"Excitatory and Inhibitory Interactions in Localized Populations of Model Neurons" by Hugh R. Wilson and Jack D. Cowan

(*BIOPHYSICAL JOURNAL*, Volume 12, 1972)

A Student Review by **Benjamin Huddell**

Mathematics 723 / Mathematical Neuroscience

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OVERVIEW: *Meaningful Population Model*

"ABSTRACT Coupled nonlinear differential equations are derived for the dynamics of spatially localized populations containing both excitatory and inhibitory model neurons. Phase plane methods and numerical solutions are then used to investigate population responses to various types of stimuli. The results obtained show simple and multiple hysteresis phenomena and limit cycle activity. The latter is particularly interesting since the frequency of the limit cycle oscillation is found to be a monotonic function of stimulus intensity. Finally, it is proved that the existence of limit cycle dynamics in response to one class of stimuli implies the existence of multiple stable states and hysteresis in response to a different class of stimuli. The relation between these findings and a number of experiments is discussed."

Sections

- Introduction
- The Model
- Time Course Graining
- Phase Plane Analysis
  - Theorem 1
- Hysteresis
  - Theorem 2
- Temporal Phenomena
  - Theorem 3
  - Theorem 4
- Conclusion
- Appendix

INTRODUCTION: Why shift focus from INDIVIDUAL CELLS to POPULATIONS?

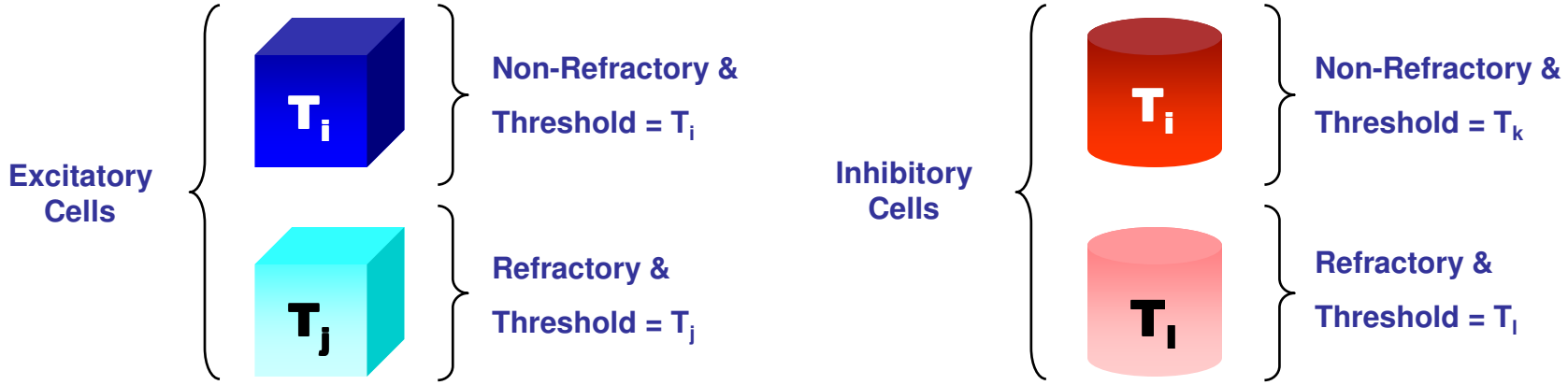
- Individual cells may be OK for primitive systems
- # Cells too vast (human brain 10^{11} neurons; connected to 10^4 other neurons)
- Higher processes global ("Relating Simple and Complex Visual Hallucinations in Charles Bonnet Syndrome" by Matthew Caldwell, Thesis, University College, London, April 2007)
- Inherent randomness in local interactions
  - Analogy to statistical mechanics ("A Mathematical Foundation for Statistical Neurodynamics" by Amari, Yoshida, & Kanatani, *SIAM J. Appl. Math.*, Vol. 33, No. 1, July 1977)
  - Wilson-Cowan a treatment of mean values underlying statistical processes
  - Local Redundancy; reliability of information processing (Von Neumann; Winograd & Cowan, 1963, "Reliable Computation in Presence of Noise, MIT Press, Cambridge, Mass.)

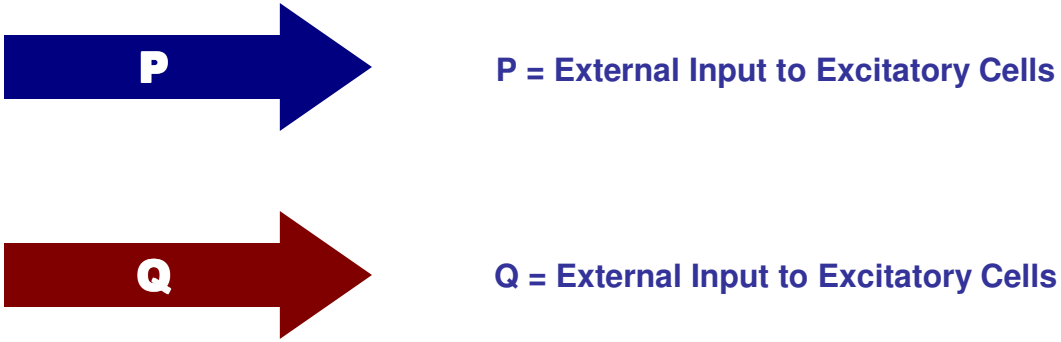
INTRODUCTION: Assumptions

- Cells in close spatial proximity
- Cell interconnections random yet dense enough so there is at least one path connecting any two cells within population
  - Neglect spatial interactions & deal with temporal dynamics of aggregate
- Key Variable- proportion of cells in population which become active per unit time
  - Only deal with spike frequency
- Time is continuous
- **"…all nervous processes of any complexity are dependent upon the interaction of excitatory and inhibitory cells."**
  - Two-variables necessary to describe population

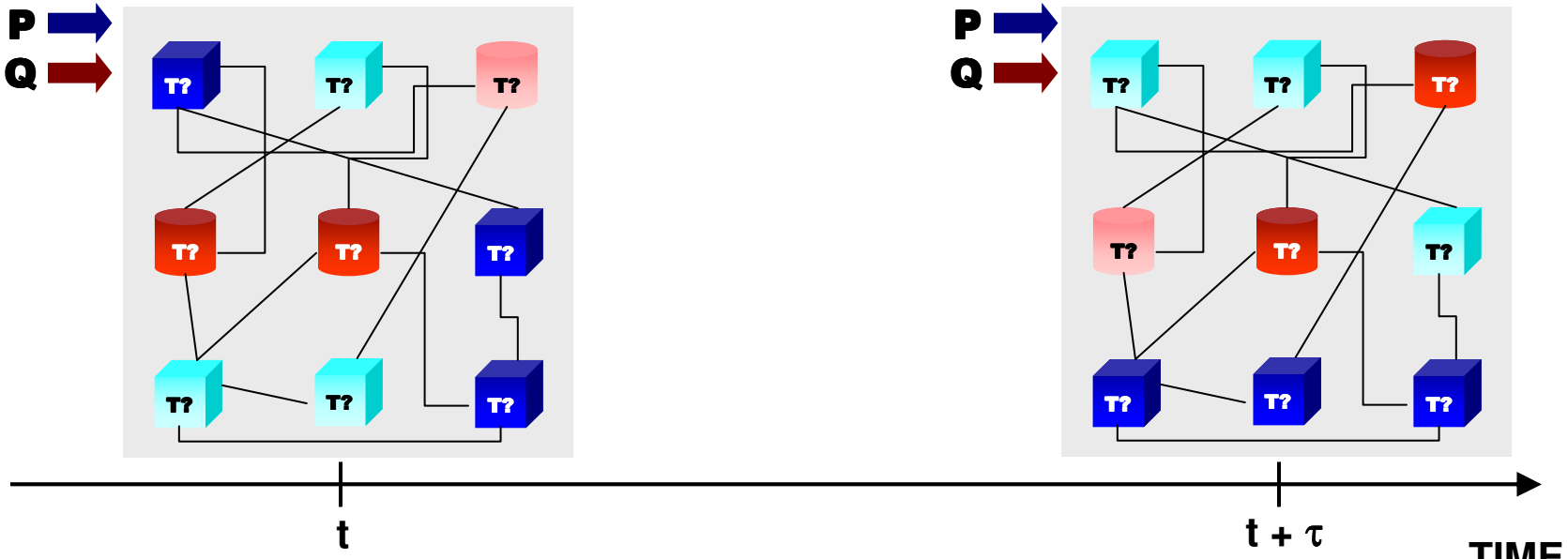
Assumptions Enable Meaningful Study of Dynamics of Spatially Localized Neural Populations

INTRODUCTION: Model Neurons





INTRODUCTION: Localized Subpopulations of Excitatory & Inhibitory Model Neurons



State of Sub-Populations Described By "Activities":

E(t + τ) = proportion of excitatory cells firing per unit time at t + τ

I(t + τ) = proportion of inhibitory cells firing per unit time at t + τ

Key Question: At time t + τ, which cells fire? Need to answer- Which cells refractory? How is stimulus related to cell thresholds?

THE MODEL: Proportion of Sensitive Cells

E(t) ⟷ **Proportion of Cells Which are Sensitive** **&** Proportion of Cells Receiving At Least Threshold Excitation

If absolute refractory period has duration r, proportion refractory cells given by

$$\int_{t-r}^{t} E\left(t'\right) dt'$$

Proportion of cells which are sensitive equals

$$1 - \int_{t-r}^{t} E\left(t'\right) dt'$$

THE MODEL: Response Function Definition

E(t)	⟷	Proportion of Cells Which are Sensitive	&	**Proportion of Cells Receiving At Least Threshold Excitation**

Response Function

Gives the expected proportion of the subpopulations receiving as least threshold excitation per unit time as a function of the average levels of excitation within the subpopulation

Notation-

- *$S_e(x)$ and $S_i(x)$ response functions for excitatory and inhibitory subpopulations.*
- *$x = x(t)$ is the average level of excitation within a subpopulation*

THE MODEL: Response Function Implemented

E(t)	⟷	Proportion of Cells Which are Sensitive	&	**Proportion of Cells Receiving At Least Threshold Excitation**

Approach 1

- *Distribution of individual neural thresholds characterized by D(θ)*
- *All cells receive same number of excitatory & inhibitory afferents*

then

$$S(x) = \int_0^{x(t)} D(\theta)\, d\theta \quad (1)$$

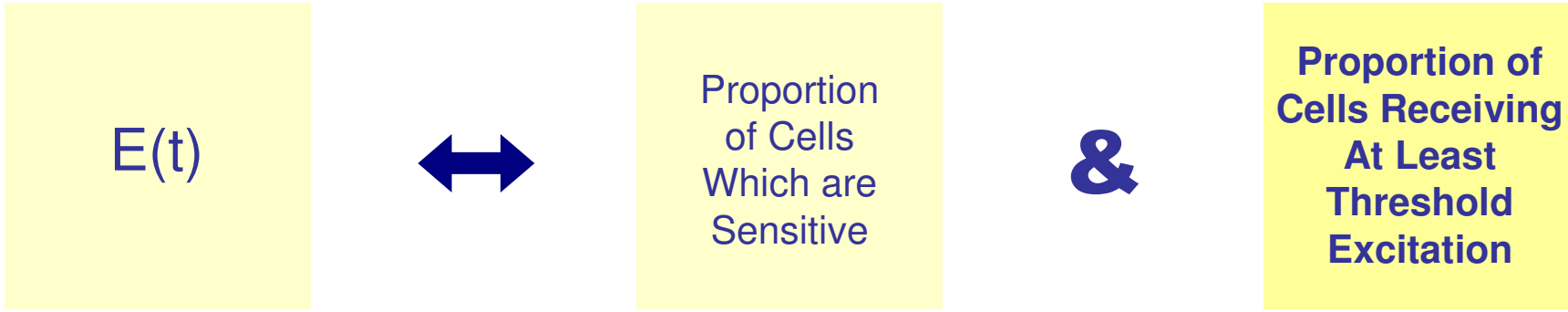
Approach 2

- *All cells within subpopulation have same threshold θ*
- *Distribution of number of afferent synapses per cell characterized by C(w)*

then

$$S(x) = \int_{\theta / x(t)}^{\infty} D(w)\, dw \quad (1a)$$

THE MODEL: Response Function as Sigmoidal



S(x) sigmoidal taken as characteristic of any subpopulation response function. sigmoidal if:

- *S(x) monotonically increasing on (-infinity, +infinity)*
- *S(x) approaches the asymptotic values 0 and 1 as x approaches –infinity and +infinity respectively*
- *S(x) has one inflection point*

(S(x) may be multinodal; viewed as weighted sum of unimodal sigmoid functions)

THE MODEL: **Figures 1 & 2** (from Wilson & Cowan)

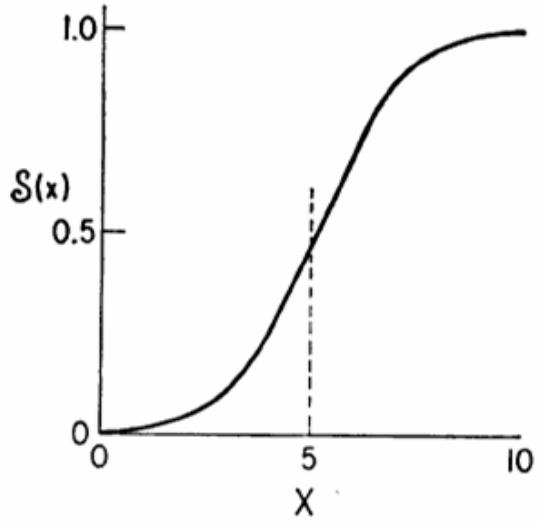


FIGURE 1

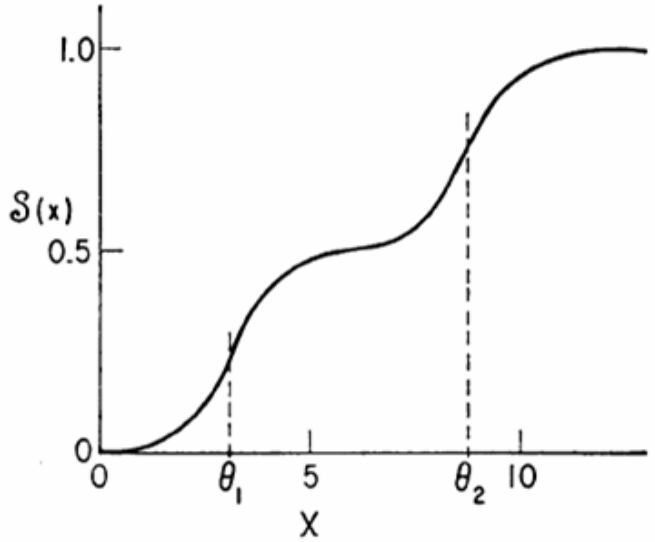


FIGURE 2

FIGURE 1 Plot of typical sigmoid subpopulation response function. X is average level of excitation in threshold units. The particular function shown here is the logistic curve: $S(x) = 1/[1 + e^{-a(x-\theta)}]$ with $\theta = 5, a = 1$.

FIGURE 2 Subpopulation response function resulting from bimodal distribution of thresholds or afferent synapses. X is excitation in threshold units, while θ_1 and θ_2 are the two local maxima of the underlying distribution. Note that this curve may be decomposed into a weighted sum of two sigmoid functions.

THE MODEL: Average Level of Excitation

E(t)	⟷	Proportion of Cells Which are Sensitive	&	**Proportion of Cells Receiving At Least Threshold Excitation**

Average Level of Excitation

$$\int_{-\infty}^{t} \alpha(t-t')\left[c_1 E(t') - c_2 I(t') + P(t')\right] dt' \quad (2)$$

where

$\alpha(t - t')$ = stimulation decay function

c_1 and c_2 = connectivity coefficients (positive) representing average number of excitatory & inhibitory synapses per cell

P(t) = external input to excitatory subpopulation (Q(t) corresponding term for inhibitory subpopulation)

THE MODEL: (almost)

E(t)	⟷	Proportion of Cells Which are Sensitive	**&**	Proportion of Cells Receiving At Least Threshold Excitation

If probability cell sensitive independent of probability cell excited above threshold, then E(t) described by

$$\left[1-\int_{t-r}^{t} E\left(t'\right)dt'\right]S_e\left(x\right)\delta t$$

THE MODEL: Complication of Correlation

E(t)	⟷	Proportion of Cells Which are Sensitive	**&**	Proportion of Cells Receiving At Least Threshold Excitation

In general, probability cell sensitive & excitation level correlated; therefore introduce correlation expression

$$\gamma\left[\int_{t-r}^{t} E\left(t'\right)dt', S_e(x)\right].$$

So that E(t) now given by

$$\left[1-\int_{t-r}^{t} E\left(t'\right)dt'\right]S_e(x)\left\{1-\gamma\left[\int_{t-r}^{t} E\left(t'\right)dt, S_e(x)\right]\right\}\delta t\,.$$

Due to fluctuations inherent in average excitation & cell thresholds, γ taken as 0.

THE MODEL: Integral Form

The equations governing the dynamics of a localized population of neurons are:

$$E(t+\tau)=\left[1-\int_{t-r}^{t}E(t')\,dt'\right]S_e\left\{\int_{-\infty}^{t}\alpha(t-t')\left[c_1E(t')-c_2I(t')+P(t')\right]dt'\right\} \quad (3)$$

$$I(t+\tau')=\left[1-\int_{t-r'}^{t}I(t')\,dt'\right]S_i\left\{\int_{-\infty}^{t}\alpha(t-t')\left[c_3E(t')-c_4I(t')+Q(t')\right]dt'\right\} \quad (4)$$

Note- τ and τ' are response delays, after which cells at time t will be firing.

TIME COURSE GRAINING: Description

The equations derived complex mathematically: non-linear, coupled & contain temporal integrals.

$$E(t+\tau)=\left[1-\int_{t-r}^{t}E(t')\,dt'\right]S_e\left\{\int_{-\infty}^{t}\alpha(t-t')\left[c_1E(t')-c_2I(t')+P(t')\right]dt'\right\} \quad (3)$$

$$I(t+\tau')=\left[1-\int_{t-r'}^{t}I(t')\,dt'\right]S_i\left\{\int_{-\infty}^{t}\alpha(t-t')\left[c_3E(t')-c_4I(t')+Q(t')\right]dt'\right\} \quad (4)$$

Equations will be simplified via "Time Course Graining";

- *A sort of moving window weighted average.*
- *Replace dependent variable f(t) with moving time average over some appropriately chose interval.*

$$\overline{f}(t)=\frac{1}{s}\int_{t-s}^{t}f(t')\,dt' \quad (5)$$

- *Effect: average out rapid temporal variations taking place on a time scale shorter than s.*

TIME COURSE GRAINING: Implementation

Application of time course graining to equation in E(t):

$$E(t+\tau)=\left[1-\int_{t-r}^{t}E(t')\,dt'\right]S_e\left\{\int_{-\infty}^{t}\alpha(t-t')\left[c_1E(t')-c_2I(t')+P(t')\right]dt'\right\} \quad (3)$$

$$\int_{t-r}^{t}E(t')\,dt' \rightarrow r\,\bar{E}(t) \qquad \int_{-\infty}^{t}\alpha(t-t')\,E(t')\,dt' \rightarrow k\,\bar{E}(t) \quad (6)$$

$$E(t+\tau)=\left(1-r\,\bar{E}\right)s_e\left[kc_1\bar{E}-c_2k\bar{I}+kP(t)\right]$$

Taylor expansion about $\tau = 0$; retention to linear term:

$$\tau\frac{d\bar{E}}{dt}=-\bar{E}+\left(1-r\,\bar{E}\right)S_e\left[kc_1\bar{E}-c_2k\bar{I}+kP(t)\right] \quad (7)$$

$$\tau'\frac{d\bar{I}}{dt}=-\bar{I}+\left(1-r\,\bar{I}\right)S_i\left[k'c_3\bar{E}-c_4k'\bar{I}+k'Q(t)\right] \quad (8)$$

TIME COURSE GRAINING: **Assessment**

Start with the integral equation

$$E(t+\tau)=\left[1-\int_{t-r}^{t}E(t')\,dt'\right]S_e\left\{\int_{-\infty}^{t}\alpha(t-t')\left[c_1E(t')-c_2I(t')+P(t')\right]dt'\right\} \quad (3)$$

Expand to lowest term in τ , assume $\alpha(t - t')$ decays exponentially, and exclude inhibitory interactions

$$\tau\frac{dE}{dt}=-E+\left[1-\int_{t-r}^{t}E(t')\,dt'\right]S_e\left\{\int_{-\infty}^{t}e^{-\alpha(t-t')}\left[c_1E(t')+P(t')\right]dt'\right\} \quad (9)$$

Compare computer solution of this equation with that generated by smoothed equation:

$$\tau\frac{d\overline{E}}{dt}=-\overline{E}+\left[1-r\overline{E}\right]S_e\left[kc_1\overline{E}(t)+kP(t)\right] \quad (10)$$

<u>Conclusion</u>: The integral equation exhibits damped oscillations while the smoothed equation exhibits smooth decay; for physiological significant values of α and r the course grained equations are valid.

(<u>Note</u>- see "A Simple Case of the Wilson-Cowan Equations" by A. Muir, ***Biophys. J.***, Vol. 27, August 1979, 267-276 for further investigation)

TIME COURSE GRAINING: **Figures 3 & 4** (from Wilson & Cowan)

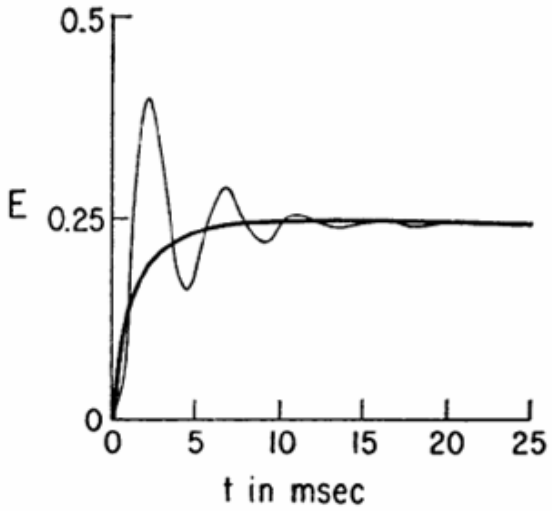


FIGURE 3

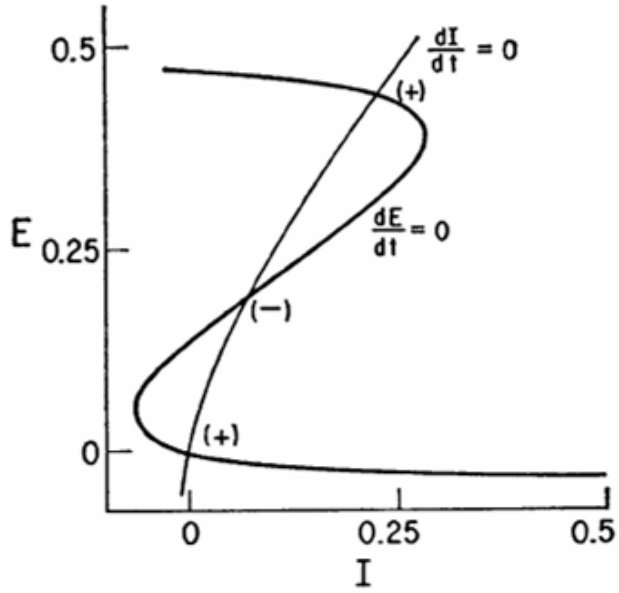


FIGURE 4

FIGURE 3 Comparison of solution to equation 9 (lighter line) with solution with the temporal coarse-grained equation 10 (heavier line). Duration of refractory period: $r = 3$ msec.

FIGURE 4 Phase plane and isoclines (equations 13 and 14). (+) denotes stability and (−), instability of steady state. Parameters: $c_1 = 12, c_2 = 4, c_3 = 13, c_4 = 11, a_e = 1.2, \theta_e = 2.8, a_i = 1, \theta_i = 4, r_e = 1, r_i = 1, P = 0, Q = 0$.

PHASE PLANE ANALYSIS: Further Simplification

E, I = 0 corresponding to background activity requires

- *E, I = 0 must be steady state solution to equations for P(t), Q(t) = 0*
- *Can be accomplished by transforming Se, Si so that Se(0), Si(0) = 0*
  - *Subtract S(0) from original function*
  - *Max values of S_e and S_i now less than 1; designate as k_e and k_i*

Equations can now be written:

$$\tau_e \frac{dE}{dt} = -E + \left(k_e - r_e E\right) S_e \left(c_1 E - c_2 I + P\right) \quad (11)$$

$$\tau_i \frac{dI}{dt} = -I + \left(k_i - r_i I\right) S_i \left(c_3 E - c_4 I + Q\right) \quad (12)$$

PHASE PLANE ANALYSIS: Wilson-Cowan Approach

Choose response function as logistic curve shifted downward so that S(0) = 0:

$$S(x) = \frac{1}{1+\exp\left(-a\left(x-\theta\right)\right)} - \frac{1}{1+\exp\left(a\theta\right)} \quad (15)$$

where

θ = position of max slope and max[S'(x)] = S'(q) = a / 4 (16).

Since S_e and S_i are sigmoidal, they have unique inverses; therefore can write equations for nullclines:

$$c_2 I = c_1 E - S_e^{-1}\left(\frac{E}{k_e - r_e E}\right) + P \quad for \quad \frac{dE}{dt} = 0 \quad (13)$$

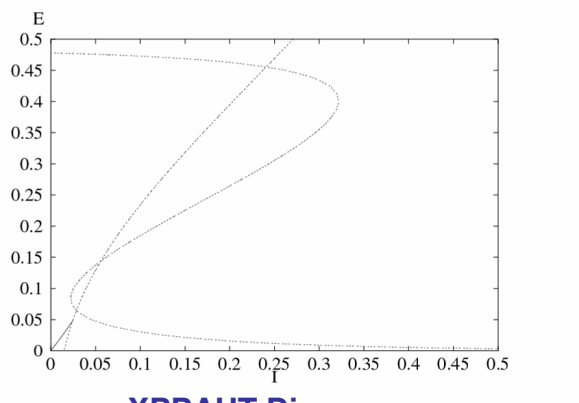
$$c_3 I = c_4 I - S_i^{-1}\left(\frac{I}{k_i - r_i I}\right) - P \quad for \quad \frac{dI}{dt} = 0 \quad (14).$$

Approach:

- *Define a stimulus configurations to be any particular choice of constant values for P and Q.*
- *Investigate important dynamical behavior based on relationships between c_1, c_2, c_3, c_4 and a_e & a_i*
- *Connect physiologically*

XPPAUT Offline: Wilson Cowan Program

```
# Wilson-Cowen Model
# WC.ode
#
# Parameters
par c1=12,c2=4,c3=13,c4=11
par ae=1.2,ai=1,theta_e=2.8,theta_i=4
par re=1,ri=1,ke=.97,ki=.98
par p=0,q=0
#
# Functions
se(x)=1/(1+exp(-ae*(x-theta_e)))
si(x)=1/(1+exp(-ai*(x-theta_i)))
#
# Diff. Eqs.
e'=-e+(ke-re*e)*se(c1*e-c2*i+p)
i'=-i+(ki-ri*i)*si(c3*e-c4*i+q)
#
# Initial Conditions
init e=0,i=0
#
done
```



XPPAUT Diagram

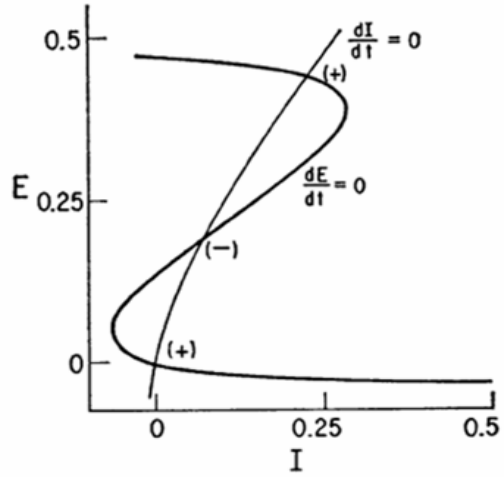
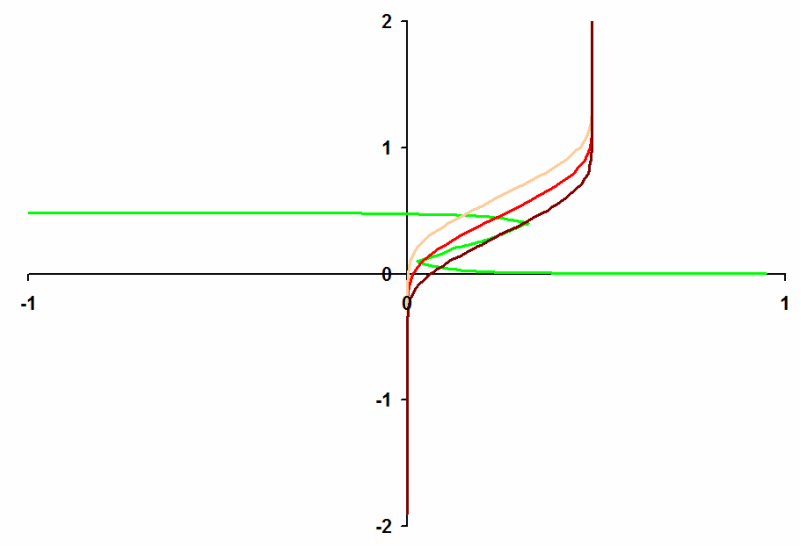


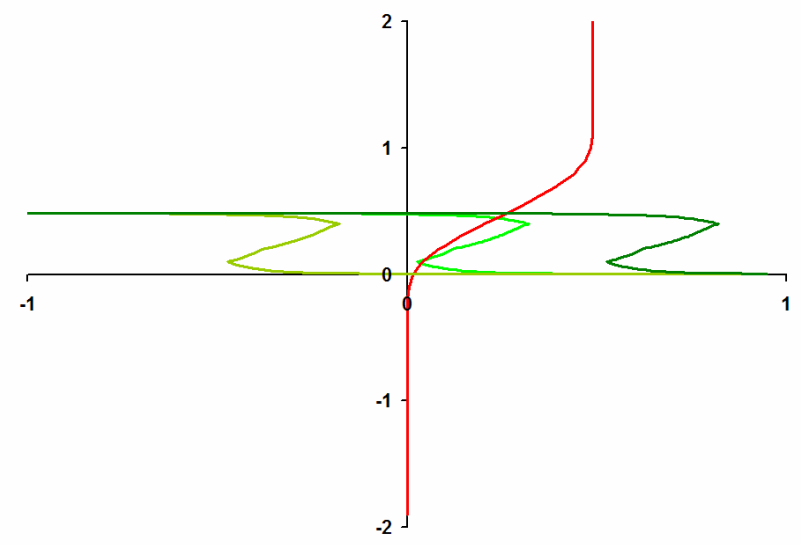
FIGURE 4 Phase plane and isoclines (equations 13 and 14). (+) denotes stability and (−), instability of steady state. Parameters: $c_1 = 12, c_2 = 4, c_3 = 13, c_4 = 11, a_e = 1.2, \theta_e = 2.8, a_i = 1, \theta_i = 4, r_e = 1, r_i = 1, P = 0, Q = 0$.

XPPAUT Offline: Dependence on External Inputs P&Q



E = external input to excitatory subpopulation

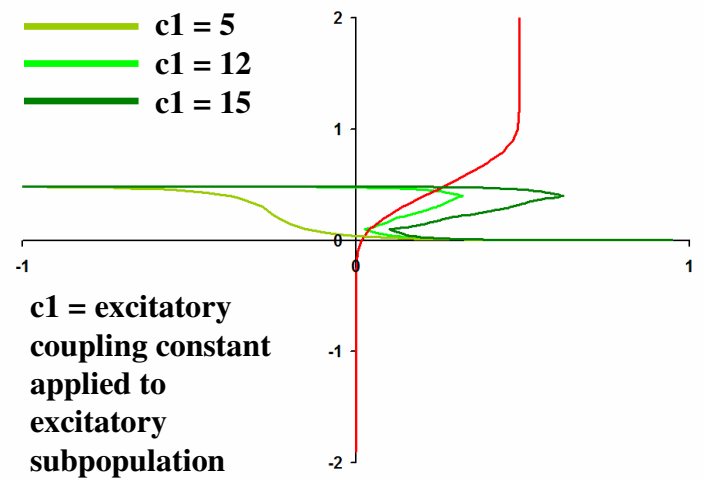
P = -2
P = 0
P = 2



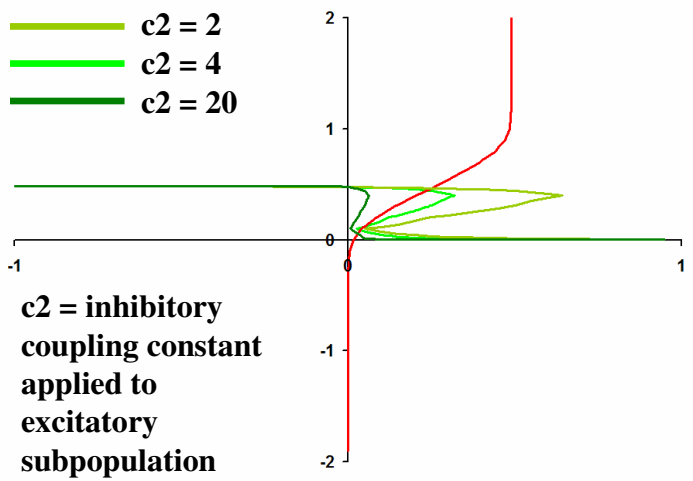
I = external input to inhibitory subpopulation

Q = -2
Q = 0
Q = 2

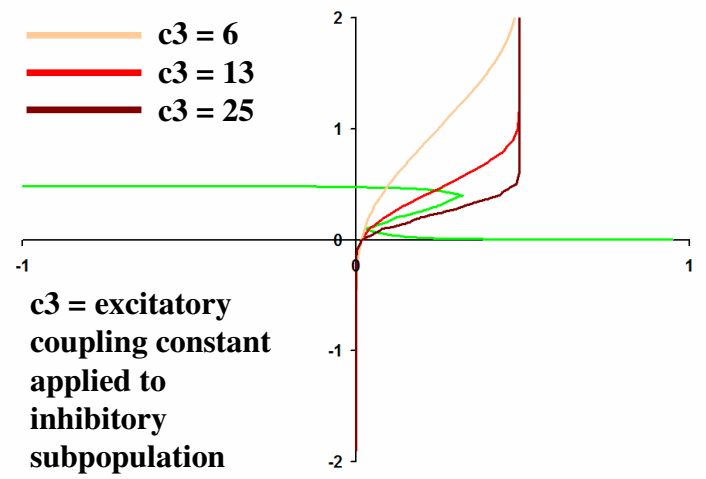
XPPAUT Offline: Dependence on Coupling Parameters c_1, c_2, c_3, & c_4



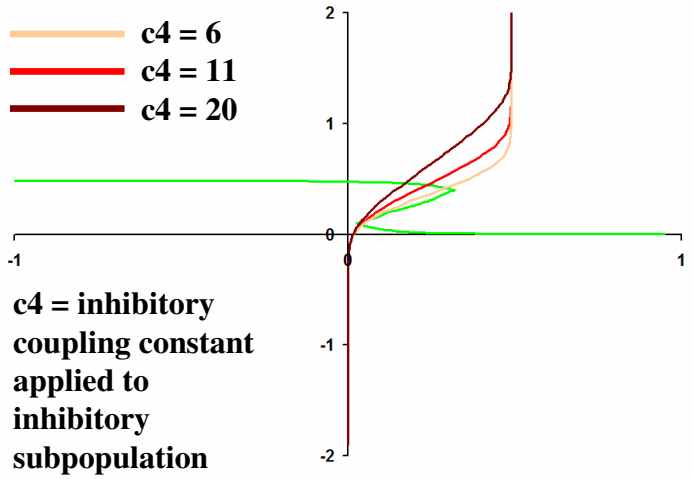
c1 = excitatory coupling constant applied to excitatory subpopulation



c2 = inhibitory coupling constant applied to excitatory subpopulation

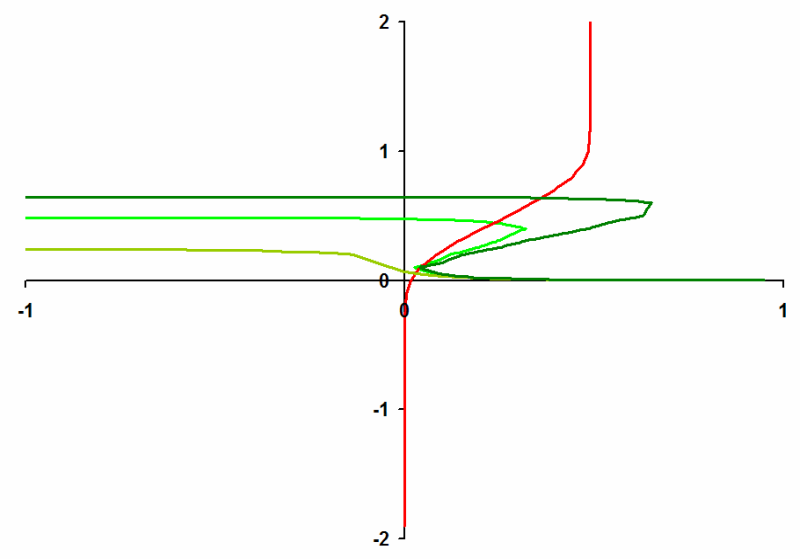


c3 = excitatory coupling constant applied to inhibitory subpopulation



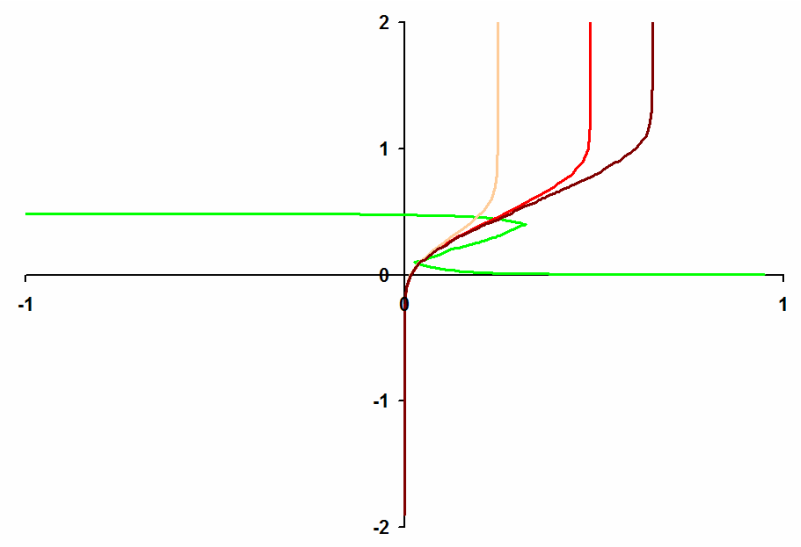
c4 = inhibitory coupling constant applied to inhibitory subpopulation

XPPAUT Offline: Dependence on Delay Parameters re & ri



re = refractory delay for excitatory subpopulation

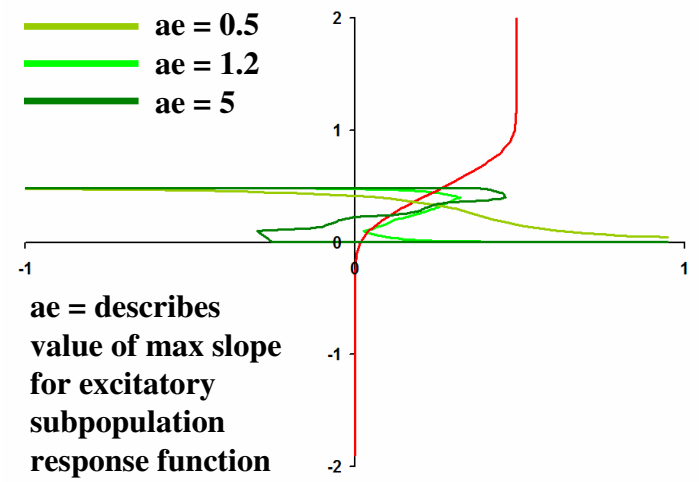
re = 0.5
re = 1
re = 3



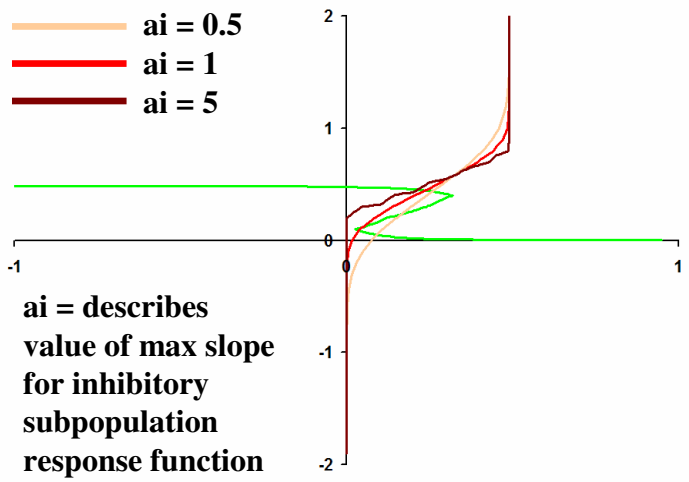
ri = refractory delay for inhibitory subpopulation

ri = 0.5
ri = 1
ri = 3

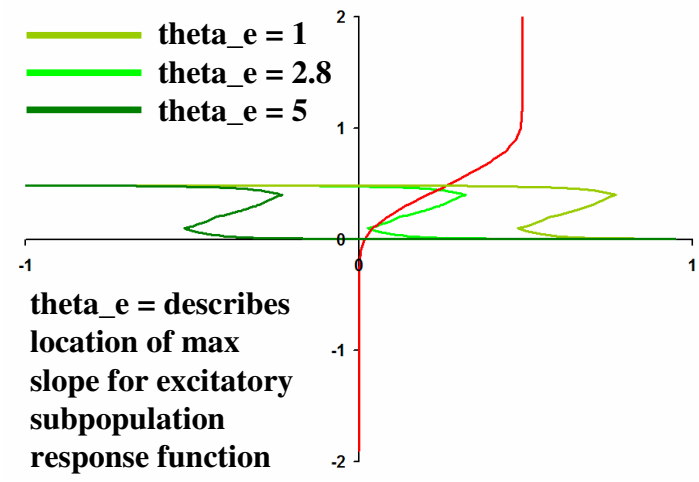
XPPAUT Offline: *Response Function Parameter Dependence* ae, ai, theta_e & theta_i



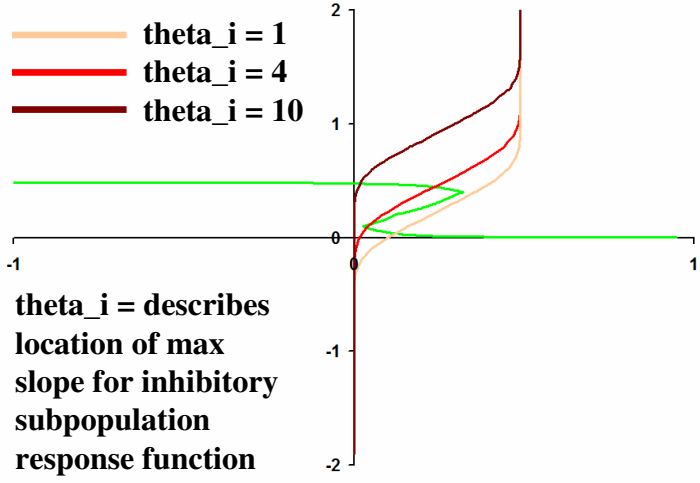
ae = describes value of max slope for excitatory subpopulation response function



ai = describes value of max slope for inhibitory subpopulation response function



theta_e = describes location of max slope for excitatory subpopulation response function

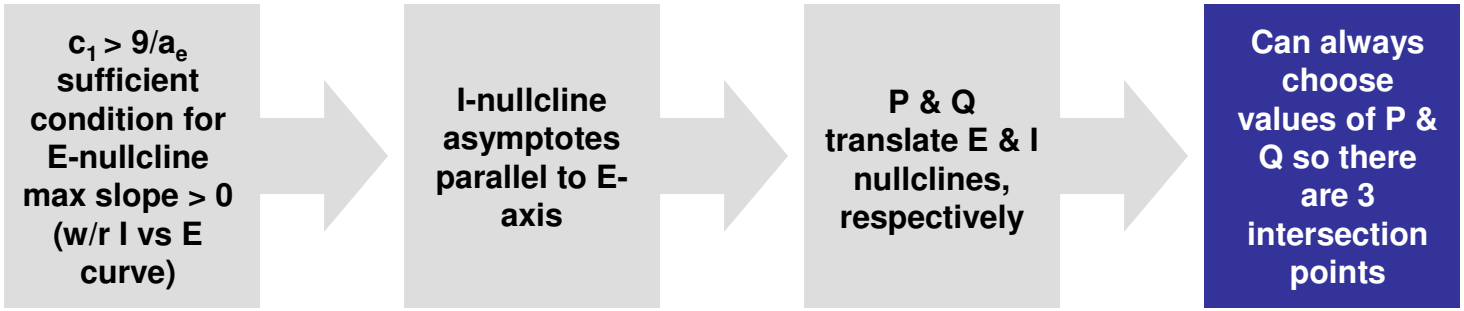


theta_i = describes location of max slope for inhibitory subpopulation response function

PHASE PLANE ANALYSIS: Theorem 1

Theorem 1. If $c_1 > 9 / a_e$ (17), then there is a class of stimulus configurations such that the isoclines defined by equations 13 and 14 will have at least three intersections. That is, equations 11 and 12 will have at least three steady-state solutions.

A stimulus configurations is defined to be any particular choice of *constant* values for P and Q.



Physiological Significance:

- $1/a_e$ directly related to variance of distribution of thresholds or synaptic connections
- A sufficient condition for multiple steady states is that the average number of synapses between neurons must exceed a function of the variance in the distribution of these connections (or alternatively, the variance in distribution of thresholds).

HYSTERESIS: Theorem 2

Theorem 2. Let the parameters of a neural population satisfy

$$\frac{a_e c_2}{a_e c_1 - 9} > \frac{a_i c_4 + 9}{a_i c_3} \quad (18)$$

Then five steady states will exist, through not necessarily concurrently, for some class of stimulus configurations.

5 steady states possible only if min slope of E-nullcline is less than reciprical of max slope at kink in I-nullcline (see Fig. 8)

$a_e c_2/(a_e c_1-9)$ > $(a_i c_4+9)/a_i c_3$

Physiological Significance:

$$\frac{a_e c_2}{a_e c_1 - 9} > \frac{a_i c_4 + 9}{a_i c_3} \quad \Leftrightarrow \quad a_e a_i c_2 c_3 > (a_e c_1 - 9)(a_i c_4 + 9)$$

$c_2 c_3$ measures strength of negative feedback

Existence of 5 steady states requires strong negative feedback loop

HYSTERESIS: **Figures 7 & 8** (from Wilson & Cowan)

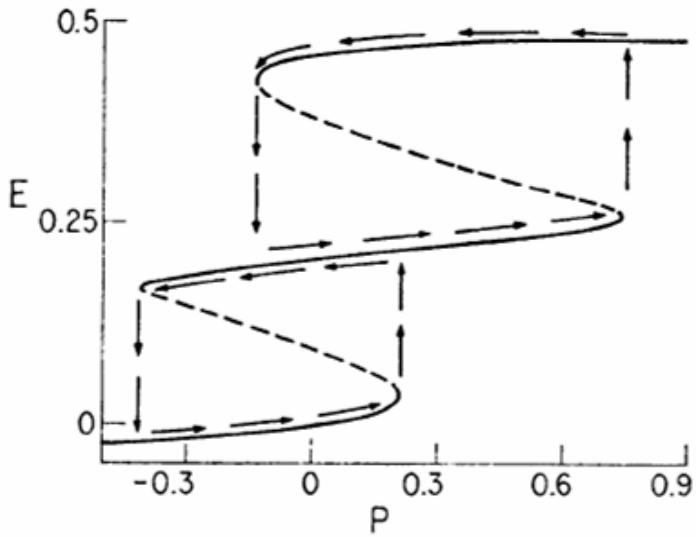


FIGURE 7

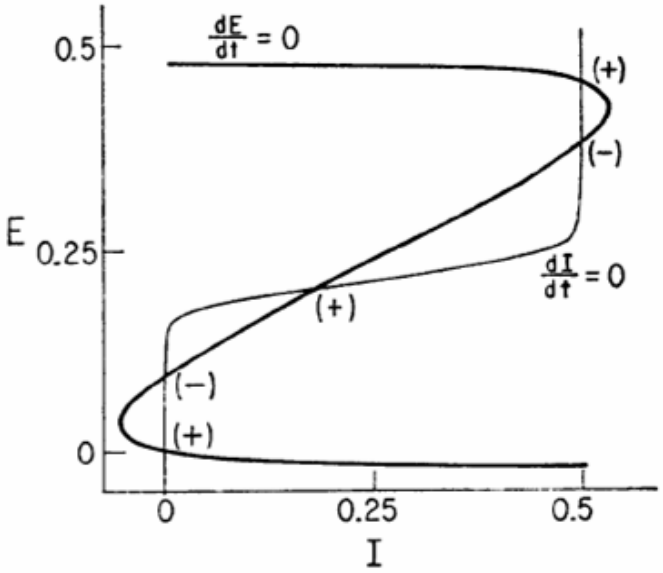


FIGURE 8

FIGURE 7 Steady-state values of E as a function of P ($Q = 0$). Solid lines indicate stability and dotted lines, instability. Here two overlapping hysteresis loops (arrows) are present: note the existence of three stable states in an interval around $P = 0$. Parameters: $c_1 = 13$, $c_2 = 4$, $c_3 = 22$, $c_4 = 2$, $a_e = 1.5$, $\theta_e = 2.5$, $a_i = 6$, $\theta_i = 4.3$, $r_e = 1$, $r_i = 1$.

FIGURE 8 Phase plane and isoclines with parameters chosen to give three stable (+) and two unstable (−) steady states. Parameters are the same as those in Fig. 7 with $P = 0$.

Theorem 3. Let parameters be defined so that the condition below is satisfied

$$c_1 a_e > c_4 a_i + 18 \quad (20)$$

Then if the condition below is *not* satisfied,

$$\frac{a_e c_2}{a_e c_1 - 9} > \frac{a_i c_4 + 9}{a_i c_3} \quad (21)$$

then multiple hysteresis phenomena will occur for some class of stimulus.

If, on the other hand, requirement (20) and the requirement (22) below are satisfied,

$$\frac{a_e c_1 - 9}{a_e c_2} > 1 \quad (22)$$

Then for some class of stimulus configuration limit cycle dynamics will be obtained.

"The proof of this theorem follows directly from a consideration of shapes of the isoclines in equations 13 and 14 plus an enumeration of the possible ways in which they can intersect. It is straightforward but tedious and will not be reproduced"

TEMPORAL PHENOMENA / LIMIT CYCLES : Theorem 3 Physiological Significance

The condition $c_1 a_e > c_4 a_i + 18 \quad (20)$

follows from instability requirement for limit cycles. Can be interpreted to mean that interaction with excitatory population significantly greater than that within inhibitory population for periodic behavior.

The conditions $\frac{a_e c_2}{a_e c_1 - 9} > \frac{a_i c_4 + 9}{a_i c_3} \quad (21)$ $\qquad \frac{a_e c_1 - 9}{a_e c_2} > 1 \quad (22)$

follow from condition that there be only one steady state (and that it be near inflection point) for limit cycle.

If limit behavior studied as function of P (with Q = 0),

- *Threshold value of P below which limit cycle activity cannot occur*
- *Exist a value of P above which limit cycle activity is extinguished*
- *Within bound above, the average value of E(t) increases monotically with P*

Similar behavior observed in stimulation of thalamic somatosensory neurons (Poggio, G. F. & Viernstein, L. J., J. Neuronphysiol., 1964, 27:517)

Limit cycles as model for some of characteristics of electroencephalogram (EEG) (Dewan, E. M., J. Theor. Biol., 1964, 7:141)

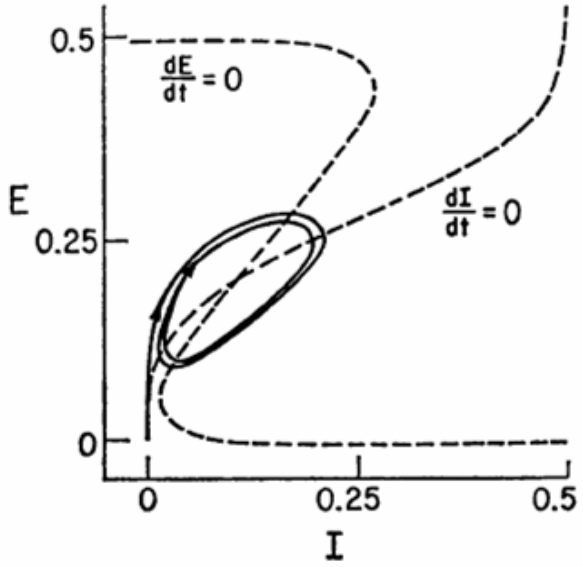


FIGURE 11 *a*

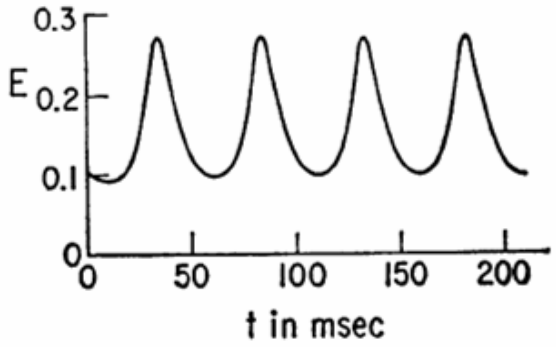


FIGURE 11 *b*

FIGURE 11 *a* Phase plane showing limit cycle trajectory in response to constant stimulation $P = 1.25$. Dashed lines are isoclines. Parameters: $c_1 = 16, c_2 = 12, c_3 = 15, c_4 = 3, a_e = 1.3, \theta_e = 4, a_i = 2, \theta_i = 3.7, r_e = 1, r_i = 1$.

FIGURE 11 *b* $E(t)$ for limit cycle shown in Fig. 11 *a*. $\tau = 8$ msec.

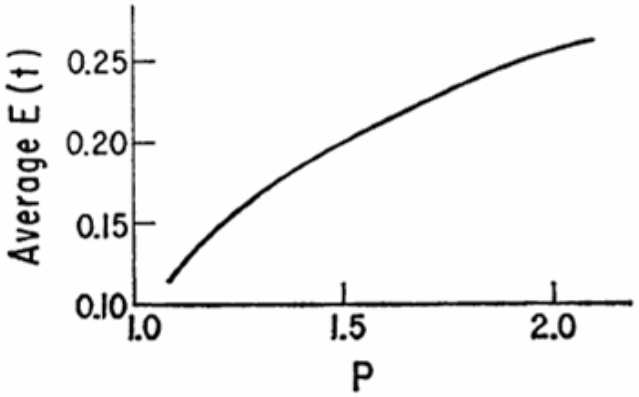


FIGURE 12 *a*

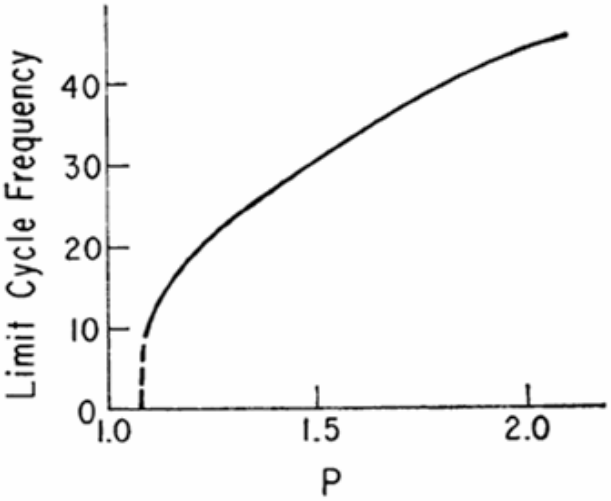


FIGURE 12 *b*

FIGURE 12 *a* ***E*(*t*)** averaged over one period of limit cycle as a function of stimulation at constant intensity ***P*.**

FIGURE 12 *b* Frequency of limit cycle (in Hz) for different levels of constant stimulation ***P*.** For very low values of ***P*** no cycle is obtained, i.e., frequency drops to zero. For very high values of ***P*** the oscillation is extinguished and only high-level, constant activity is observed. Parameters are those given in Fig. 11 ***a*.**

TEMPORAL PHENOMENA / LIMIT CYCLES : Theorem 4

Theorem 4. Any neural population which exhibits limit cycle activity for some class of stimulus configurations will also display simple hysteresis phenomena for some other class of stimulus phenomena.

Proof:

Compare condition $c_1 > 9 / a_e$ (17), *with* $c_1 a_e > c_4 a_i + 18 \quad (20)$ *and* $\frac{a_e c_2}{a_e c_1 - 9} > \frac{a_i c_4 + 9}{a_i c_3} \quad (21)$.

The min value of RHS of equation 20 is 18.

The LHS of equation 21 must be greater than 0.

Therefore, whenever equations 20 and 21 are satisfied equation 17 will also be satisfied.

Physiological Significance:

"Theorem 4 is very strong in light of the suggested functional significance of both limit cycles and hysteresis."

CONLUSIONS

"The most fundamental difference between this study and previous work, therefore, is in the treatment of inhibition as arising exclusively from inhibitory neruons."

- *Dale's Law*
- *Necessitates two-variable approach*
- *Enables study of rich dynamical behavior*

The "minimal model" for populations (in Izhikevich sense)

Foundation model that has frequently been used to develop more complex models. (see Dynamical Principles in Neuroscience" by M.I. Rabinovich, P. Varona, A. I. Selverston, & H. D. I. Abarbanel in Reviews of Modern Physics, Vol. 78, Oct. – Dec., 2006.)

Extensions & Further Development

- *Appendix- Extend model to include relative refractoriness*
- *(Wilson & Cowan) Generalize model to include spatial interactions within sheets of neural tissue ("A Mathematical Theory of the Functional Dynamics of Cortical and Thalamic Nervous Tissue", Kybernetik, 12:55-80, 1973)*
- *With respect to visual cortex see "Cortical Population Dynamics and Psychophysics" by U. A. Ernst and C. W. Eurich, Institute for Theoretical Neurophysics, University of Bremen*
- *General extensions & further development- vast.*