Threshold, excitability and isochrones in the Bonhoeffer–van der Pol system

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Some new insight is obtained for the structure of the Bonhoeffer–van der Pol system. The problems of excitability and threshold are discussed for all three types of the system classified according to the existing attractors: a focus only, a limit cycle only and a limit cycle together with a focus. These problems can be treated by the T-repellers and the T-attractors of the system which are mutually reciprocal under time inversion. The threshold depends on the structure of the T-repeller (unstable part of integral manifold). This structure is then used to understand the behavior and the properties of the two different types of isochrones: Winfree isochrones (W-isochrones) and regular isochrones. Winfree's description of a W-isochrone is extended to excitable systems. Both W-isochrones and regular isochrones are calculated for the Bonhoeffer–van der Pol system in its limit cycle and excitable regimes. The important role of the T-repeller as an asymptotic limit for both types of isochrones is manifested. © *1999 American Institute of Physics.* [S1054-1500(99)00304-3]

Excitable systems are prevalent in many branches of science. A clear understanding of the meaning of excitability is therefore of importance. In this paper we provide a description of excitable systems for a set of nonlinear ordinary differential equations of the ''relaxation oscillator'' type (e.g., Bonhoeffer–van der Pol system). This description is based on the definition of a a ''transient attractor'' and a ''transient repeller'' (T-repeller). A ''transient'' attractor (T-attractor) means that it attracts trajectories which leave it after a finite time. A T-repeller means that trajectories are repelled from it. The difference between a boundary between two basins of attraction (BBA) and a T-repeller is that while the BBA separates between two different attractors, the T-repeller separates between trajectories that eventually flow into the same attractor. A T-repeller is a necessary condition for a threshold to exist. An excitable system is taken to be a system for which both T-attractor and a T-repeller exist. One of the important tools of studying excitable systems are isochrones. Here we differentiate between two types of isochrones which we analyze in the phase space of an excitable system. We show the relation between isochrones and the T-repeller.

I. INTRODUCTION

The term ''excitable medium'' has been used repeatably for decades in many fields notably for biological systems such as axons, the heart muscles, nonlinear electrical systems, chemical reactors, etc.[1–7] However the nature of excitability still remains a subject of discussion. Winfree heuristically tried to describe an excitable system as follows:[1] ''A reaction is excitable if it has a unique steady state that the system will approach from all initial conditions, but there exists a locus of initial conditions near which either of two quite different paths may be taken toward the unique steady state. If one of these paths is a lot longer than the other the system is excitable.'' However, this description is not exact enough.[5]

We elaborate on Winfree's description of excitability to gain additional insight for this problem, which is then used to address the issue of isochrones in the medium's phase space. The problems of excitability and threshold are discussed for all three types of the system classified according to the existing attractors: a focus only, a limit cycle only and a limit cycle together with a focus.

Isochrones are important tools of understanding in many branches of science. In recent years this notion has been used in two different meanings and applications even when confined to phase space. In the first (regular) meaning, an isochrone describes the surface all points of which have the same physical property simultaneously, for example all points in the heart having the same action potential[2,8] at the same time constitute an isochrone in real space. In this sense, the evolution of a specific property (e.g., luminosity of stars starting from the big bang[9,10]) can be viewed as the development of an isochrone with time.

The second type of isochrones (isochrons) was invented by Winfree[11] three decades ago and has frequently been used since to help in understanding ''timing relations in oscillators perturbed off their attracting cycles.''[1] The reason for this abundant use is that such oscillators' behavior is characteristic of many phenomena in chemistry, biology, electronics, medicine, etc. (e.g., pacing in the heart, neuronal function, triggering of the Belousov-Zhabotinsky reaction[3]).

II. T-REPELLERS AND T-ATTRACTORS

Regarding the excitability problem, firstly Winfree's ''unique steady state'' is interpreted to be either a focus, a node, a limit cycle or a strange attractor. Secondly, an excitable medium is considered as a medium, in every spatial

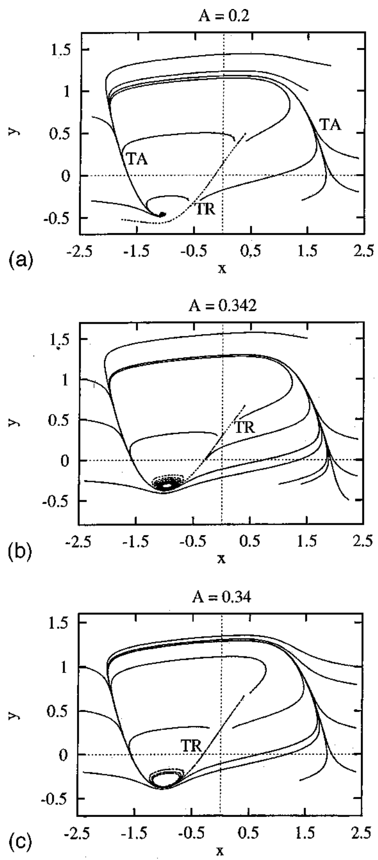

FIG. 1. (a) Trajectories in phase space of a ‘stable focus only’ case; $A=0.2$; dashed–dotted line: T-repeller (TR); TA denotes T attractor. (b) Trajectories in phase space of the ‘stable limit cycle and unstable focus’ case; $A=0.342$; dashed–dotted line: T-repeller (TR); (c) Trajectories in phase space of the ‘two limit cycles (outer stable, inner unstable) and a stable focus’ case; $A=0.34$; dashed–dotted line: T-repeller (TR).

point of which there is a ‘‘threshold.’’ That is, if we consider the equations of motion without the spatial part we find that there exists a special ‘‘locus’’ in their phase space. This locus is a geometrical structure: a line in a two dimensional phase space or a surface (of $n-1$ dimensions or less) in a three or a higher dimensional phase space. It could possibly be a geometrical structure of a fractal dimension although none has been reported by now. The heuristic definition involving ‘‘sides’’ of the geometrical structure is obviously invalid for a fractal case, but the T-repeller one (see below) is.

The ‘‘transient repeller’’ (T-repeller) is the geometrical structure which repels all trajectories. This structure separates between initial conditions on its two ‘‘sides.’’ Trajectories starting at two points which are close to each other but situated on both sides of the geometrical structure will, at some later time separate from each other, before eventually flowing into the steady state (see, e.g., Fig. 1, where the geometrical structure is the dashed–dotted line). The difference between a T-repeller and other lines in phase space is as follows: (i) a T-repeller repels all trajectories in its vicinity; (ii) The divergence of trajectories from a T-repeller is very fast (exponential like in time),[12] while the separation of trajectories from any other line is much slower. A similar treatment applies to a ‘‘transient’’ attractor (T-attractor) for its trajectory attractions (see below).

We call the geometrical structure a T-repeller since it obviously repels trajectories while the qualification ‘‘transient’’ is discussed below. We prefer this nomenclature to the more general ‘‘unstable part of integral manifold’’ (see below) used in mathematics. Changing the direction of time ($t\rightarrow -t$) this geometrical structure becomes a T-attractor, attracting trajectories for a limited time only, before they approach a real attractor.

The term ‘‘transient’’ applied to the repeller is now clarified, i.e., a T-repeller is a repeller, which under time inversion becomes a transient attractor. Note that a T-attractor for positive times transforms into a T-repeller for $t\rightarrow -t$. Note also that the T-attractors and T-repellers are parts of the ‘‘integral manifolds’’ of the system of differential equations.[13–16]

We thus have a ‘‘dual’’ system of geometrical structures for an excitable system: its phase space can have a set of T-repellers as well as a set of T-attractors. Those sets are interchanged for a negative time direction. Let us stress the point that the T-attractors considered here are ‘‘transient’’ structures. Trajectories are attracted to them but only for a finite time. Eventually these trajectories flow into some ‘‘steady state’’ or a real attractor, which is in the basin of attraction of this geometrical structure. For the T-repellers too, trajectories starting on both sides of it are eventually flowing into the *same* real attractor. Thus in this respect these structures are different than a ‘‘BBA’’ which defines the boundary between basins of attraction of *different* steady states. The ‘‘BBA’’ can be considered as a ‘‘real repeller.’’

In other words, the difference between a regular attractor and a T-attractor (i.e., a transient attractor) can be understood crudely as follows. Both, regular attractors and T-attractors attract trajectories. However, for a regular attractor the trajectories remain on it (or in its immediate vicinity) for all future times; for a T-attractor trajectories leave it after a finite time.

Now, a threshold effect exists for a system with a repeller (either a real one or a T-repeller). The effect of a threshold is manifested when one crosses the repeller. Starting on two sides of the repeller leads to two distinct outcomes. Due to the difference between a real repeller and a T-repeller, there is an induced difference in behaviors of thresholds effects in each of these systems. Thus while for a real repeller, two initial points on its two sides eventually lead to different attractors, for a T-repeller such two initial points lead to the same attractor.

While the dual structure of real attractors and repellers (which interchange under time reversal) always exists in a dynamical system, the T-attractors or T-repellers appear only in excitable systems and we therefore can describe an ‘‘excitable system’’ as one for which a T-attractor and a T-repeller exist. Note that a system can have one set and not the other [e.g., a T-repeller and not a T-attractor for positive times, see, e.g., Fig. 1(b)].

Note that in[17] the T-attractor is termed ‘‘local attractor,’’ in[18] it is termed ‘‘phanton attractor’’ and in[19] a ‘‘hidden

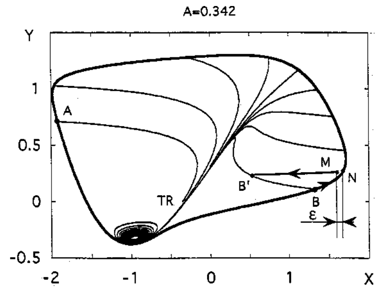

FIG. 2. The W-isochrones including a detailed calculation of point B' on it for a limit cycle case.

structure.'' In the latter the T-repeller is termed ''separatrix.''

Recall that previous description of excitable systems[1] is not complete since it does not include T-attractors which we consider to be an essential part of excitable systems.

Finding the geometrical structures numerically when the differential equations of trajectories in phase space are known, is a simple task: starting at a grid of points, say, of phase space as initial conditions the trajectories ensuing therefrom are calculated. Trajectories which approach a certain geometrical structure, continue along it only for a limited time before approaching a steady state, define a T-attractor (see Fig. 1). Reversing the direction of time,[17] the same procedure will yield the T-repellers, as T-attractors for a negative time.

In the following we treat a specific two dimensional example, namely the Bonhoeffer–van der Pol (BVP) system, and show the different T-repeller–T-attractor configurations and isochrones obtained for the different attractor cases. The Bonhoeffer–van der Pol system can obviously serve as the ''nonspatial'' part of a reaction-diffusion partial differential equation which describes information propagation through excitable media.[20–22]

III. THE BVP MODEL

The BVP system was chosen since albeit being a very simple two-dimensional system, it includes a rich infrastructure. For example, we consider here the BVP in three of its regions, separated by the structure of the attractors present: a focus alone [Fig. 1(a)]; a limit cycle alone [Fig. 1(b)]; a focus and a limit cycle [Fig. 1(c)]. We calculate for these regions the T-repeller–T-attractor structures, and the two types of isochrones, the regular isochrones (denoted hereafter as R-Isochrones) and the Winfree isochrons (denoted hereafter as W-Isochrones). In order to calculate W-Isochrones for region *a* we shall have to extend Winfree's definition, which was constructed and used only for a limit cycle case, to an excitable system.

The Bonhoeffer–van der Pol system[21,20] is

$$\frac{dx}{dt}=x-\frac{x^3}{3}-y+A, \tag{1}$$

$$\frac{dy}{dt}=c(x+a-by), \tag{2}$$

where a, b, and A are constants, c is a small parameter, and to avoid the coexistence of two equilibrium points,[21] $b<1$, and $3a+2b\geqslant 3$. This system has been recently thoroughly investigated.[19,23–25] Such systems with a small parameter are of the ''relaxation oscillator'' type. Trajectories in phase space of these systems include a ''slow motion'' part [e.g., in Eqs. (1) and (2), close to the cubic curve $y=x-x^3/3+A$] and a ''fast motion'' part.[20,26]

The system (1)–(2) can obviously be transformed into a second order equation for x, say. The latter can be cast in the ''simplest'' form by a change of variables $x=\alpha X$ and $t=\beta T$ with α and β judicially chosen to get rid of unnecessary terms, as follows:

$$X''-\mu(1-X^2)X'+X(1+\xi X^2)=f \tag{3}$$

with

$$X'=\frac{dX}{dT},\quad \alpha=(1-cb)^{1/2},\quad \beta=[c(1-b)]^{-1/2},$$

$$\mu=\beta\alpha^2,\quad \xi=\frac{1}{3}cb\beta^2\alpha^2,\quad f=\frac{\beta^2 c}{\alpha}(bA-a).$$

Equation (3) is nonlinear in both the second (X') and the third (X) terms. Whereas the first nonlinearity is inherent for the BVP system, the second disappears for the special case $b=0$. Equation (3) with $b=0$ is called the van der Pol equation[27] and has been extensively treated by numerous authors. Here we concentrate on the ''strict'' BVP model, namely $b\neq 0$, since the Hopf bifurcation for $b\neq 0$ is subcritical giving rise to the above mentioned three different regions. For $b=0$ the second region is absent.

Equations (1) and (2) were partially numerically analyzed before,[19,28] both for the case where a focus is the only steady state and for the case of a limit cycle with an additional stable focus. Our present results which emphasize the T-attractor and T-repeller configuration are shown in Fig. 1. In Fig. 1(a) which describes the case for which a stable focus is the sole regular attractor, a system of both a T-repeller and a T-attractor is shown. Figure 1(b) depicts the situation, following the subcritical Hopf bifurcation, in which the T-attractor of Fig. 1(a) transformed into a regular attractor (limit cycle) while the focus became unstable. The T-repeller and the spiral part of the T-attractor of Fig. 1(a) seem to have been transformed to the T-repeller of Fig. 1(b). Figure 1(c) shows the case where two limit cycles exist as real structures; the outer one is an attractor while the inner one is a regular repeller or a BBA. The T-repeller in this case spirals around and approaches the inner unstable limit cycle.[28] The focus here is a stable one.

Several points can be gleaned from these figures.

(1) Consider, e.g., Fig. 1(a). Although trajectories go along a whole curve to the focus, only two parts of it (transiently) attract other trajectories [T-attractor in Fig. 1(a)], while the part for $y\approx 1$ does not. We see that the T-attractors and T-repellers (in the sense that trajectories actually approach them or pull away from them) only reside close to the ''slow motion'' part of the system. We expect that in line with the Van der Pol case treated by Dorodnitcyn[12] the width

of the slow motion curve is of the order of $\epsilon \sim \exp(-\mu^2)$, namely, for negative times, starting within ϵ, no repelling is obtained.

(2) The existence and extent of the T-repellers and T-attractors depend on the value of c [see Eq. (2)]. For large values of c the whole configuration ceases to exist. On the other hand, $c=0$ is completely out of the BVP regime. It is therefore only for a limited range of c values that the configuration exists and the system is excitable.

(3) The problem of the exact point where the T-repeller ends for high y values can be of practical importance since this point marks the limit between the ''absolutely refractory'' zone (for larger y values) and the ''relatively refractory'' zone (for smaller y values[21]). This limit point is however vague and the exact extent of the T-repeller is not well defined. This problem is due to the fact that the region of the end of the T-repeller is a transient region between two different asymptotic solutions.[12]

To recapitulate, in order to calculate a T-repeller in excitable systems, many points in phase space are used as initial conditions. Changing the time direction, trajectories emanating from each initial point are calculated. Coalescence of these trajectories define the T-repeller. The problem of the definition of the right end of the T-repeller can be numerically overcome by using many initial points in the general vicinity of the end of the T-repeller. To calculate the T-attractors a similar procedure is used but in the positive time direction. Note that T-attractors reside in the region of ''slow motion,'' and the ends of the T-attractors are associated with the transition region between ''slow and fast motions.''[12]

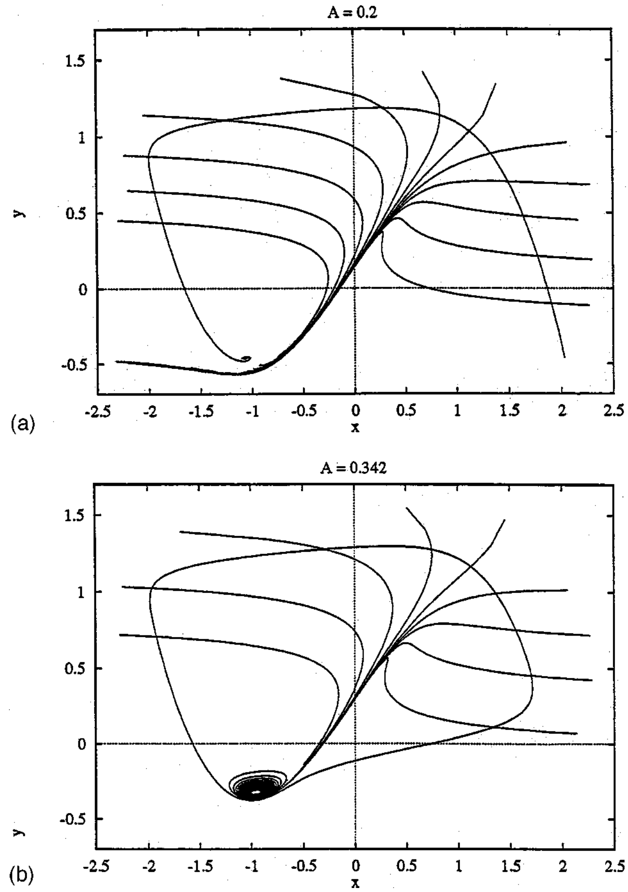

FIG. 3. The W-isochrones for $A=0.2$ (a) and for $A=0.342$ (b).

IV. ISOCHRONES

We extend the idea of isochrones to excitable systems since with isochrones it is easy to build the phase resetting curves. The latter are important for the theoretical and experimental analysis of these systems (see, e.g., Ref. 19).

Winfree's description[11,2] of a W-isochrones for a limit cycle region can be recast in the following manner. Consider a limit cycle (LC) attractor of flow (Fig. 2). Starting from any point in phase space as an initial condition, the trajectory eventually converges to the limit cycle and moves along it subsequently. A point ''B'' on the LC is chosen as zero, and for any other point (A, say) of the LC a time (or phase) t_A can be defined (modulo the period T of the LC) by the time elapsed from zero until a trajectory (starting at B) has reached A along the LC. A t_A–W-isochrone is, by Winfree, the set of points in phase space which have the characteristic that if one starts from each of them (and simultaneously from A) its trajectory would ''reach'' the LC together with the trajectory from A (which traversed along the LC). An ϵ-neighborhood is usually implied (see above). It is therefore the eventual or ''final'' time that is common to all points of an isochrone of this type.

A simple practical method of calculation of points on a W-Isochrone is as follows: starting from B we move along the LC for a certain time-interval τ. We then move a short distance $[\varepsilon > \epsilon \sim \exp(-\mu^2)]$ away from the LC (so that we get out of its width), and move backwards in time (i.e., solving the system of differential equations for a negative time) for the same amount of time τ. The point B', thus obtained is on the W-isochrone, for, starting from B and from B' and moving in the positive time direction (from B' to M and from B to N) we arrive simultaneously at two points, one on the LC and the other a distance ε away. The accuracy of the W-isochrone thus obtained therefore depends on ε. Moving in the positive time direction from these two points (of separation ε), the trajectories approach each other even further (convergence to the LC).

Consider an excitable system [Fig. 3(a)] namely a system (of type 1) where a focus is the sole attractor. In addition to the focus there exist a T-attractor and a T-repeller [see Fig. 1(a)]. Trajectories, whose initial points are other than the focus, are firstly attracted to the T-attractor and then flow along it to the focus, while trajectories starting on both sides of the T-repeller [see Fig. 1(a)] are driven away from it, such that a trajectory starting on its right moves to the right before reaching the T-attractor, and a trajectory starting on its left moves firstly to the left before reaching the T-attractor. The important role of the T-repeller as ''attractor'' for both types of isochrones will presently be discussed.

Designing a specific point on the T-attractor as an origin of time (not a phase here), any point on the T-attractor (1, say) can be endowed with a time label t_1, which is the time taken to go over from the origin to the point 1 along the T-attractor (see Fig. 1 in Ref. 19). The W-isochrone of t_1 is

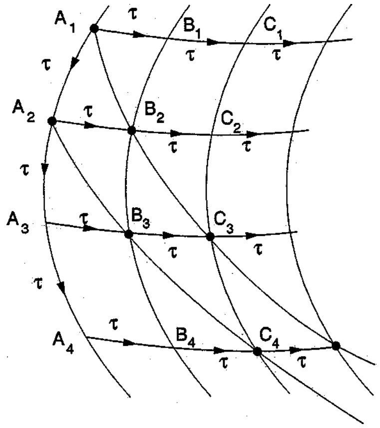

FIG. 4. Illustration of the method of calculations of the W-isochrones, the R-isochrones and the data matrix.

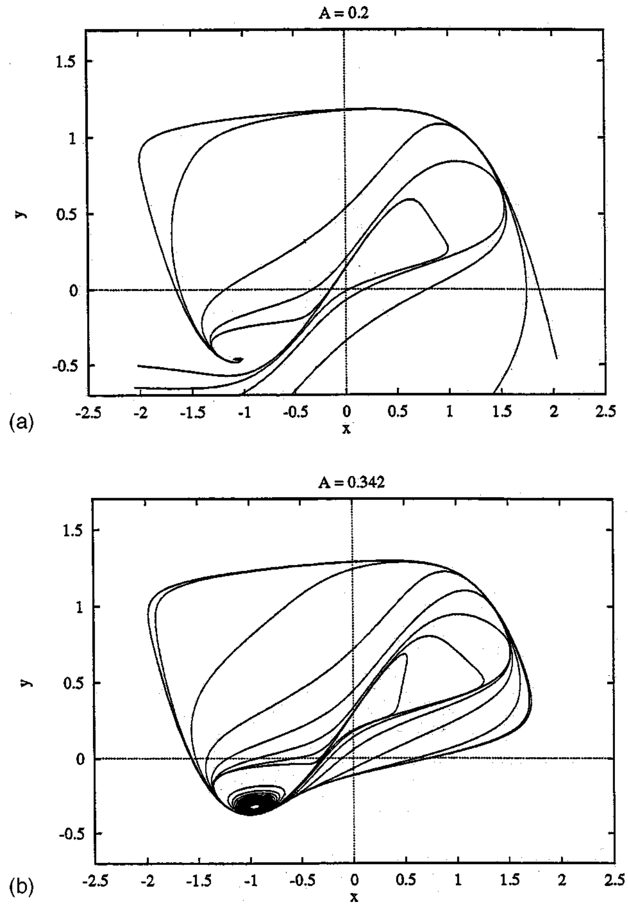

FIG. 5. The R-isochrones for $A=0.2$ (a) and for $A=0.342$ (b).

now described in a similar way to the definition of the W-isochrone for the limit cycle. That is, the W-isochrone is the set of points in phase space, the trajectories simultaneously started from them and from 1, ''reach'' the T-attractor at the same time. The numerical calculation of the W-isochrones is carried out in a similar way to that in the LC case [Fig. 3(a)].

The regular isochrones (R-isochrones) in phase space are the loci there of points for a fixed time on all the trajectories which started from a certain curve in phase space at a fixed time in the past. Here we treat R-isochrones which eventually approach the attractors of the different cases and would like to know their ''starting curves.'' Thus, for the limit cycle case for instance, we calculate the R-isochrones which approach the limit cycle. These R-isochrones can be calculated by starting from an ε neighborhood of the limit cycle and going backwards in time.

Since W-isochrones are defined in phase space, we extend the definition of the R-isochrones also to phase space because there we can easily compare these two types of isochrones. As we show this extended definition enables us to extract additional information about the system. Both the W-isochrones and the phase space regular isochrones (i.e., R-isochrones) will be shown for the two regions of the BVP system (a focus alone and a limit cycle alone). To facilitate the numerical calculation we use the following method, shown in detail in Fig. 4 for the LC case. A somewhat similar method was used before for W-isochrone calculations.[29] Suppose an overall of N isochrones are needed. The LC is divided into N segments (one of which is $A_1A_2,\ldots$ Fig. 4). The phase difference (or time difference) of each segment is $\tau(=T/N$ for the LC). From each of the points A_1, A_2, etc. as initial conditions, the trajectories are calculated in the negative time direction for periods τ, and 2τ, and etc., reaching points $B_1, B_2, \ldots,$ and $C_1, C_2, \ldots,$ and etc., respectively. A ''data matrix'' of the points A_i, B_i, C_i (for a given τ) has thus been obtained, and can be used to calculate the R-isochrones and W-isochrones (and the trajectories). Thus, the lines joining all the B_i points or all C_i points, etc. are obviously the R-isochrones while the lines joining $A_1, B_2, C_3, \ldots,$ and $A_2, B_3, C_4,$ and etc. are the W-isochrones. The latter is easily seen as follows. It takes a period of τ to get from A_1 and from B_2 to A_2 in the positive time direction. Similarly going from A_1 and from C_3 in the positive time direction, A_3 is reached after 2τ, etc.

The R-isochrones are shown in Fig. 5(a) $(A=0.2)$ and Fig. 5(b) $(A=0.342)$, while the W-isochrones are given in Fig. 3(a) $(A=0.2)$ and Fig. 3(b) $(A=0.342)$. For $A=0.2$ the situation is that of a focus as a sole attractor. Two main points can be noted regarding the W-isochrones. Firstly, the W-isochrones are seen to converge to the T-repeller. Secondly, the T-repeller is never crossed. W-isochrones coming from the ''left'' stay on the left side of the T-repeller while those coming from the ''right'' remain on that side.

These properties can be understood by the method of building the W-isochrone. If we start from a point A on the T-attractor to the left, say, of the T-repeller, the W-isochrone is obtained by going along the T-attractor towards the focus, and then going in the negative time direction from there. For the latter part, the T-repeller is an attractor, so the W-isochrone converges to the T-repeller and does so from the left. Similar results are obtained for the region of an LC as the sole attractor and for an LC and a focus together.

The asymptotic behavior of the W-isochrones is therefore rather simple. Since they all converge to the T-repeller and the latter is not crossed, then, eventually the W-isochrones move along the T-repeller to the focus. This

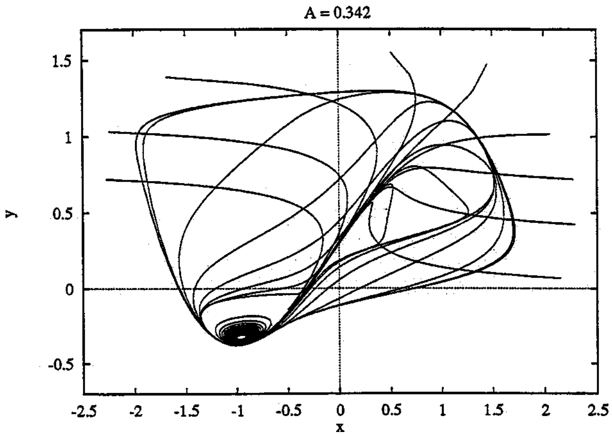

FIG. 6. The network of the W-isochrones and the R-isochrones.

structure should help to understand such problems raised in Ref. 1 (p. 153).

The R-isochrones for the two cases are shown in Figs. 5(a) and 5(b). Here, again there are convergences towards the T-repellers (in the negative time direction). This convergence is, however, seen to be ''complex,'' in that a ''dog's bone'' is formed which shrinks slowly into the T-repeller. This behavior is not yet understood as is the importance of the point in the middle of the ''dog's bone'' which seems to attract the R-isochrones. These problems are currently under investigation.

We would like to emphasize that a mutual grid of W-isochrones and R-isochrones on the same phase space (Fig. 6) provides complete information about its structure (as does a mutual description of the trajectories and R-isochrones, say). This information can be understood from the building procedure and is represented in the ''data matrix'' discussed above.

Globally, the rate of change of a process (see below) is given by the density of the isochrone lines (or cells) of the grid, such that the process is faster for sparser lines and larger cells, and slower for denser lines and smaller cells. If a point in phase space is considered as representing the state of the system at a specific time, both its past and its future can be gleaned from this grid. Its Winfree's ''time'' or ''phase'' is given immediately by its W-isochrone. It is possible to obtain rates of change of the trajectory in phase space (its velocity there), of the Winfree phase (or time) along the trajectory (by the W-isochrones), and of the approach to the attractor (by the R-isochrones).

Experimentally, the data matrix for a specific system can be obtained in the following way. Consider, e.g., a limit cycle case as measured for example in embryonic atrial heart cell aggregates.[11] The first assumption is of course, that the complete information can be obtained from a 2D representation or projection. Firstly, the limit cycle itself in phase space is calculated from the measured potential (V) as a function of t (see Fig. 2 in Ref. 11), by computing dV/dt as a function of V for all t values $0<t<T$ (where T is period). Responses for a single current pulse are then used for W-isochrones and trajectories calculations. Thus, if it is assumed that the impulse is applied in a capacitor mode, the point (P) in phase space immediately after the pulse is given by its initial position along the LC plus a straight line parallel to the V axis and of a magnitude proportional to the area under the pulse. The phase response curve at this point defines its W-isochrone while the trajectory from point P can be obtained by the transient response measured following pulse application. Evidently, accuracy will crucially depend on the quality of measurement, since numerical derivatives are involved both for dV/dt and for the trajectory calculations. Note that these calculations would provide knowledge of the T-repeller as well as the R-isochrones.

V. DISCUSSION

By our analysis of the structure of the solutions of the Bonhoeffer–van der Pol system new insight was obtained of both excitability and isochrones. Thus, the important role of the dual structure of T-repellers and T-attractors was demonstrated for these problems. In particular, an ''excitable system'' is described as a system in which a T-attractor and a T-repeller exist. Moreover, the T-repeller was shown to act as a ''guiding barrier'' to both types of isochrones, the regular isochrones and the Winfree ones, thus shedding light on their asymptotic behaviors (for $t\to\infty$ for the W-isochrones and for $t\to-\infty$ for the R-isochrones). The threshold effect was considered and its different dependence on the types of repellers was pointed out. A ''data grid'' was suggested as a means of facilitating analysis and information gain from the system.

In the present paper we treat only systems of ordinary differential equations. In such systems there exist two types of thresholds: a BBA or T-repeller. The difference between these two is that while the BBA separates between two different attractors (say, focus and limit cycle, two limit cycles, etc.), the T-repeller separates between trajectories that eventually flow into the same attractor (say, focus or limit cycle).

If a system has a T-repeller it can either be an excitable or a limit cycle system (or other). If however, in addition to the T-repeller the system has also a T-attractor it is an excitable system.

Note added in proof: In the final stages of preparation of this manuscript, the authors became aware of a manuscript dealing with similar problems: N. Ichinose, K. Aihara, K. Judd. ''Extending the concept of isochrons from oscillatory to excitable systems for modeling an excitable neuron.'' International Journal of Bifurcation and Chaos **8**, 2375–2385 (1998).

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