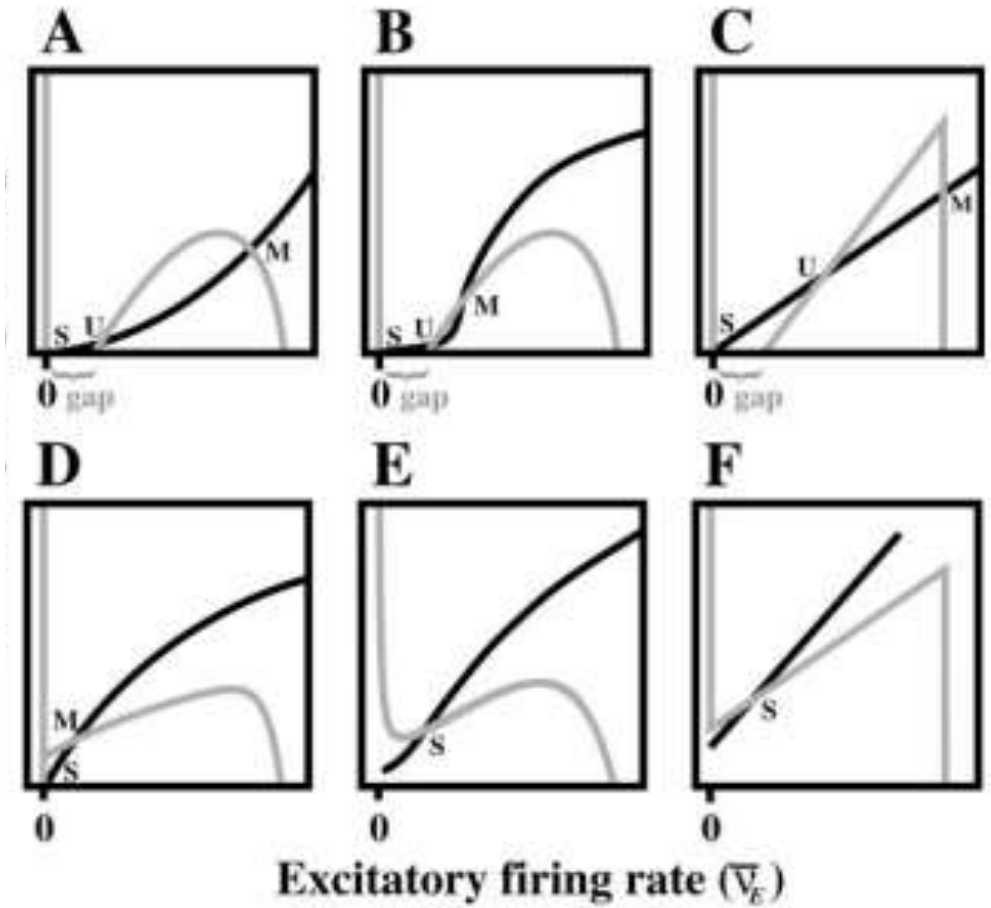
The r_e, r_i nullcline and fixed points

- Project the null-points onto the phase space
- Interpolate the null points to get nullcline
- Look at the intersection of nullclines



Latham, 2000

FIG. 4. Nullclines in the 3 regimes described in the main text. Excitatory and inhibitory nullclines are shown with gray and black lines, respectively. As in Fig. 3, $d\bar{\nu}_E/dt$ is positive below the excitatory nullcline and negative above it, whereas $d\bar{\nu}_I/dt$ is positive to the right of the inhibitory nullcline and negative to its left. S, M, and U indicate stable, metastable, and unstable equilibria, respectively. *A*: *regime 1*, none of the cells have their resting membrane potential within one EPSP of threshold. There is a stable equilibrium at zero firing rate and a metastable one at high firing rate, but the low firing rate equilibrium is unstable. *B*: *regime 1*, with strong curvature introduced in the inhibitory nullcline to create a metastable, low firing rate state. *C*: *regime 1*, in the very high connectivity limit where the nullclines are straight. In this limit 3 properties conspire to eliminate the possibility of a low firing rate equilibrium: the inhibitory nullcline is tied to the origin, there is a gap between the origin and the unstable branch of the excitatory nullcline, and the nullclines are straight. *D*: *regime 2*, some cells are within one EPSP of threshold. A metastable state can exist. This state persists even in the high connectivity limit, where the nullclines become straight. *E*: *regime 3*, endogenously active cells are present. A single, globally attracting equilibrium can exist. *F*: same as *E* except in the very high connectivity regime.



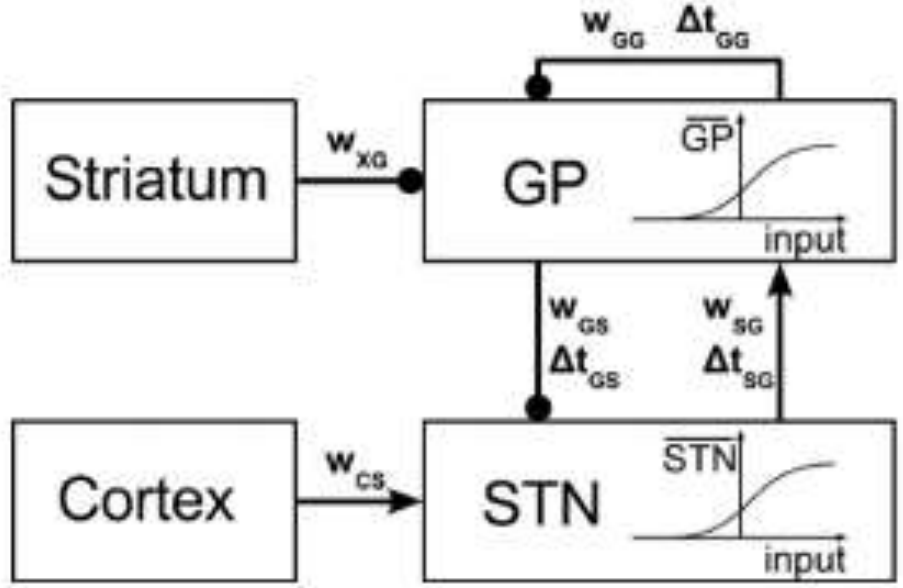
Latham, 2000

Network modeling to study disease

- E.g. Parkinson’s disease
- Occurs due to loss of dopaminergic neurons in substantia nigra

STn-Gpe network and emergence of pathological beta oscillations

- Exc: STN -> Gpe
- Inh: Gpe –o STn
- Cortex excites STn
- Striatum inhibits GP
- General rule, when Striatum fires, all motor circuitry is inhibited, in order to ensure that the best decision is made



- Holgado et al 2010

The devil is in the details !!!

- Choosing model parameters is the greatest test of a modeler !!
- Values may be obtained directly from experimental results or published literature, if you are lucky
- You will have to interpolate or extrapolate to get some others
- For yet others, choose the params that best match a given set of observations
- Last option, guess !. But ensure that you don't hide what you have done…
- Play devil's advocate and ways to break your own model and challenge your results

Table 1. Values of the parameters of the model and sources used to establish each value

Parameter	Value	Source
Δt_{SG}	6 ms	Kita et al. (2005)
Δt_{GS}	6 ms	Extrapolation to monkeys based on Fujimoto and Kita (1993) and Δt_{SG}
Δt_{GG}	4 ms	Based on proximity between cells
τ_S	6 ms	Kita et al. (1983); Nakanishi et al. (1987a); Paz et al. (2005)
τ_G	14 ms	Kita and Kitai (1991)
Ctx	27 spk/s	Lebedev and Wise (2000)
Str	2 spk/s	Schultz and Romo (1988)
M_S	300 spk/s	Hallworth et al. (2003)
B_S	17 spk/s	Hallworth et al. (2003)
M_G	400 spk/s	Kita et al. (2005); Kita (2007)
B_G	75 spk/s	Kita et al. (2004); Kita (2007)

- Holgado et al 2010

Modeling advance of parkinson

- Loss of dopaminergic neurons reduces input to the D2 receptor
- Dopamine inputs from D2 reduce the synaptic activity
- Loss of D2 causes increase in synaptic efficacy and hence increased weights
- Details →

- Holgado et al 2010

Table 4. Summary of literature supporting increase in specific synaptic weights with the advance of Parkinson's disease

Weight	Literature supporting weight increase in Parkinson's disease
w_{SG}	Dopamine reduces the effect of glutamate on GPe neurons (Johnson and Napier, 1997; Kita, 2007) D_2 receptors are present in GPe (Hoover and Marshall, 2004; Kita, 2007)
w_{GS}	In the parkinsonian state, GABA agonists in GPe evokes greater currents in STN (Shen and Johnson, 2005) Dopamine reduces the effect of GABA on STN neurons (Cragg et al., 2004) D_2 receptors are present in STN (Shen and Johnson, 2000)
w_{GG}	Increased ambient GABA in GPe in animal models of Parkinson's disease (Robertson et al., 1991; Ochi et al., 2000; Schroeder and Schneider, 2002) D_2 receptors are present in GPe (Hoover and Marshall, 2004; Kita, 2007)
w_{CS}	In the parkinsonian state, STN neurons are excited to a greater extent by cortex (Magill et al., 2001) In the parkinsonian state, AMPA and NMDA currents are greater in the STN (Shen and Johnson, 2005) D_2 receptors are present in STN (Shen and Johnson, 2000)
w_{XG}	Striatal neurons activity is increased after dopamine depletion (Kish et al., 1999; Tseng et al., 2001; O'Donnell, 2003) D_2 receptors reduce the excitability of striatopallidal neurons (Obeso et al., 2000; Surmeier et al., 2007) Increased GPe ambient GABA in animal models of Parkinson's disease (Robertson et al., 1991; Ochi et al., 2000; Schroeder and Schneider, 2002) D_2 receptors are present in GPe (Hoover and Marshall, 2004; Kita, 2007) Striatopallidal neurons are activated by dopamine lesion (Mallet et al., 2006)

The indexes of the weights refer to the origin and target nuclei of the connection they describe, and these can be C (cortex), X (striatum), S (STN), or G (GPe).

STN-Gpe oscillations with advancement of Parkinson

- Holgado et al 2010

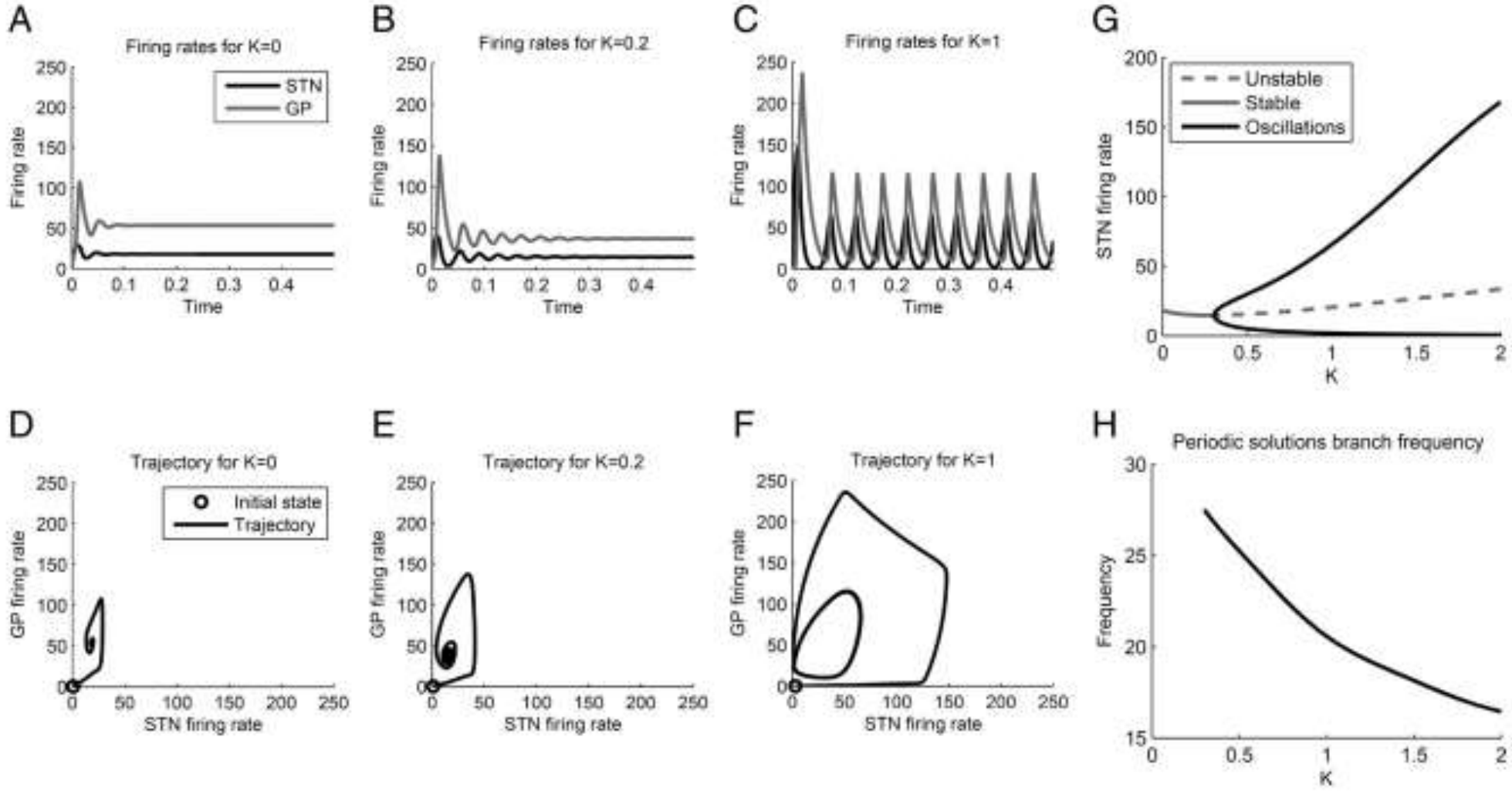


Figure 5. Simulations of the original model. ***A–C***, Firing rate as a function of time for different values of *K*. ***D–F***, Phase portraits of the system showing the same firing rates as in ***A–C***. ***G***, Range of firing rates of STN as a function of parameter *K*. A stable steady state is shown with a solid gray line. The unstable steady state is shown with a dashed gray line. The maximum and minimum values in a cycle of oscillations are shown in black. ***H***, Frequency of the oscillations for different values of *K*. Note that the model predicts a decrease in frequency of oscillation as the weights increase.

Summary of rate based models

- Simpler network equations
- Good qualitative insight
- But synapse and neuron parameters are not explicitly built into the model (remember we directly started with an equation for the network firing rate)
- Cannot model (un)correlated activity