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APPLYING THE CONLEY INDEX TO FAST-SLOW SYSTEMS WITH ONE SLOW VARIABLE AND AN ATTRACTOR

WILLIAM M. KINNEY

ABSTRACT. Chay and Keizer [**3**] created a five-dimensional model of bursting activity in pancreatic β-cells which was subsequently reduced to a three-dimensional model by Chay [**2**]. Kinney has used the Conley index to show that the three-dimensional model has a nonempty attractor [**11**, pages 451–472]. This paper is intended to provide an introduction to the Conley index by showing how it can be applied to extend these results to prove the existence of a periodic orbit for the three-dimensional model, the existence of a nonempty attractor for the five-dimensional model and the existence of a periodic orbit for the five-dimensional model.

1. Introduction. Conley index theory consists of topological and algebraic tools for understanding the global dynamics of flows and maps on compact invariant sets. It is useful for proving the existence of various objects and properties, such as equilibria, periodic orbits [**15**], connecting orbits [**7, 8, 13, 16, 18, 23, 24, 26, 30, 34**], traveling waves [**7, 16, 18, 23, 30, 34**] and chaotic dynamics [**19, 20**]. Some fundamental references for the theory include [**6**], which traces its early development in the context of smooth flows on manifolds, Conley's classic monograph [**4**], Salamon's paper [**31**] for clarity of proof, Rybakowski and Smoller's books [**30, 34**] for applications to partial differential equations, and Mischaikow and Mrozek's surveys [**17, 21**]. Also recommended is an article by Moeckel [**25**] for an intuitive introduction to the index and to the related topic of connection matrices. The purpose of this paper is to introduce the reader to the Conley index by showing how even basic aspects of the theory can be used to prove nontrivial results in the context of certain kinds of fast-slow singular perturbation problems. More general references for

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applying the Conley index to singular perturbation problems are [**5, 9, 12, 22**]. Also see [**1**] for a related perspective.

In [**11**], the Conley index is used to prove the existence of a nonempty attractor for a fast-slow system with one slow variable arising as a model of bursting behavior in excitable membranes. This model consists of a system of three first-order ordinary differential equations, the third of which contains a small parameter. The system is degenerate (but easy to understand because of the assumptions made) when the parameter is set to zero, giving a singular perturbation problem with a fast-slow nature. This system was first developed by Chay and Keizer [**3**] as a five-dimensional Hodgkin-Huxley type model of electrical activity in pancreatic β-cells. The model was subsequently reduced to three dimensions by Chay [**2**] and described as a qualitative model by Terman [**36**]. It is this qualitative model that is analyzed using the Conley index in [**11**].

The three-dimensional system actually contains two important parameters, the small parameter mentioned previously and another parameter which is related to glucose concentration. The other parameter is the "control" parameter. As it increases, the solutions to the system undergo transitions from near steady-state behavior (experimentally for low glucose levels ~ 7 mM and below), to quasiperiodic and chaotic bursting behavior, to periodic behavior (experimentally for high glucose levels ~ 20 mM and above) [**32**].

Though the control parameter is very important in the model, see [**37**], it will not play a role in our analysis. We will assume that its value is in a range where the bursting behavior occurs. Our main concern is with the small parameter. The effect of the small parameter is that it gives the bursting solutions a fast-slow character typical of many singular perturbation problems. In the model we analyze, the slow variable is related to calcium concentration, although in subsequent experimental studies it has been found that this variable is not quite slow enough to be the true slow variable [**32, 33**].

In this paper we will review the results of [**11**] and then expand on them. We will illustrate how to use Conley index results of McCord, Mischaikow and Mrozek [**15**] to prove the existence of a periodic orbit for the three-dimensional model in [**2, 11, 36**] (Terman [**36**] already proved the periodic orbit exists using a Poincaré map), then we will

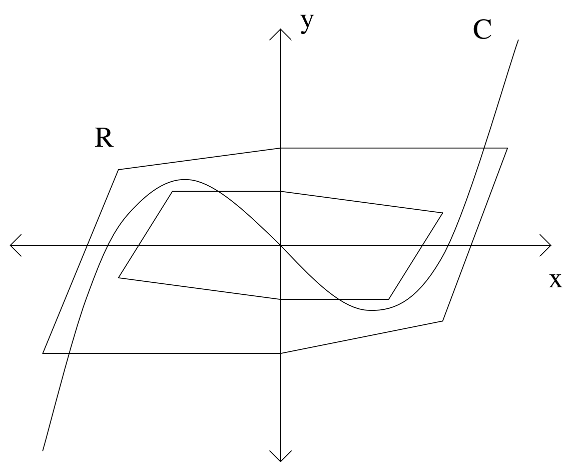

FIGURE 1. The trapping region R for (1) and the graph C of $y = F(x)$.

use the Conley index to prove the existence of a nonempty attractor and a periodic orbit for the original five-dimensional model of Chay and Keizer [**2**]. Along the way we will simplify some of the ideas in [**11, 12**] by taking a less general approach. We begin by using the Van der Pol equations to give an intuitive idea of the relevant issues and by reviewing the relevant parts of Conley index theory, with a focus on theorems which allow us to prove the existence of attractors and periodic orbits. We then move on to applying the index to the three- and five-dimensional models. Finally, we provide an appendix with more details on the models and some remarks about applying the Conley index to singular perturbation problems.

2. An illustrative example. In this section we provide an intuitive description of some of the relevant issues for applying Conley index theory to singular perturbation problems in the context of the unforced (and transformed) Van der Pol equations. Let $F(x) = x^3/3 - x$, and consider the system

$$\begin{aligned} \dot{x} &= y - F(x) \\ \dot{y} &= -\varepsilon x \end{aligned} \tag{1}$$

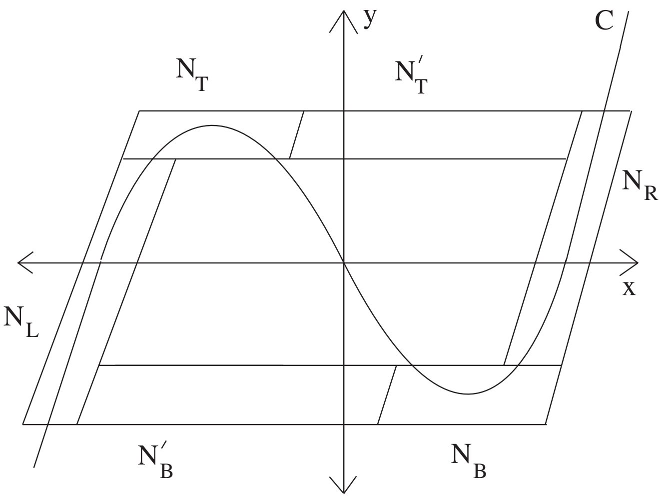

FIGURE 2. The compact set N obtained from φ^0 and the graph C of $y = F(x)$.

Let φ^ε be the flow of (1) at the parameter value $\varepsilon \geq 0$. For a sufficiently small $\varepsilon > 0$, we can easily construct a trapping region R as shown in Figure 1 (where C is the graph of $y = F(x)$) and then use the Poincaré-Bendixson theorem to prove the existence of a periodic orbit inside R. We can then also show that this periodic orbit is attracting and unique, see [**10**].

While this approach works well in this example, in higher-dimensional problems the construction of a trapping region can be much more difficult. Also, when qualitative assumptions about higher-dimensional problems are made, such as in [**11, 36**], it is more natural to construct a region analogous to the compact set $N = N_L \cup N_R \cup N_T \cup N_B \cup N_T' \cup N_B'$ shown in Figure 2. Although N is no longer a trapping region, it clearly contains the attracting periodic orbit for sufficiently small $\varepsilon > 0$. The best way to view the construction of this set in order to facilitate a natural extension to higher-dimensional problems is to first construct the tubes N_L and N_R, then construct the boxes N_T and N_B, and finally construct the tubes N_T' and N_B' by using the singular flow φ^0 to "push forward" the right boundary of N_T until it is inside N_R and the left boundary of N_B until it is inside N_L.

The Conley index can now be used to prove the existence of a nonempty attractor inside N for small $\varepsilon > 0$. The basic idea is as follows. For a fixed small $\varepsilon > 0$, use smooth bump functions to deform the flow φ^0 on small neighborhoods of the four points in the set $C \cap \partial N$ so that it matches φ^ε on even smaller neighborhoods of these points. Call this deformation ψ^ε. Though the vector field for ψ^ε is not pointing transversely inwards along much of ∂N, the set N is a trapping region of ψ^ε in the sense that all points in ∂N will eventually move into the interior of N as t increases and, more crucially for Conley index theory, all points in ∂N will eventually move into the exterior of N as t decreases. Because of this last fact, the maximal invariant set for ψ^ε inside N must be in the interior of N. This means that N is an *isolating neighborhood* for ψ^ε. Next, the Conley index of the maximal invariant set for ψ^ε inside N can be easily computed in this situation because no points leave N as t increases. This index can be shown to be nontrivial and, as a result, the maximal invariant set inside N can be shown to be nonempty. In addition, the fact that all boundary points of N eventually move into the exterior of N as t decreases means that this nonempty maximal invariant set inside N is also an attractor. The final step is to relate the facts just proved about ψ^ε to φ^ε. This is done by deforming ψ^ε to φ^ε and using the *continuation* property of the Conley index. Basically, the continuation property says that, if a set N remains an isolating neighborhood as a flow is continuously deformed, then the Conley index stays constant throughout the deformation. In addition to all this, by constructing a *Poincaré section*, we can use the Conley index theory from [**15**] to prove the existence of a periodic orbit for φ^ε inside N.

Another important point to make here is that, in order to prove that N remains an isolating neighborhood as we deform ψ^ε into φ^ε, it is necessary to prove that N is a *singular isolating neighborhood* for the family of flows $\{\varphi^\varepsilon\}_{\varepsilon \geq 0}$. This means that N is not an isolating neighborhood for φ^0 but it is an isolating neighborhood for φ^ε for all sufficiently small $\varepsilon > 0$. In order to do this, it is necessary to examine the points in ∂N which prevent N from being an isolating neighborhood for φ^0 and show that these points do not prevent N from being an isolating neighborhood for φ^ε for small $\varepsilon > 0$. The points in question are those points of ∂N which are in the maximal invariant set for φ^0 inside N. In this case, that includes the two points of $C \cap \partial N$ on the top and bottom outer boundaries of N and all the points on the line segments which form the top and bottom inner boundaries of N. In this paper we will see that such points satisfy the condition of being *fast-slow*-1 *simple* C*-slow entrance points*. This condition is sufficient to guarantee that N is a singular isolating neighborhood for the family $\{\varphi^\varepsilon\}_{\varepsilon \geq 0}$, see Theorem 3.12.

While all this is more than what is needed for this example, we shall illustrate that it pays dividends for higher-dimensional problems in Section 4. Indeed, the application of Conley index theory to the five-dimensional model of Chay and Keizer [**3**] in subsections 4.3, 4.4 and 4.5 is one of the main driving forces for this paper.

3. The Conley index.

3.1. Isolated invariant sets, attractors, the index, and continuation.

In all that follows, [**4, 17**] are used freely as references. A newer reference of interest is [**21**]. We assume the reader is familiar with basic dynamical systems and algebraic topology, [**10, 29, 35**].

Let X be a locally compact metric space, and let $\varphi : X \times \mathbf{R} \to X$ be a continuous flow on X. We will often suppress X and φ in our notation, and we will often refer to the second variable in φ as "time." Given $N \subset X$, let $\operatorname{Inv}(N) := \{x \mid \varphi(x,t) \in N \text{ for all } t \in \mathbf{R}\}$. Clearly $\operatorname{Inv}(N)$ is the maximal invariant subset of N.

An *isolating neighborhood* is a compact set N such that $\operatorname{Inv}(N) \subset \operatorname{int}(N)$, the interior of N in X. Equivalently, N is an isolating neighborhood if every point in the boundary set ∂N eventually leaves N in either forward or backward time. An *isolated invariant set* is a compact set S for which there exists an isolating neighborhood N such that $S = \operatorname{Inv}(N)$.

Let $S \subset X$ be an isolated invariant set. We will define a subset $A \subset S$ to be an *attractor in* S if there exists a neighborhood $\mathcal{U}$ of A, in X, such that $\omega(\mathcal{U} \cap S) = A$. If A is an attractor in S, then A is an isolated invariant set. The following theorem of Conley guarantees that a compact set will contain an attractor in its interior if it maps into its interior under the flow for some positive time.

Theorem 3.1. *Suppose* $\mathcal{U} \subset S$ *and, for some* $t_0 > 0$, $\varphi(\mathrm{cl}\,(\mathcal{U}), t_0) \subset \mathrm{int}\,(\mathcal{U})$. *Then* $\omega(\mathcal{U})$ *is an attractor contained in* $\mathrm{int}\,(\mathcal{U})$.

Some compact sets are trapping regions in the sense that they map into their interiors for all positive times. An isolating neighborhood N is called an *attractor block* if $\varphi(N, t) \subset \mathrm{int}\,(N)$ for all $t > 0$. The following theorem of Conley guarantees the existence of attractor blocks.

Theorem 3.2. *Let* S *be a compact invariant set, and let* $A \subset S$ *be an attractor in* S. *Choose a neighborhood* $\mathcal{U} \subset S$ *of* A *such that* $\omega(\mathcal{U}) = A$. *Then there exists a neighborhood* $\mathcal{W}$ *of* A *in* S *such that* $\mathcal{W} \subset \mathrm{int}\,(\mathcal{U})$ *and* $\varphi(\mathrm{cl}\,(\mathcal{W}), t) \subset \mathrm{int}\,(\mathcal{W})$ *for all* $t > 0$. *Hence,* $\mathrm{cl}\,(\mathcal{W})$ *is an attractor block.*

Remark 3.1. Sometimes a restriction is put on the definition of an attractor block for smooth flows on manifolds by requiring N and ∂N to be smooth submanifolds and by requiring the vector field for φ to be transverse to ∂N. The existence of such attractor blocks in the interior of $\mathcal{U}$ is also guaranteed in that context, see [**6**].

Another theorem about attractors is used to prove the main results of [**11**].

Theorem 3.3. *Suppose that* N *is a compact subset of* S *with the property that each point of* ∂N *is carried out of* N *as* t *decreases. Then* $\mathrm{Inv}\,(N)$ *is an attractor.* (*However,* $\mathrm{Inv}\,(N)$ *could be empty*).

In our applications we may use these theorems for a flow defined by a system of ordinary differential equations by rescaling time as necessary, to obtain a full flow, and by considering the flow as defined on the one-point compactification of $\mathbf{R}^n$ via a stereographic projection onto a sphere with the point at infinity considered as an unstable equilibrium.

The Conley index is an index for isolated invariant sets (and also for isolating neighborhoods). To define the index, we need a few more preliminary definitions. A set $L \subset N$ is called *positively invariant in*

N if $x \in L$, $t > 0$, and $\varphi(x, [0,t]) \subset N$ imply that $\varphi(x, [0,t]) \subset L$. A set $L \subset N$ is called an *exit set for* N if $x \in N, t_1 > 0$, and $\varphi(x, t_1) \notin N$ imply that there exists a $t_0 \in [0, t_1]$ such that $\varphi(x, [0, t_0]) \subset N$ and $\varphi(x, t_0) \in L$.

Let S be an isolated invariant set. A compact pair (N, L) is called an *index pair* for S if the following conditions hold:

(a) $S = \mathrm{Inv}\,(\mathrm{cl}\,(N \setminus L))$ and $N \setminus L$ is a neighborhood of S,

(b) L is positively invariant in N, and

(c) L is an exit set for N.

For example, let S be the origin, considered as the saddle point for the system $\dot{x} = -x$, $\dot{y} = y$. Let N be the unit square, and let L be the union of the top and bottom boundaries of N; then (N, L) is an index pair for S. In the case that the system is $\dot{x} = -x$, $\dot{y} = -y$, then $(N, \varnothing)$ serves as an index pair for S.

It can be proven that index pairs of isolated invariant sets always exist and can always be chosen as subsets of a given isolating neighborhood. Furthermore, it can be proven that for any two index pairs of a given isolated invariant set, the pointed spaces formed by collapsing the second member of the pair to a point are homotopy equivalent. This leads us to the foundational definition of Conley index theory.

Definition 3.1. Let S be an isolated invariant set, and let (N, L) be an index pair for S.

The *homotopy Conley index of* S, denoted by $h(S)$, is the homotopy type $[N/L]$ of the pointed space $(N/L, [L])$, where $[L]$ denotes the equivalence class of L in the quotient space N/L.

The *cohomology Conley index of* S, denoted by $CH^*(S)$, is defined by the equation

$$CH^*(S) := H^*(N/L, [L]),$$

where H^* denotes Alexander-Spanier cohomology with integer coefficients.

For example, if S is a hyperbolic equilibrium with a k-dimensional unstable manifold, then by choosing appropriate coordinates it is easy to see that $h(S) = \Sigma^k$, the homotopy type of a pointed k-sphere, and $CH^*(S) \approx (0, 0, \ldots, 0, \mathbf{Z}, 0, \ldots)$, where the nontrivial cohomology occurs at level k.

Once the Conley index has been defined, the most basic and important result is the following.

Theorem 3.4. *If S is an isolated invariant set and if $h(S)$ is nontrivial (so $h(S)$ is not the homotopy type of a pointed one-point space), or if $CH^*(S)$ is nontrivial, then S is nonempty.*

Another basic theorem tells how to compute the Conley index in a special situation which is of interest in this paper.

Theorem 3.5. *Let N be an attractor block for an isolated invariant set S. Then $(N, \varnothing)$ is an index pair for N and thus $h(S) = [N/\varnothing]$. (Note that $(N/\varnothing, [\varnothing])$ is a disconnected space and thus $h(S)$ is nontrivial in this situation since $N \neq \varnothing$.)*

The *continuation* property we now discuss gives the Conley index its power. Let Λ be a compact, locally contractible, connected metric space (Λ is often a compact interval). Given a family of continuous flows $\{\varphi^\lambda\}_{\lambda \in \Lambda}$ on X, we can define a flow Φ on $X \times \Lambda$ by the equation

$$\Phi((x, \lambda), t) := (\varphi^\lambda(x, t), \lambda).$$

Φ is called the *parameterized flow* associated with the family $\{\varphi^\lambda\}_{\lambda \in \Lambda}$, and this family is said to be *continuously parameterized* (or a *continuous family of flows*) if Φ is continuous.

The following theorem on the stability of isolating neighborhoods under perturbation is an easy consequence of the definition of an isolating neighborhood.

Theorem 3.6. *Let N be an isolating neighborhood for the flow φ^{λ_0} for some $\lambda_0 \in \Lambda$. Then there is an $\varepsilon > 0$ such that N is an isolating neighborhood for φ^λ if $d(\lambda, \lambda_0) < \varepsilon$.*

Index *pairs* do not behave so nicely under perturbation however. Because of this, the two theorems that follow are nontrivial.

Theorem 3.7. *Let N be an isolating neighborhood for φ^{λ_0}. Choose $\varepsilon > 0$ such that if $d(\lambda, \lambda_0) < \varepsilon$, then N is an isolating neighborhood for φ^{λ}. Then $h(\operatorname{Inv}(N, \varphi^{\lambda})) = h(\operatorname{Inv}(N, \varphi^{\lambda_0}))$ if $d(\lambda, \lambda_0) < \varepsilon$.*

To extend the preceding perturbation theorem to a global continuation theorem, we must use the parameterized flow. First, we give some notation. Given $N \subset X \times \Lambda$ and $\lambda \in \Lambda$, define the slice N^{λ} by

$$N^{\lambda} := N \cap (X \times \{\lambda\}).$$

Definition 3.2. Let S^{λ_0} and S^{λ_1} be isolated invariant sets for φ^{λ_0} and φ^{λ_1}, respectively. S^{λ_0} and S^{λ_1} are said to be *related by continuation* if there exists an isolating neighborhood $N \subset X \times \Lambda$ for the parameterized flow Φ such that $\operatorname{Inv}(N^{\lambda_0}, \varphi^{\lambda_0}) = S^{\lambda_0}$ and $\operatorname{Inv}(N^{\lambda_1}, \varphi^{\lambda_1}) = S^{\lambda_1}$.

The main continuation result is the following.

Theorem 3.8. *If S^{λ_0} and S^{λ_1} are related by continuation, then $h(S^{\lambda_0}, \varphi^{\lambda_0}) = h(S^{\lambda_1}, \varphi^{\lambda_1})$.*

We will illustrate the use of the continuation property in subsection 4.4, although we could do what we need to do without it in the particular application of that section, see Remark 4.2. However, the continuation property does form the foundation for that application because it is used in [**11**] to prove Theorem 3.13, which ultimately leads to the application.

3.2. The Conley index and periodic orbits. Here we state results which can be used to prove the existence of periodic orbits and which will be applied in subsections 4.2 and 4.5. We will not go into any of the background material required for the proofs of these results. The interested reader can consult [**15, 21**]. We remark that we are stating these results in less generality than those found in [**15**].

First we need a theorem which tells us how to compute the index for hyperbolic periodic orbits with orientable unstable manifolds.

Theorem 3.9. *Let $\mathcal{U} \subset \mathbf{R}^n$ be open and $f : \mathcal{U} \to \mathbf{R}^n$ smooth. Let γ be a hyperbolic periodic orbit of the differential equation $\dot{x} = f(x)$. Suppose that γ has p Floquet exponents with positive real part. Suppose further that the unstable manifold of γ is orientable. Then*

$$CH^k(\gamma) \approx \begin{cases} \mathbf{Z} & \text{if } k = p \text{ or } k = p+1, \\ 0 & \text{otherwise.} \end{cases}$$

The key for going from index information about an isolated invariant set to information about periodic behavior is to define a Poincaré section for an isolating neighborhood.

Definition 3.3. A set $\Xi \subset X$ is a *Poincaré section for an isolating neighborhood N under φ* if Ξ is a local section, $\Xi_N := \Xi \cap N$ is closed, and for every $x \in N$, there exists a $t_x > 0$ such that $\varphi(x, t_x) \in \Xi$.

Remark 3.2. Ξ need not be a subset of N. Indeed, Ξ will not be a subset of N in most cases of interest and Ξ cannot be a subset of N if N has an exit set. It turns out that Ξ is not a subset of N in our applications to the bursting models.

We are ready to state the main results found in [**15**].

Theorem 3.10. *If N is an isolating neighborhood for φ which admits a Poincaré section Ξ and for all $n \in \mathbf{Z}$, either*

$$\operatorname{rank} CH^{2n}(\operatorname{Inv}(N)) = \operatorname{rank} CH^{2n+1}(\operatorname{Inv}(N))$$

or

$$\operatorname{rank} CH^{2n}(\operatorname{Inv}(N)) = \operatorname{rank} CH^{2n-1}(\operatorname{Inv}(N))$$

where not all the above ranks are zero, then φ has a periodic orbit in $\operatorname{Inv}(N)$.

Theorems 3.9 and 3.10 lead to the following corollary, which we will make use of in subsections 4.2 and 4.5.

Corollary 3.1. *If N is an isolating neighborhood for φ which admits a Poincaré section and if* $\operatorname{Inv}(N)$ *has the Conley index of a hyperbolic periodic orbit, then* $\operatorname{Inv}(N)$ *contains a periodic orbit.*

3.3. The Conley index and certain fast-slow systems. To relate the Conley index to fast-slow systems, we consider the special case of a flow defined by the singularly perturbed system of ordinary differential equations with one slow variable

$$\begin{aligned} \dot{x} &= g(x, \lambda) \\ \dot{\lambda} &= \varepsilon h(x, \lambda), \end{aligned} \tag{2}$$

where g and h are smooth (say $\mathcal{C}^1$), $\varepsilon \geq 0$, $x \in \mathbf{R}^n$, and $\lambda \in \mathbf{R}$. Let φ^ε denote the flow generated by (2) at the parameter value ε.

In [**5, 9, 22**], a more general theory for using the Conley index to analyze systems similar to (2) is developed. Here, however, we simplify some ideas and results from these references and from [**11**] related to this system. First, we need an important definition.

Definition 3.4. A compact set $N \subset \mathbf{R}^n \times \mathbf{R}$ is said to be a *singular isolating neighborhood* for the family of flows $\{\varphi^\varepsilon\}_{\varepsilon \geq 0}$ of (2) if N is not an isolating neighborhood for φ^0, but there is an $\bar{\varepsilon} > 0$ such that N is an isolating neighborhood for φ^ε for all $\varepsilon \in (0, \bar{\varepsilon}]$.

Given a compact set $N \subset \mathbf{R}^n \times \mathbf{R}$, let $S = \operatorname{Inv}(N, \varphi^0)$ and let $S_\partial = S \cap \partial N$. Also, for a given $\lambda_0 \in \mathbf{R}$, let $\ell_{\lambda_0}(x, \lambda) = \lambda - \lambda_0$.

The following definitions of certain special "slow entrance" and "slow exit" points are simplifications of definitions in [**5, 11, 12, 22**]. As such, they facilitate a simpler route to applying the Conley index while at the same time being applicable to a wide variety of examples. We will state and prove Theorem 3.11 with a focus on exit points, since that is the way most of the literature is framed. However, since our main concern here is with attractors, we will ultimately be more interested in entrance points and therefore our first definition will focus on these.

Definition 3.5. A point $(x, \lambda_0) \in S_\partial$ is called a *fast-slow*-1 (*fs*1) *simple C-slow entrance point* of (2) if there exists a compact set

$K_{(x,\lambda_0)} \subset S_\partial$ which is invariant under φ^0 such that the following conditions are satisfied

(a) $\alpha((x,\lambda_0),\varphi^0) \subset K_{(x,\lambda_0)}$

(b) There is a neighborhood $U_{(x,\lambda_0)}$ of $K_{(x,\lambda_0)}$ such that either (i) $h|_{\mathrm{cl}\,(U_{(x,\lambda_0)})} < 0$ and $\ell_{\lambda_0}|_{\mathrm{cl}\,(U_{(x,\lambda_0)})\cap N} \leq 0$ or (ii) $h|_{\mathrm{cl}\,(U_{(x,\lambda_0)})} > 0$ and $\ell_{\lambda_0}|_{\mathrm{cl}\,(U_{(x,\lambda_0)})\cap N} \geq 0$.

We now define the dual exit point concept.

Definition 3.6. A point $(x,\lambda_0) \in S_\partial$ is called a *fast-slow*-1 (*fs*1) *simple* C*-slow exit point* of (2) if it is an fs1 simple C-slow entrance point for the time-reversed flow. Equivalently, the above definition holds with α replaced by ω and with $h|_{\mathrm{cl}\,(U_{(x,\lambda_0)})} < 0$ replaced by $h|_{\mathrm{cl}\,(U_{(x,\lambda_0)})} > 0$ in (b) (i) and vice versa in (b) (ii).

Remark 3.3. The "1" in "fast-slow-1" refers to the fact that there is a one-dimensional slow variable in (2). The "C" is because the original ideas came from Conley [**5**].

Remark 3.4. In [**11**], definitions are given of simple C-slow exit and entrance points (without the "fs1"). Those definitions need to be modified to make things work out there. This modification is given in the appendix of the present paper and is proven in [**12**] to make everything work in [**11**].

Remark 3.5. In [**22**], definitions of slow exit and slow entrance points and of C-slow exit and C-slow entrance points are given.

Remark 3.6. Note that $\nabla\ell_{\lambda_0}(x,\lambda)\cdot(g(x,\lambda),\varepsilon h(x,\lambda))^T = \varepsilon h(x,\lambda)$ so that, for $\varepsilon > 0$, ℓ_{λ_0} will increase along solutions if $h(x,\lambda) > 0$ and decrease along solutions if $h(x,\lambda) < 0$.

Basically, we can think of the various kinds of slow exit points defined in the literature as being points which, although they might not exit the set N immediately for small $\varepsilon > 0$, they will eventually do so as t increases. The various kinds of slow "entrance" points defined in the literature might not enter the set N as t increases, but they will eventually *leave* N as t decreases. This is the content of Theorem 3.11 and similar theorems for other kinds of slow exit and slow entrance points [**5, 11, 12, 22**].

Remark 3.7. In the Van der Pol system of Section 2, we have $g(x,\lambda) = \lambda - F(x)$ and $h(x,\lambda) = -x$. All points on the top and bottom *inner* boundaries of N and the two points in $\partial N \cap C$ on the top and bottom *outer* boundaries of N are fs1 simple C-slow entrance points. For example, for any point (x,λ_0) on the bottom inner boundary of N we can take $U_{(x,\lambda_0)}$ to be a small disk centered at the point $(x_0,\lambda_0) \in \partial N \cap C$ and $K_{(x,\lambda_0)} = \{(x_0,\lambda_0)\}$.

Let S_∂^- and S_∂^+ denote the sets of fs1 simple C-slow exit and entrance points, respectively. The following two theorems and their proofs are analogs of theorems and proofs in [**5, 12, 17**]. Besides making application in many examples much clearer, the definitions of fs1 simple C-slow exit and entrance points make the proof of Theorem 3.11 much simpler than the corresponding proofs of the analogous theorems for other kinds of slow exit and slow entrance points.

Theorem 3.11. *If* $(x,\lambda_0) \in S_\partial^-$ $((x,\lambda_0) \in S_\partial^+)$, *then there exists an* $\bar{\varepsilon} > 0$ *and a neighborhood* $\Omega_{(x,\lambda_0)}$ *of* (x,λ_0) *such that if* $\varepsilon \in (0,\bar{\varepsilon}]$ *and* $y \in \Omega_{(x,\lambda_0)}$, *then* $\varphi^\varepsilon(y,[0,\infty)) \not\subset N$ $(\varphi^\varepsilon(y,(-\infty,0]) \not\subset N)$.

Proof. Since $(x,\lambda_0) \in S_\partial^-$, there exists a compact set $K_{(x,\lambda_0)} \subset S_\partial$ and a neighborhood $U_{(x,\lambda_0)}$ of $K_{(x,\lambda_0)}$ which satisfy the conditions of Definition 3.6.

Assume that condition (b) (i) holds, for Definition 3.6, so that $h|_{\mathrm{cl}\,(U_{(x,\lambda_0)})} > 0$, and $\ell_{\lambda_0}|_{\mathrm{cl}\,(U_{(x,\lambda_0)})\cap N} \leq 0$. Since $\{\varphi^\varepsilon\}_{\varepsilon\geq 0}$ is a continuous family of flows and since $K_{(x,\lambda_0)}$ is invariant under φ^0, it follows from Remark 3.6 that there is an $\bar{\varepsilon} > 0$ and a neighborhood $V_{(x,\lambda_0)}$ of $K_{(x,\lambda_0)}$ such that, for all $\varepsilon \in (0,\bar{\varepsilon}]$ we have $\varphi^\varepsilon(V_{(x,\lambda_0)}, T(\varepsilon)) \subset U_{(x,\lambda_0)} \setminus N$ for some $T(\varepsilon) > 0$.

Since $\omega((x,\lambda_0),\varphi^0) \subset K_{(x,\lambda_0)}$, by choosing $\bar{\varepsilon} > 0$ smaller if necessary, we can guarantee that there exists a neighborhood $\Omega_{(x,\lambda_0)}$ of (x,λ_0) such that if $\varepsilon \in (0,\bar{\varepsilon}]$ and $y \in \Omega_{(x,\lambda_0)}$, then $\varphi^\varepsilon(y,t(\varepsilon,y)) \in V_{(x,\lambda_0)}$ for some $t(\varepsilon,y) > 0$. But this means that, if $y \in \Omega_{(x,\lambda_0)}$ and $\varepsilon \in (0,\bar{\varepsilon}]$, then $\varphi^\varepsilon(y,t(\varepsilon,y)+T(\varepsilon)) \notin N$. In other words, $\varphi^\varepsilon(y,[0,\infty)) \not\subset N$.

The proof is basically the same if condition (b) (ii) holds. □

Theorem 3.12. *If $\varnothing \neq S_\partial \subset S_\partial^+ \cup S_\partial^-$, then N is a singular isolating neighborhood.*

Proof. By definition, we must find an $\bar{\varepsilon} > 0$ such that if $\varepsilon \in (0,\bar{\varepsilon}]$ and $(x,\lambda_0) \in \partial N$, then $\varphi^\varepsilon((x,\lambda_0),\mathbf{R}) \not\subset N$.

For each $(x,\lambda_0) \in S_\partial \subset S_\partial^+ \cup S_\partial^-$, Theorem 3.11 implies there is an $\varepsilon_{(x,\lambda_0)} > 0$, such that for each $\varepsilon \in (0,\varepsilon_{(x,\lambda_0)}]$, there is an open neighborhood $\Omega_{(x,\lambda_0)}$ of (x,λ_0) such that $\varphi^\varepsilon(y,\mathbf{R}) \not\subset N$ for all $y \in \Omega_{(x,\lambda_0)}$.

Since S_∂ is compact, there exists a finite cover $\{\Omega_{(x_1,\lambda_0)},\Omega_{(x_2,\lambda_0)},\dots,\Omega_{(x_n,\lambda_0)}\}$ of S_∂. Let $\varepsilon_1 := \min_i \varepsilon_{(x_i,\lambda_0)}$ and let $W_1 := \cup_i \Omega_{(x_i,\lambda_0)}$.

For each $(x,\lambda_0) \in \partial N \setminus W_1 \subset N \setminus S_\partial$, we know that $\varphi^0((x,\lambda_0),\mathbf{R}) \not\subset N$. Thus, there exists an $\varepsilon_{(x,\lambda_0)} > 0$ and an open neighborhood $\Theta_{(x,\lambda_0)}$ of (x,λ_0) such that $\varphi^\varepsilon(y,\mathbf{R}) \not\subset N$ for all $\varepsilon \in (0,\varepsilon_{(x,\lambda_0)}]$ and for all $y \in \Theta_{(x,\lambda_0)}$.

Since $\partial N \backslash W_1$ is compact, there exists a finite cover $\{\Theta_{(x_1,\lambda_0)},\Theta_{(x_2,\lambda_0)},\dots,\Theta_{(x_m,\lambda_0)}\}$ of $\partial N \backslash W_1$. Let $\varepsilon_2 := \min_i \epsilon_{(x_i,\lambda_0)}$ and $W_2 := \cup_i \Theta_{(x_i,\lambda_0)}$.

Let $\bar{\varepsilon} := \min\{\varepsilon_1,\varepsilon_2\} > 0$, let $(x,\lambda_0) \in \partial N$, and let $\varepsilon \in (0,\bar{\varepsilon}]$. Since $W_1 \cup W_2$ is a neighborhood of ∂N, it follows from the preceding paragraphs that $\varphi^\varepsilon((x,\lambda_0),\mathbf{R}) \not\subset N$, and we are done. □

An important class of fs1 simple C-slow entrance points are those that enter immediately. It is usually clear which points will satisfy this definition in an application, see [**11**].

Definition 3.7. An fs1 simple C-slow entrance point x is called a *strict* fs1 *simple C-slow entrance point* if there exists a neighborhood Θ_x of x and an $\bar{\varepsilon} > 0$ such that if $y \in \Theta_x \cap N$ and $\varepsilon \in (0,\bar{\varepsilon}]$. Then there exists $t_y(\varepsilon) > 0$ for which

$$\varphi^\varepsilon(y, [0, t_y(\varepsilon)]) \subset N.$$

The next theorem is a modification of the main theorem proved in [**11**] and facilitates the proof, also in [**11**], of the existence of a nonempty attractor for the three-dimensional model of bursting in excitable membranes. The proof of this theorem uses Theorems 3.3, 3.11 and 3.12.

Before stating the theorem, we need to recall the definition of the chain recurrent set. Given ε, $T > 0$ and $x, y \in X$, an (ε, T)-*chain* from x to y is a finite sequence $\{(x_i, t_i)\} \subset X \times [0, \infty)$, $i = 1, \dots, n$ such that $x = x_1, t_i \geq T$, and $d(\varphi(x_i, t_i), x_{i+1}) \leq \varepsilon$ for each $i = 1, \dots, n-1$ and $d(\varphi(x_n, t_n), y) \leq \varepsilon$. If there exists an (ε, T)-chain from x to y, then we write $x \succeq_{(\varepsilon,T)} y$. If $x \succeq_{(\varepsilon,T)} y$ for all ε, $T > 0$, then we write $x \succeq y$.

The *chain recurrent set of a compact invariant set S under the flow φ* is defined by $\mathcal{R}(S) = \mathcal{R}(S, \varphi) := \{x \in S \mid x \succeq x\}$ We note that $\mathcal{R}(S)$ is also a compact invariant set and if $x \in S$, then $\omega(x) \subset \mathcal{R}(S)$. The chain recurrent set of S can also be characterized as the intersection, over all possible attractor-repeller pair decompositions of S, of the union of the corresponding pairs (where a repeller is the dual concept of an attractor).

Theorem 3.13. *Let S_∂^+ be the set of* fs1 *simple C-slow entrance points in N and suppose that*

(a) $S_\partial = S_\partial^+$.

(b) *No points in ∂N leave N in forward time under φ^0.*

Then Inv (N) *is an attractor for sufficiently small $\varepsilon > 0$.*

Furthermore, if

(c) $\cup_{x \in S_\partial^+} \mathcal{R}(K_x)$ *consists of strict* fs1 *simple C-slow entrance points,*

then $h(\text{Inv}\,(N)) = [N/\varnothing]$ for sufficiently small $\varepsilon > 0$.

Remark 3.8. The proof of this Theorem given in [**11**] uses Theorems 3.11 and 3.12 in a "formal" way. That is, it is only the properties of fs1

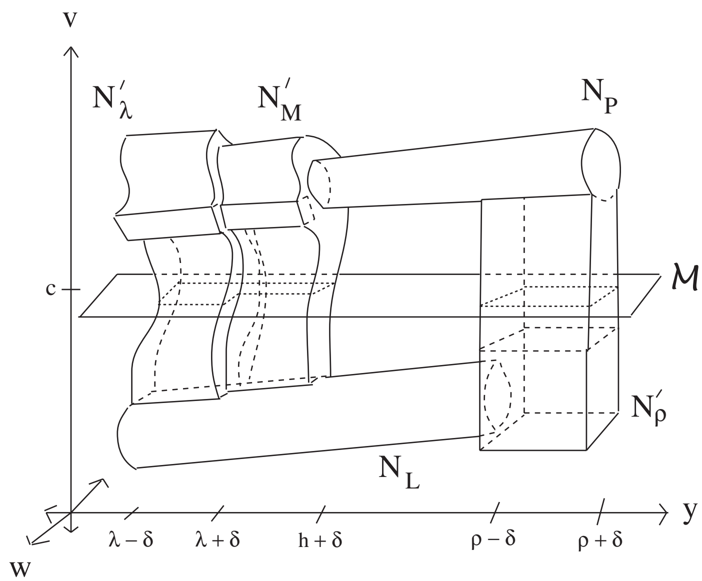

FIGURE 3. The singular isolating neighborhood N for (3) constructed in [**11**].

simple C-slow entrance points as represented by the *form* of Theorems 3.11 and 3.12 that are used. The actual details of the definition of fs1 simple C-slow entrance points are not used. In fact, the theorem is also true if we assume that S_∂^+ consists of simple C-slow entrance points and $\cup_{x \in S_\partial^+} \mathcal{R}(K_x)$ consists of strict simple C-slow entrance points as defined in the appendix. It is also true if these sets consist, respectively, of C-slow entrance and strict C-slow entrance as defined in [**22**].

Remark 3.9. This theorem can be considered to be a simplification, in the case of an attractor, of the main theorem in [**22**]. It is useful because it is more directly applicable in some situations, such as in [**11**]. The main theorem in [**22**] uses the concept of a *singular index pair*, which is a pair (N, L) that gives the correct cohomology index of an isolated invariant set of (2) for small $\varepsilon > 0$ but is not necessarily an index pair.

4. Applications.

4.1. The three-dimensional model. The three-dimensional model of bursting in excitable membranes formulated in [**2**] and described qualitatively in [**11, 36, 37**] can be written as

$$\begin{aligned} \dot{v} &= f_1(v, w, y) \\ \dot{w} &= f_2(v, w, y) \\ \dot{y} &= \varepsilon g(v, w, y, k). \end{aligned} \tag{3}$$

In this model, v is the electric potential across the membrane of a pancreatic β-cell and is the "bursting" variable of interest, $\varepsilon \geq 0$ is the small parameter, y is related to calcium concentration and is the slow variable, k is the control parameter (which, as mentioned in the introduction, we take as fixed), and w is a so-called "channel-state" variable. The functions f_1, f_2, and g are $\mathcal{C}^\infty$ smooth in a neighborhood of the solutions of interest. More details about these variables and functions will be given in subsection 4.3 and the appendix.

By letting $\mathbf{x} = (v, w, y)^T$ and $\mathbf{f}(\mathbf{x}, \varepsilon) = (f_1(v, w, y), f_2(v, w, y), \varepsilon g(v, w, y, k))^T$, we can write (3) as

$$\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}, \varepsilon). \tag{4}$$

Let Φ^ε be the flow for (4) at the parameter value ε. Figure 3 shows a compact set $N = N_L \cup N_P \cup N'_\rho \cup N'_\lambda \cup N'_M$ which is constructed in [**11**] using qualitative assumptions about Φ^0 that are given in [**11, 36**]. The number $\delta > 0$ is small and the numbers λ, h and ρ (with $\lambda + \delta < h - \delta$) are bifurcation values of the fast-subsystem of (3), where y is treated as a parameter when $\varepsilon = 0$. The set N_L contains a curve of asymptotically stable equilibria for the fast-subsystem and the set N_P contains a surface of asymptotically stable periodic orbits for the fast-subsystem. In Figure 4 we see the flow of the fast-subsystem of (3) as it would look in N'_M and N_L for values of y near $y = h$, where a homoclinic bifurcation occurs. The point l is the equilibrium in N_L and the points m and u are equilibria in N'_M. A saddle-node bifurcation to create m and u occurs in N'_λ at $y = \lambda$ and a saddle-node bifurcation to destroy m and l occurs in N'_ρ at $y = \rho$. The set $\mathcal{M}$ is the zero set of the function g from system (3) which, for qualitative purposes, we may

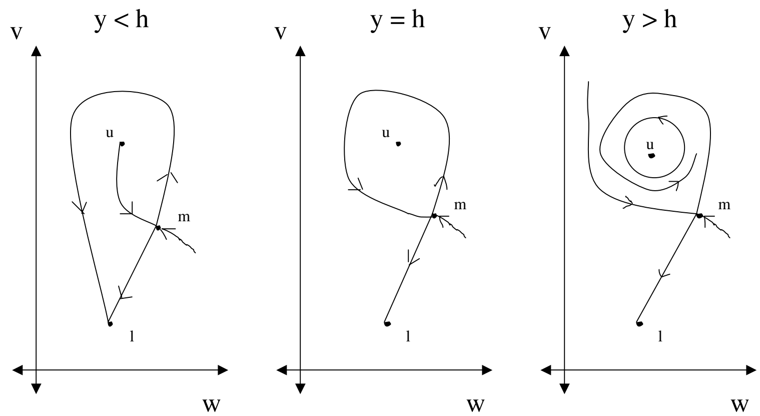

FIGURE 4. The flow for the fast-subsystem of (3) for values of y close to $y = h$.

assume takes the form $\mathcal{M} = \{(v, w, y) \mid v = c\}$ for some constant c as illustrated and also has the property that $\mathcal{M} \cap N$ is a local section of Φ^0. We also assume that $g(v, w, y) > 0$ when $v < c$ and $g(v, w, y) < 0$ when $v > c$ and that the various pieces of N are oriented as illustrated with respect to $\mathcal{M}$. Finally, we can take $\delta > 0$ sufficiently small so that the interval $[\lambda - 2\delta, \rho + 2\delta]$ does not contain the value $y = -1$ (see the equations in subsection 4.3 for the reason this is done).

Given a set $A \subset \mathbf{R}^3$ and $y \in \mathbf{R}$, we will let A^y denote the set $A \cap (\mathbf{R}^2 \times \{y\})$. We now describe the relevant properties of Φ^0 on N that will give insight into why N contains a nonempty attractor of Φ^ε for small $\varepsilon > 0$ (Theorem 4.2) and that will allow us to prove that N contains a periodic orbit of Φ^ε for small $\varepsilon > 0$ (Theorem 4.3).

1. For each $y \in [\lambda - \delta, \rho - \delta]$, all points in $\partial(N_L^y)$ immediately enter the interior of N_L^y as t increases (where the boundary and interior are with respect to $\mathbf{R}^2 \times \{y\}$). We may take each curve $\partial(N_L^y)$ to be smooth and constructed so that the vector field for Φ^0 is transverse to each curve.

2. All points in N'_ρ either stay in N'_ρ for all $t > 0$ or go into N_P for some $t > 0$. The upper part of N'_ρ is constructed by "pushing forward" the top of the "box" indicated in the lower part of N'_ρ until it is inside N_P (this can be done in a finite amount of time). As a result, points on the boundary of the upper part of N'_ρ stay on the boundary as they

move upwards toward N_P. This is a natural construction to make, although it means that N is not a trapping region for small $\varepsilon > 0$. However, one of the main points of [**11**] is that this is irrelevant (also recall the discussion in Section 2). In addition, all points in N'_ρ with y-coordinate greater than ρ go into N_P for some $t > 0$.

3. For each $y \in [h+\delta, \rho+\delta]$, all points in $\partial(N_P^y)$ immediately enter the interior of N_P^y as t increases (where the boundary and interior are with respect to $\mathbf{R}^2 \times \{y\}$). We may take each curve $\partial(N_P^y)$ to be smooth and constructed so that the vector field for Φ^0 is transverse to each curve.

4. All points in N'_M or N'_λ either stay in N'_M or N'_λ, respectively, for all $t > 0$ or go into N_L for some $t > 0$. (Here Φ^0 is used to "push forward" certain pieces of the upper parts of N'_M and N'_λ to construct the lower parts of N'_M and N'_λ, respectively.) In addition, all points in N'_λ with y-coordinate less than λ go into N_L for some $t > 0$.

5. We may choose $\eta > 0$ sufficiently small so that $N \cap \{(v, w, y) \mid v = c + \eta\}$ and $N \cap \{(v, w, y) \mid v = c - \eta\}$ are local sections for Φ^0 and so that N_P is above the plane $\{(v, w, y) \mid v = c + \eta\}$ and N_L is below the plane $\{(v, w, y) \mid v = c - \eta\}$.

6. We may take $\eta > 0$ smaller if necessary so that if $N_\rho'^+ := N'_\rho \cap \{(v, w, y) \mid v \geq c - \eta\}$, then there exists a time $T > 0$ such that $\Phi^0(N_\rho'^+, T) \subset \mathrm{int}_{\mathbf{R}^3}(N_P) \cup \mathrm{int}_{\mathbf{R}^2 \times \{\rho+\delta\}}(N_P \cap \{(v, w, y) \mid y = \rho + \delta\})$ (where the subscripts for int specify the set we are taking the interiors with respect to) and such that $\Phi^\varepsilon(N_\rho'^+, T) \subset \mathrm{int}_{\mathbf{R}^3}(N_P)$ for small $\varepsilon > 0$ (see the assumptions about the function g).

7. We may take $\eta > 0$ smaller if necessary so that if $N_{\lambda,M}'^- := (N'_\lambda \cup N'_M) \cap \{(v, w, y) \mid v \leq c + \eta\}$, then there exists a time $T > 0$ such that $\Phi^0(N_{\lambda,M}'^-, T) \subset \mathrm{int}_{\mathbf{R}^3}(N_L) \cup \mathrm{int}_{\mathbf{R}^2 \times \{\lambda-\delta\}}(N_L \cap \{(v, w, y) \mid y = \lambda - \delta\})$ and such that $\Phi^\varepsilon(N_{\lambda,M}'^-, T) \subset \mathrm{int}_{\mathbf{R}^3}(N_L)$ for small $\varepsilon > 0$.

The following two theorems are the main applied theorems in [**11**]. The first is proven using Theorem 3.12. The second is proven using Theorems 3.13 and 4.1.

Theorem 4.1. *The set N is a singular isolating neighborhood for the family $\{\Phi^\varepsilon\}_{\varepsilon \geq 0}$.*

Theorem 4.2. *For $\varepsilon > 0$ sufficiently small,* $\mathrm{Inv}\,(N, \Phi^\varepsilon)$ *is a nonempty attractor. Furthermore,* $h(\mathrm{Inv}\,(N, \Phi^\varepsilon))$ *is the homotopy type of the disjoint union of a circle and a distinguished point.*

The list of properties above should give intuition as to why N contains a nonempty attractor for small $\varepsilon > 0$. The attractor consists of solution curves which slowly travel to the right through N_L near the curve of asymptotically stable equilibria for the fast-subsystem of (3), pass into N'_ρ before quickly moving up into N_P (at least once $y > \rho$), slowly travel to the left through N_P while quickly rotating near the surface of asymptotically stable periodic orbits of the fast-subsystem of (3), pass into N'_M and possibly into N'_λ before quickly moving back down into N_L (at least once $y < \lambda$) and then repeating this cycle.

What may not be so clear is why Theorem 4.1 is true. As mentioned above, Theorem 3.12 is the key to the proof. But to use this theorem, we need to know what the sets S_∂, S_∂^+ and S_∂^- are. It turns out that $S_\partial = S_\partial^+$ and that this set consists of one point on the left side of N_L, a curve on the right side of N'_M, a curve on the left side of N'_ρ and a disk on the right side of N_P. The details are in [**11**] although the definition referred to in Remark 5.4 should be used rather than the definition given in [**11**]. If Definition 3.5 is used, the details are quite similar to those alluded to in Section 2 and Remark 3.7.

We will find it useful in subsection 4.4 to have an attractor block at our disposal. Choose $\bar{\varepsilon} > 0$ so that N is an isolating neighborhood and Theorem 4.2 holds for all $\varepsilon \in (0, \bar{\varepsilon}]$.

Lemma 4.1. *For each $\varepsilon \in (0, \bar{\varepsilon}]$, there exists a set $B^\varepsilon \subset N \subset \mathbf{R}^3$ which is an attractor block for Φ^ε and which is homotopy equivalent to the circle $\mathbf{S}^1$.*

Proof. Let $\varepsilon \in (0, \bar{\varepsilon}]$. By Theorem 3.2, there exists a (bounded) open neighborhood $\mathcal{W}^\varepsilon$ of $\mathrm{Inv}\,(N, \Phi^\varepsilon)$ such that $\Phi^\varepsilon(\mathrm{cl}\,(\mathcal{W}^\varepsilon), t) \subset \mathcal{W}^\varepsilon \subset \mathrm{int}\,(N)$ for all $t > 0$. Let $B^\varepsilon := \mathrm{cl}\,(\mathcal{W}^\varepsilon)$. Clearly B^ε is an attractor block for Φ^ε and $h(\mathrm{Inv}\,(N, \Phi^\varepsilon)) = [B^\varepsilon/\varnothing]$, see Theorem 3.5. But now Theorem 4.2 implies that B^ε is homotopy equivalent to $\mathbf{S}^1$. $\square$

4.2. Existence of a periodic orbit for the three-dimensional system. In [**36**], Terman proved the existence of a periodic orbit for (3) by doing constructions similar to those done in [**11**] (Terman's constructions were done first) and then by proving there is a Poincaré map with a fixed point. Here we illustrate how to prove the existence of a periodic orbit using the Conley index. By the content in subsection 3.2, we know that one thing that must be done is to construct a Poincaré section for N under Φ^ε. Let $\bar{\varepsilon} > 0$ be chosen so that N is an isolating neighborhood and Theorem 4.2 is applicable for all $\varepsilon \in (0, \bar{\varepsilon}]$. Let $M_v := \max\{|v| : (v, w, y) \in N\}$, $M_w := \max\{|w| : (v, w, y) \in N\}$, and let $M > \max\{M_v, M_w\}$.

Let

$$
\begin{aligned}
A_{\text{front}} &:= \{(v, w, y) \mid w = M, c + \eta \le v \le M, \lambda - 2\delta \le y \le h + \delta\} \\
A_{\text{back}} &:= \{(v, w, y) \mid w = -M, c + \eta \le v \le M, \lambda - 2\delta \le y \le h + \delta\}, \\
A_{\text{top}} &:= \{(v, w, y) \mid -M \le w \le M, v = M, \lambda - 2\delta \le y \le h + \delta\}, \\
A_{\text{bot}} &:= \{(v, w, y) \mid -M \le w \le M, v = c + \eta, \lambda - 2\delta \le y \le h + \delta\}, \\
A_{\text{left}} &:= \{(v, w, y) \mid -M \le w \le M, c + \eta \le v \le M, y = \lambda - 2\delta\}, \\
B_{\text{front}} &:= \{(v, w, y) \mid w = M, -M \le v \le c - \eta, \rho - \delta \le y \le \rho + 2\delta\}, \\
B_{\text{back}} &:= \{(v, w, y) \mid w = -M, -M \le v \le c - \eta, \rho - \delta \le y \le \rho + 2\delta\}, \\
B_{\text{bot}} &:= \{(v, w, y) \mid -M \le w \le M, v = -M, \rho - \delta \le y \le \rho + 2\delta\}, \\
B_{\text{top}} &:= \{(v, w, y) \mid -M \le w \le M, v = c - \eta, \rho - \delta \le y \le \rho + 2\delta\},
\end{aligned}
$$

and

$$
B_{\text{right}} := \{(v, w, y) \mid -M \le w \le M, -M \le v \le c - \eta, y = \rho + 2\delta\}.
$$

Let $\Xi_L := A_{\text{front}} \cup A_{\text{back}} \cup A_{\text{top}} \cup A_{\text{bot}} \cup A_{\text{left}}$, $\Xi_R := B_{\text{front}} \cup B_{\text{back}} \cup B_{\text{bot}} \cup B_{\text{top}} \cup B_{\text{right}}$, and $\Xi := \Xi_L \cup \Xi_R$. For each $\varepsilon \in (0, \bar{\varepsilon}]$, deform the flow of Φ^ε outside N as necessary to make Ξ a local section, also see Property 5 in subsection 4.1.

Lemma 4.2. *For Φ^ε deformed outside N as above and $\varepsilon > 0$ sufficiently small, the set Ξ is a Poincaré section for N under Φ^ε.*

Proof. First note that $\Xi \cap N$ is closed and that Ξ is a local section for each Φ^ε with $\varepsilon \in (0, \bar{\varepsilon}]$ by assumption (choose $\bar{\varepsilon}$ smaller if necessary so that Ξ remains a local section inside N). Now let $\xi = (v_0, w_0, y_0) \in N$.

Suppose first that $v_0 \geq c + \eta$ and $\xi \in N'_\lambda \cup N'_M$. By the properties of Φ^0 described in subsection 4.1, the construction of Ξ_L, and since $g(v, w, y) < 0$ is bounded away from zero on N for $v \geq c + \eta$ it is clear that if $\varepsilon \in (0, \bar{\varepsilon}]$, then there exists a time $T = T(\xi, \varepsilon) > 0$ such that $\Phi^\varepsilon(\xi, T) \in \Xi_L \subset \Xi$.

Next suppose that $\xi \in N_P$. By the properties describing the behavior of Φ^0 on the boundary of N_P, there exists an $0 < \varepsilon_1 \leq \bar{\varepsilon}$ such that if $\varepsilon \in (0, \varepsilon_1]$, then there exists a time $T_1 = T_1(\xi, \varepsilon) > 0$ such that $\Phi^\varepsilon(\xi, T_1) \in N_P \cap N'_M$. Therefore, by the preceding paragraph we can say that there exists a time $T = T(\Phi^\varepsilon(\xi, T_1), \varepsilon) > 0$ such that $\Phi^\varepsilon(\Phi^\varepsilon(\xi, T_1), T) \in \Xi_L \subset \Xi$. In other words, we can write that $\Phi^\varepsilon(\xi, T_1 + T) \in \Xi_L \subset \Xi$.

Now suppose that $v_0 \geq c - \eta$ and $\xi \in N'_\rho$. Then $\xi \in N'^+_\rho$ and Property 6 in subsection 4.1 implies that there exists a time $T_2 > 0$ such that $\Phi^0(N^+_\rho, T_2) \subset \mathrm{int}_{\mathbf{R}^3}(N_P) \cup \mathrm{int}_{\mathbf{R}^2 \times \{\rho+\delta\}}(N_P \cap \{(v, w, y) \mid y = \rho + \delta\})$ and there exists an $0 < \varepsilon_2 \leq \varepsilon_1$ such that for all $\varepsilon \in (0, \varepsilon_2]$, we have $\Phi^\varepsilon(N'^+_\rho, T_2) \subset \mathrm{int}_{\mathbf{R}^3}(N_P)$. It follows that for $0 < \varepsilon \leq \varepsilon_2$, there exists a time $\tau = \tau(\xi, \varepsilon) > 0$ such that $\Phi^\varepsilon(\xi, T_2 + \tau) \in \Xi_L \subset \Xi$. Let $\bar{\varepsilon}_L := \varepsilon_2$.

Similar arguments apply to the cases (a) $v_0 < c - \eta$ and $\xi \in N'_\rho$, (b) $\xi \in N_L$, and (c) $v_0 \leq c + \eta$ and $\xi \in N'_\lambda \cup N'_M$. In these cases, we would obtain a number $\bar{\varepsilon}_R > 0$ for which the forward orbits of these points would intersect Ξ_R for any $\varepsilon \in (0, \bar{\varepsilon}_R]$. Taking $\bar{\varepsilon} = \min\{\bar{\varepsilon}_L, \bar{\varepsilon}_R\}$ gives us an upper bound on ε sufficient to reach the desired conclusion. □

Remark 4.1. Note that, since $B^\varepsilon \subset N$, for sufficiently small $\varepsilon > 0$, Ξ is also a Poincaré section for B^ε under Φ^ε if we deform Φ^ε appropriately outside N.

Since deforming Φ^ε outside N has no bearing on what happens inside N, Theorem 4.3 below now follows as an immediate consequence of Theorem 4.2, Theorem 3.9, Corollary 3.1 and Lemma 4.2.

Theorem 4.3. *For $\varepsilon > 0$ sufficiently small, there exists a periodic orbit for Φ^ε inside N.*

It should be noted that, in addition to the fact that Terman [**36**] already proved the existence of a periodic orbit for this model, Lee and Terman [**14**] characterized the set of parameters for which there is a unique and asymptotically stable periodic orbit.

4.3. Relating the five- and three-dimensional models. Next, we move on to the five-dimensional model. This is where use of Conley index theory pays dividends, especially in subsections 4.4 and 4.5. The notation used here is meant to be somewhat consistent, on an overall level, with the varying notations found in [**2, 3, 11, 36**].

In constructing the original five-dimensional model of the electrical activity in an isolated pancreatic β-cell with no applied current, Chay and Keizer [**3**] used Hodgkin-Huxley formalisms to create the following five-dimensional system of ordinary differential equations.

$$\begin{aligned} C_m \dot{v} &= \left(\bar{g}_{K,Ca} \frac{y}{1+y} + \bar{g}_{K,HH} w^4 \right) (v_K - v) \\ &\quad + 2\bar{g}_{Ca,HH} m^3 h (v_{Ca} - v) + g_L (v_L - v) \\ \dot{w} &= \frac{w_\infty(v) - w}{\tau_w(v)} \\ \varepsilon^{-1} \dot{y} &= \alpha m^3 h (v_{Ca} - v) - k_{Ca} y \\ \dot{m} &= \frac{m_\infty(v) - m}{\tau_m(v)} \\ \dot{h} &= \frac{h_\infty(v) - h}{\tau_h(v)}. \end{aligned} \tag{5}$$

The meanings of some of the parameters and variables were alluded to earlier. More detail on these quantities and on the nature of $w_\infty(v)$, $m_\infty(v)$, $h_\infty(v)$ $\tau_w(v)$, $\tau_m(v)$, and $\tau_h(v)$ are given in [**2, 3**] and in the appendix. In addition to what was said earlier, suffice it to say here that k_{Ca} is the control parameter (called k earlier) which we take as a constant, α is taken as a constant, the vs and gs with subscripts are taken as constants, and the τs are functions with small positive values for all values of v.

If we let

$$g^*_{C,v} = \frac{2\bar{g}_{Ca,HH}}{C_m}, \quad g^*_{K,C} = \frac{\bar{g}_{K,Ca}}{C_m}, \quad g^*_{K,v} = \frac{\bar{g}_{K,HH}}{C_m}, \quad g^*_L = \frac{g_L}{C_m},$$

and $k = k_{Ca}$, then system (5) can be written as

$$\begin{aligned}
\dot{v} &= g^*_{C,v} m^3 h(v_{Ca} - v) + \left(g^*_{K,C} \frac{y}{1+y} + g^*_{K,v} w^4 \right)(v_K - v) \\
&\quad + g^*_L (v_L - v) \\
\dot{w} &= \frac{w_\infty(v) - w}{\tau_w(v)} \\
\dot{y} &= \varepsilon \left(\alpha m^3 h(v_{Ca} - v) - ky \right) \qquad (6) \\
\dot{m} &= \frac{m_\infty(v) - m}{\tau_m(v)} \\
\dot{h} &= \frac{h_\infty(v) - h}{\tau_h(v)}.
\end{aligned}$$

The reduced three variable model of Chay [**2**] is obtained by replacing the variable m by the function $m_\infty(v)$ and the variable h by the function $h_\infty(v)$ in the first and third equations and deleting the last two equations to give us

$$\begin{aligned}
\dot{v} &= g^*_{C,v} (m_\infty(v))^3 h_\infty(v)(v_{Ca} - v) \\
&\quad + \left(g^*_{K,C} \frac{y}{1+y} + g^*_{K,v} w^4 \right)(v_K - v) + g^*_L (v_L - v) \\
\dot{w} &= \frac{w_\infty(v) - w}{\tau_w(v)} \\
\dot{y} &= \varepsilon \left(\alpha (m_\infty(v))^3 h_\infty(v)(v_{Ca} - v) - ky \right).
\end{aligned} \tag{7}$$

This reduction is justified from a modeling perspective because the relaxation times for m and h (relative to their v-dependent "steady states" $m_\infty(v)$ and $h_\infty(v)$) are small relative to the relaxation time for w and the reduction produces the same type of behavior in v and y, the variables of most interest.

To simplify this system to look like (3), we first define

$$\phi(v, w, y) := \left(g^*_{K,C} \frac{y}{1+y} + g^*_{K,v} w^4 \right)(v_K - v) + g^*_L (v_L - v),$$

(the reason this is convenient will be clear soon) and then we make the definitions

$$\begin{aligned}
f_1(v,w,y) &:= g^*_{C,v}(m_\infty(v))^3 h_\infty(v)(v_{Ca}-v)+\phi(v,w,y),\\
f_2(v,w,y) &:= \frac{w_\infty(v)-w}{\tau_w(v)},\\
g(v,w,y,k) &:= \alpha(m_\infty(v))^3 h_\infty(v)(v_{Ca}-v)-ky
\end{aligned}$$

(we write f_2 as if it is dependent on y and g as if it is dependent on w to stay consistent with notation in [**11, 36**]). Also, though k plays no role, we will include it for the sake of consistency and as a reminder that it is an important part of the model.

With these definitions in hand, we can now write system (7) as

$$\begin{aligned}
\dot v &= f_1(v,w,y)\\
\dot w &= f_2(v,w,y)\\
\dot y &= \varepsilon g(v,w,y,k),
\end{aligned} \tag{8}$$

which is the same as (3). The qualitative assumptions in [**11, 36**] can also be verified from these equations.

As before, let $\mathbf{x}=(v,w,y)^T$ and $\mathbf{f}(\mathbf{x},\varepsilon)=(f_1(v,w,y),f_2(v,w,y),\varepsilon g(v,w,y,k))^T$, so that (8) becomes

$$\dot{\mathbf{x}}=\mathbf{f}(\mathbf{x},\varepsilon). \tag{9}$$

To prove the existence of a nonempty attractor in the five-dimensional model, it will be beneficial to relate system (7) (and (8) and (9)) to a transformed version of the five variable system (6). We start by introducing new variables z_m and z_h by $m := z_m + m_\infty(v)$ and $h := z_h + h_\infty(v)$. Also, we define

$$\begin{aligned}
\bar f_1(v,w,y,z_m,z_h) &:= g^*_{C,v}(z_m+m_\infty(v))^3\\
&\qquad\times(z_h+h_\infty(v))(v_{Ca}-v)+\phi(v,w,y), \text{ and}\\
\bar g(v,w,y,z_m,z_h,k) &:= \alpha(z_m+m_\infty(v))^3(z_h+h_\infty(v))(v_{Ca}-v)-ky.
\end{aligned}$$

With these definitions, the five variable system (6) can be transformed to

$$
\begin{aligned}
\dot{v} &= \bar{f}_1(v, w, y, z_m, z_h) \\
\dot{w} &= f_2(v, w, y) \\
\dot{y} &= \varepsilon \bar{g}(v, w, y, z_m, z_h, k) \\
\dot{z}_m &= -\frac{1}{\tau_m(v)} z_m - m'_\infty(v) \bar{f}_1(v, w, y, z_m, z_h) \\
\dot{z}_h &= -\frac{1}{\tau_h(v)} z_h - h'_\infty(v) \bar{f}_1(v, w, y, z_m, z_h).
\end{aligned} \tag{10}
$$

Furthermore, if we let

$$\psi(v, z_m, z_h) := (z_m + m_\infty(v))^3 (z_h + h_\infty(v)) - (m_\infty(v))^3 h_\infty(v),$$

then we see that

$$\bar{f}_1(v, w, y, z_m, z_h) = f_1(v, w, y) + g^*_{C,v}(v_{Ca} - v)\psi(v, z_m, z_h)$$

and

$$\bar{g}(v, w, y, z_m, z_h, k) = g(v, w, y, k) + \alpha(v_{Ca} - v)\psi(v, z_m, z_h).$$

Thus, we can write the transformed five variable system (10) as

$$
\begin{aligned}
\dot{v} &= f_1(v, w, y) + g^*_{C,v}(v_{Ca} - v)\psi(v, z_m, z_h) \\
\dot{w} &= f_2(v, w, y) \\
\dot{y} &= \varepsilon g(v, w, y, k) + \varepsilon \alpha (v_{Ca} - v)\psi(v, z_m, z_h) \\
\dot{z}_m &= -\frac{1}{\tau_m(v)} z_m - m'_\infty(v) \bar{f}_1(v, w, y, z_m, z_h) \\
\dot{z}_h &= -\frac{1}{\tau_h(v)} z_h - h'_\infty(v) \bar{f}_1(v, w, y, z_m, z_h)
\end{aligned} \tag{11}
$$

where, if we let $\mathbf{z} = (z_m, z_h)^T$, we have $\psi(v, z_m, z_h) = O(|\mathbf{z}|)$.

We now write this system in vector form by defining the functions

$$
\begin{aligned}
\mathbf{r}(\mathbf{x}, \mathbf{z}, \varepsilon) &:= (g^*_{C,v}(v_{Ca} - v)\psi(v, z_m, z_h), 0, \varepsilon\alpha(v_{Ca} - v)\psi(v, z_m, z_h))^T, \\
A(\mathbf{x}) &:= \operatorname{diag}\left(\frac{1}{\tau_m(v)}, \frac{1}{\tau_h(v)}\right), \text{ and} \\
\mathbf{s}(\mathbf{x}, \mathbf{z}) &:= (-m'_\infty(v)\bar{f}_1(v, w, y, z_m, z_h), -h'_\infty(v)\bar{f}_1(v, w, y, z_m, z_h))^T.
\end{aligned}
$$

Then system (11) becomes

$$\begin{aligned} \dot{\mathbf{x}} &= \mathbf{f}(\mathbf{x},\varepsilon) + \mathbf{r}(\mathbf{x},\mathbf{z},\varepsilon) \\ \dot{\mathbf{z}} &= -A(\mathbf{x})\mathbf{z} + \mathbf{s}(\mathbf{x},\mathbf{z}), \end{aligned} \tag{12}$$

where $\mathbf{r}(\mathbf{x},\mathbf{z},\varepsilon) = O(|\mathbf{z}|)$ and all functions are smooth when $y \neq -1$. This is the transformed five-dimensional system. In the next section, we will use this system and Conley index theory to prove the existence of a nonempty attractor for (5).

4.4. Existence of an attractor for the five-dimensional system. Choose $\bar{\varepsilon} > 0$ as in subsection 4.2 so that N is an isolating neighborhood of the flow Φ^ε for (4) and so that Theorem 4.2 holds for all $\varepsilon \in (0, \bar{\varepsilon}]$. Consider the system

$$\begin{aligned} \dot{\mathbf{x}} &= \mathbf{f}(\mathbf{x},\varepsilon) + \eta\,\mathbf{r}(\mathbf{x},\mathbf{z},\varepsilon) \\ \dot{\mathbf{z}} &= -A(\mathbf{x})\mathbf{z} + \mathbf{s}(\mathbf{x},\mathbf{z}) \end{aligned} \tag{13}$$

where $\eta \in [0,1]$.

Let $\Gamma^{\epsilon,\eta}$ be the flow for (13), and let Ψ^ε be the flow for (12). Note that $\Gamma^{\varepsilon,1} = \Psi^\varepsilon$ and that Ψ^ε is a small perturbation of $\Gamma^{\varepsilon,\eta}$ when $|\mathbf{z}|$ is small since $\mathbf{r}(\mathbf{x},\mathbf{z},\varepsilon) = O(|\mathbf{z}|)$. Also note that if $\pi_{\mathbf{x}} : \mathbf{R}^5 \to \mathbf{R}^3$ is the projection onto the first three coordinates $(\mathbf{x},\mathbf{z}) \mapsto \mathbf{x}$, then $\pi_{\mathbf{x}}(\Gamma^{\varepsilon,0}((\mathbf{x},\mathbf{z}),t)) = \Phi^\varepsilon(\mathbf{x},t)$. Let $\pi_{\mathbf{z}} : \mathbf{R}^5 \to \mathbf{R}^2$ be the projection onto the last two coordinates $(\mathbf{x},\mathbf{z}) \mapsto \mathbf{z}$.

For $r > 0$, let $D_r := \{\mathbf{z} : |\mathbf{z}| \leq r\}$. The next lemma says that if r is sufficiently small and if the τs are sufficiently small functions, then $B^\varepsilon \times D_r$ will eventually get mapped into itself under $\Gamma^{\varepsilon,\eta}$, where B^ε is the attractor block constructed in Lemma 4.1.

Lemma 4.3. *Given $\varepsilon \in (0,\bar{\varepsilon}]$, there exists $\bar{r} > 0$ and functions $\bar{\tau}_m : (0,\bar{r}] \to (0,\infty)$ and $\bar{\tau}_h : (0,\bar{r}] \to (0,\infty)$ such that if $0 < r \leq \bar{r}$, $0 < \tau_m(v) \leq \bar{\tau}_m(r)$ for all v, and $0 < \tau_h(v) \leq \bar{\tau}_h(r)$ for all v, then there is a number $t_0(\eta,r) > 0$ with the property that, for each $\eta \in [0,1]$, we have*

$$\Gamma^{\varepsilon,\eta}(B^\varepsilon \times D_r, t_0(\eta,r)) \subset \operatorname{int}(B^\varepsilon \times D_r).$$

Proof. Fix $\varepsilon \in (0,\bar{\varepsilon}]$. Our first step is to show that, for a given $r > 0$, if $\tau_m(v)$ and $\tau_h(v)$ are chosen sufficiently small for all v, then

$\Gamma^{\varepsilon,0}(B^\varepsilon \times D_r, t) \subset \operatorname{int}(B^\varepsilon \times D_r)$ for all $t > 0$. To accomplish this, we begin by noting that $\pi_{\mathbf{x}}(\Gamma^{\varepsilon,0}(B^\varepsilon \times D_r, t)) = \Phi^\varepsilon(B^\varepsilon, t) \subset \operatorname{int}(B^\varepsilon)$ for all $t > 0$ by Lemma 4.1.

Since the continuous function $\mathbf{s}(\mathbf{x}, \mathbf{z})$ is bounded on the compact set $B^\varepsilon \times \partial D_r$, for any given $r > 0$, we can choose $\tau_m(v)$ and $\tau_h(v)$ so small (say $0 < \tau_m(v) \leq \bar{\tau}_m(r)$ for all v and $0 < \tau_h(v) \leq \bar{\tau}_h(r)$ for all v) that the term $-A(\mathbf{x})\mathbf{z}$ will dominate the equation $\dot{\mathbf{z}} = -A(\mathbf{x})\mathbf{z} + \mathbf{s}(\mathbf{x}, \mathbf{z})$ on $B^\varepsilon \times \partial D_r$ for (13) to the extent that $\pi_{\mathbf{z}}(\Gamma^{\varepsilon,\eta}(B^\varepsilon \times \partial D_r, t)) \subset \operatorname{int}(D_r)$ for each $\eta \in [0, 1]$ and for all sufficiently small $t > 0$. Combining this fact with the observation at the end of the previous paragraph, we see that $\Gamma^{\varepsilon,0}(B^\varepsilon \times D_r, t) \subset \operatorname{int}(B^\varepsilon) \times \operatorname{int}(D_r) = \operatorname{int}(B^\varepsilon \times D_r)$ for all $t > 0$.

Since $\mathbf{r}(\mathbf{x}, \mathbf{z}, \varepsilon) = O(|\mathbf{z}|)$, the interval $[0, 1]$ is compact, and the family $\{\Gamma^{\varepsilon,\eta}\}_{\eta \in [0,1]}$ is continuously parameterized, the conclusion of the previous paragraph implies that we can choose $\bar{r} > 0$ so small that if $r \in (0, \bar{r}]$, $0 < \tau_m(v) \leq \bar{\tau}_m(r)$ for all v, and $0 < \tau_h(v) \leq \bar{\tau}_h(r)$ for all v, then for each $\eta \in [0, 1]$, there exists a number $t_0(\eta, r) > 0$ such that $\Gamma^{\varepsilon,\eta}(B^\varepsilon \times D_r, t_0(\eta, r)) \subset \operatorname{int}(B^\varepsilon \times D_r)$. $\square$

We can now state and prove a theorem which leads to one of the main results of this paper, Corollary 4.1.

Theorem 4.4. *Given $\varepsilon \in (0, \bar{\varepsilon}]$, there exists $\bar{r} > 0$ and functions $\bar{\tau}_m : (0, \bar{r}] \to (0, \infty)$ and $\bar{\tau}_h : (0, \bar{r}] \to (0, \infty)$ such that if $0 < r \leq \bar{r}$, $0 < \tau_m(v) \leq \bar{\tau}_m(r)$ for all v, and $0 < \tau_h(v) \leq \bar{\tau}_h(r)$ for all v, then $\operatorname{Inv}(B^\varepsilon \times D_r, \Psi^\varepsilon)$ is a nonempty attractor for (12) and $h(\operatorname{Inv}(B^\varepsilon \times D_r, \Psi^\varepsilon))$ is the homotopy type of the disjoint union of a circle and a distinguished point.*

Proof. Fix $\varepsilon \in (0, \bar{\varepsilon}]$. Choose $\bar{r}$, $\bar{\tau}_m$, and $\bar{\tau}_h$ so that Lemma 4.3 applies. Fix $r \in (0, \bar{r}]$ and choose τ_m and τ_h so that $0 < \tau_m(v) \leq \bar{\tau}_m(r)$ for all v and $0 < \tau_h(v) \leq \bar{\tau}_h(r)$ for all v. As in the proof of Lemma 4.3, $B^\varepsilon \times D_r$ is an attractor block for $\Gamma^{\varepsilon,0}$. Thus, $h(\operatorname{Inv}(B^\varepsilon \times D_r, \Gamma^{\varepsilon,0})) = [(B^\varepsilon \times D_r)/\varnothing]$ by Theorem 3.5.

By Lemma 4.3 and Theorem 3.1, $B^\varepsilon \times D_r$ isolates an attractor for $\Gamma^{\varepsilon,\eta}$ for all $\eta \in [0, 1]$. Therefore, since $\Psi^\varepsilon = \Gamma^{\varepsilon,1}$, the continuation property of the Conley index (Theorem 3.8) gives $h(\operatorname{Inv}(B^\varepsilon \times D_r, \Psi^\varepsilon)) = [(B^\varepsilon \times D_r)/\varnothing]$.

But $B^\varepsilon \times D_r$ is homotopy equivalent to $\mathbf{S}^1 \times \mathbf{D}^2$ (where $\mathbf{D}^2$ is the unit disk) which, in turn, is homotopy equivalent to $\mathbf{S}^1$. An application of Theorem 3.4 implies $\operatorname{Inv}(B^\varepsilon \times D_r, \Psi^\varepsilon) \neq \varnothing$. $\square$

Using the change-of-variables in the previous section to transform back to the original equations gives us a result about the system of Chay and Keizer.

Corollary 4.1. *System* (5) *has a nonempty attractor for* $\varepsilon > 0$ *sufficiently small.*

Remark 4.2. Our work would have been easier if we had used the fact that B^ε could have been taken to be a "strong" attractor block, one with the vector field for Φ^ε pointing transversely inward everywhere along the boundary, see Remark 3.1. Since $\mathbf{r}(\mathbf{x}, \mathbf{z}, \varepsilon) = O(|\mathbf{z}|)$, such a choice would have implied, for $\bar{r}, \bar{\tau}_m$, and $\bar{\tau}_h$ sufficiently small, that $B^\varepsilon \times D_r$ is an attractor block for $\Gamma^{\varepsilon,\eta}$ for all $\eta \in [0,1]$, including $\Gamma^{\varepsilon,1} = \Psi^\varepsilon$.

We purposely chose B^ε to be a "weak" attractor block to illustrate the continuation property and to illustrate that the same conclusion about the index of the attractor can still be drawn in that setting. It is often the case that similarly weak notions must be used and therefore the continuation property of the Conley index is not irrelevant (continuation is also important in, for example, the proof of Theorem 3.13 [**11**]).

4.5. Existence of a periodic orbit for the five-dimensional system. Our final application is to prove the existence of a periodic orbit for (5). First, we provide ourselves with a buffer by extending the set Ξ from subsection 4.2 as follows. Choose $\beta > 0$ so small that $h + \delta + \beta < \rho - \delta - \beta$. Construct the strips

$$\begin{aligned} A := \partial\{(v,w,y) \mid c + \eta \le v \le M, \\ -M \le w \le M, h + \delta \le y \le h + \delta + \beta\}\setminus \\ \{(v,w,y) \mid y = h + \delta \text{ or } y = h + \delta + \beta\} \end{aligned}$$

and

$$B := \partial\{(v,w,y) \mid -M \le v \le c-\eta,\\ -M \le w \le M, \rho-\delta-\beta \le y \le \rho-\delta\}\setminus\\ \{(v,w,y) \mid y=\rho-\delta-\beta \text{ or } y=\rho-\delta\}.$$

Next, let $\Xi'_L := \Xi_L \cup \mathrm{cl}\,(A)$, $\Xi'_R := \Xi_R \cup \mathrm{cl}\,(B)$, and $\Xi' := \Xi'_L \cup \Xi'_R$. Furthermore, choose β smaller if necessary so that Ξ' is a local section for Φ^ε for $\varepsilon \in (0,\bar\varepsilon]$.

For given $\varepsilon > 0$ and $r > 0$, let $N^\varepsilon_r := B^\varepsilon \times D_r$ and let $\Xi'_r := \Xi' \times D_r$. We will prove, for small r, τ_m, τ_h and ε, that Ξ'_r is a Poincaré section for N^ε_r under Ψ^ε and that there is a periodic orbit for Ψ^ε inside N^ε_r.

Since Ξ' is a local section for Φ^ε when $\varepsilon \in (0,\bar\varepsilon]$ and since $\mathbf{r}(\mathbf{x},\mathbf{z},\varepsilon) = O(|\mathbf{z}|)$, we can choose $\bar\varepsilon$ smaller if necessary and choose $\bar r > 0$ so that Ξ'_r is a local section for Ψ^ε for all $\varepsilon \in (0,\bar\varepsilon]$ and for all $r \in (0,\bar r]$.

Lemma 4.4. *Given $\varepsilon \in (0,\bar\varepsilon]$, there exists $\bar r > 0$ and functions $\bar\tau_m : (0,\bar r] \to (0,\infty)$ and $\bar\tau_h : (0,\bar r] \to (0,\infty)$ such that if $0 < r \le \bar r$, $0 < \tau_m(v) \le \bar\tau_m(r)$ for all v, and $0 < \tau_h(v) \le \bar\tau_h(r)$ for all v, then the set Ξ'_r is a Poincaré section for N_r under Ψ^ε.*

Proof. Clearly $\Xi'_r \cap N_r$ is closed for any $r > 0$. Choose $\bar\varepsilon$ and $\bar r$ as above so that Ξ'_r is a local section for Ψ^ε for $\varepsilon \in (0,\bar\varepsilon]$ and $r \in (0,\bar r]$.

Fix $\varepsilon \in (0,\bar\varepsilon]$. As in the proof of Lemma 4.3, for a given $r > 0$, we can find $\bar\tau_m(r) > 0$ and $\bar\tau_h(r) > 0$ so that if $0 < \tau_m(v) \le \bar\tau_m(r)$ for all v and $0 < \tau_h(v) \le \bar\tau_h(r)$ for all v, then $\pi_{\mathbf{z}}(\Psi^\varepsilon(B^\varepsilon \times \partial D_r, t)) \subset \mathrm{int}\,(D_r)$ for all sufficiently small $t > 0$.

Now the (geometric) boundary of Ξ at $y = h+\delta$ and $y = \rho-\delta$ is bounded away from the (geometric) boundary of Ξ' at $y = h+\delta+\beta$ and $y = \rho-\delta-\beta$. Also, as noted in Remark 4.1, for every $\xi \in B^\varepsilon \subset N$, we have $\Phi^\varepsilon(\xi, T) \in \Xi$ for some $T > 0$. Therefore, we can once again use the fact that $\mathbf{r}(\mathbf{x},\mathbf{z},\varepsilon) = O(|\mathbf{z}|)$, this time to say we can choose $\bar r > 0$ smaller if necessary so that for every $\xi \in N_r$, we have $\Psi^\varepsilon(\xi, T) \in \Xi'_r$ for some $T > 0$ and we are done. $\square$

Since N_r is homotopy equivalent to $\mathbf{S}^1$ it follows (as in subsection 4.2) that

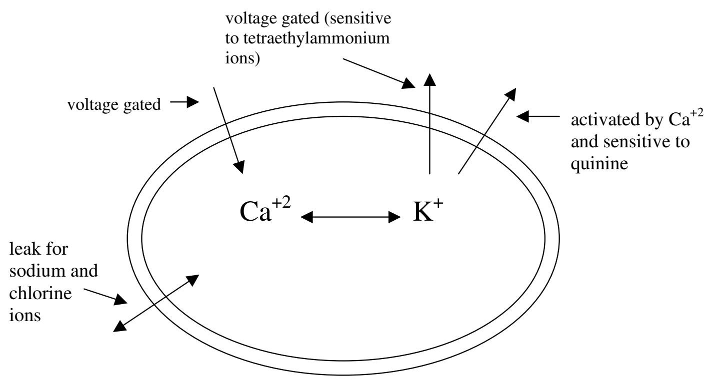

FIGURE 5. Relevant ions for the model in a pancreatic β-cell.

Theorem 4.5. *For $\varepsilon > 0$ sufficiently small, there exists a periodic orbit for Ψ^{ε} inside N.*

And, via deformation and change-of-variables,

Corollary 4.2. *System* (5) *has a periodic orbit for $\varepsilon > 0$ sufficiently small.*

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APPENDIX

5.1. More on the model of bursting in pancreatic β-cells. Here we briefly describe the meanings of the various parameters and variables in system (5) as well as describe the nature of the functions $w_\infty(v)$, $m_\infty(v)$, $h_\infty(v)$, $\tau_w(v)$, $\tau_m(v)$ and $\tau_h(v)$. A fuller treatment is given in [**2, 3, 27**]. The reader should also consult [**28, 32**] for more on Hodgkin-Huxley type models of bursting.

The parameter C_m represents the membrane capacitance of the pancreatic β-cell. The parameters $\bar{g}_{K,Ca}$, $\bar{g}_{K,HH}$, $\bar{g}_{Ca,HH}$, and g_L represent conductances of various channels. In particular, $\bar{g}_{K,Ca}$ represents the maximum conductance per unit area for the potassium channel activated by intracellular calcium ions and is sensitive to quinine, $\bar{g}_{K,HH}$ represents the maximum conductance per unit area of a voltage-gated potassium ion channel sensitive to tetraethylammonium ions, $\bar{g}_{Ca,HH}$ is the maximum conductance per unit area for a voltage-gated calcium channel, and g_L is a leak conductance for sodium ions and chlorine ions, see Figure 5. The parameter ε represents the fraction of free calcium ions inside the cell to total calcium in the cell and k_{Ca} is the rate constant for the removal of calcium and is glucose dependent.

The variable v represents the electric potential across the cell membrane, w represents the fraction of the potassium channel activation, y represents the intracellular calcium ion concentration divided by its dissociation constant to the channel gate, m represents the fraction of the mixed channel activation and h represents the fraction of the mixed channel inactivation.

Following Hodgkin-Huxley formalism, the function $w_\infty(v)$ is the steady-state probability for potassium channel activation. Likewise, the functions $m_\infty(v)$ and $h_\infty(v)$ are the steady state probabilities of activation and inactivation of the mixed channel. These functions are all sigmoidal in shape, bounded between 0 and 1, and approach 0 as $v \to -\infty$ and 1 as $v \to +\infty$.

The functions $\tau_w(v)$, $\tau_m(v)$ and $\tau_h(v)$ are the so-called relaxation times of w, m, and h, respectively. These functions have positive values, are bounded above by small numbers, and end up being somewhat bell-shaped.

Here are explicit formulae used in [**3**] for computer simulations:

$$\begin{aligned}
\alpha_m(v) &= 0.1(25+v)/(1-e^{-0.1v-2.5}),\\
\beta_m(v) &= 4e^{-(v+50)/18},\\
m_\infty(v) &= \frac{\alpha_m(v)}{\alpha_m(v)+\beta_m(v)};\\
\alpha_h(v) &= 0.07e^{-0.05v-2.5},\\
\beta_h(v) &= 1/(1+e^{-0.1v-2}),
\end{aligned}$$

$$
\begin{aligned}
h_\infty(v) &= \frac{\alpha_h(v)}{\alpha_h(v)+\beta_h(v)};\\
\alpha_w(v) &= 0.01(20+v)/(1-e^{-0.1v-2}),\\
\beta_w(v) &= 0.125e^{-(v+30)/80},\\
w_\infty(v) &= \frac{\alpha_w(v)}{\alpha_w(v)+\beta_w(v)};\\
\tau_w(v) &= \frac{1}{230(\alpha_w(v)+\beta_w(v))}.
\end{aligned}
$$

Here are some relatively realistic parameter values that lead to bursting (some values are taken directly from [**2, 3**]):

$$
\begin{gathered}
g^*_{C,v} = 1800\ \mathrm{s}^{-1}, \quad g^*_{K,C} = 10\ \mathrm{s}^{-1}, \quad g^*_{K,v} = 1700\ \mathrm{s}^{-1}, \quad g^*_L = 7\ \mathrm{s}^{-1}\\
v_{Ca} = 100\ \mathrm{mV}, \quad v_K = -75\ \mathrm{mV}.\ v_L = -40\ \mathrm{mV}.
\end{gathered}
$$

Setting $k = 0.012\ \mathrm{ms}^{-1}$, $\alpha = 0.2\ \mathrm{C\cdot mol/J\cdot s\cdot \mu m}$, and $\varepsilon = 0.1$ (which is between 10-100 times too big, but gives nicer pictures) leads to bursting solutions (that is, solutions which approach the attractor consisting of solutions which have the "burst-like" behavior, see [**2, 3, 36**] for pictures of these solutions). For these functions and constants, the overall bursting time scale is on the order of 75 seconds and v typically varies between about -50 mV and -20 mV. In fact (using notation for equilibria described in [**11, 36**]), for the fast-subsystem of (8), where we set $\varepsilon = 0$ and treat y as a parameter in the first two equations, we get a saddle-node bifurcation to create the equilibria m and l at $y \approx 0.52$ (so $\rho \approx 0.52$), a homoclinic bifurcation at $y \approx 0.548$ (so $h \approx 0.548$), and a saddle-node bifurcation to destroy the equilibria m and u at $y \approx 3.5$ (so $\lambda \approx 3.5$) (in Figure 3 we are visualizing the positive direction for the y-axis in reverse of what the equations actually give us).

5.2. Remarks on various kinds of C-slow exit and entrance points. The definitions of fs1 simple C-slow entrance and exit points (Definitions 3.5 and 3.6) are easy to use, but not as general as might be useful in other circumstances. Other types of slow exit and entrance points have been defined, see [**5, 9, 11, 17, 21, 22**], and, while they are more general, they are somewhat unwieldy to use and are not always as directly applicable as would be desirable [**11, 12**]. Furthermore, as mentioned in Remark 3.4, the definitions of simple C-slow exit and entrance points given in [**11**] need modifications to make things work out there. In particular, they need to be modified so that the corresponding analogs of Theorems 3.11 and 3.12 are true. It also needs to be shown that this does not affect the application in [**11**], see Remark 3.8. All of this is done in [**12**] and will be alluded to presently.

The following definition is a preliminary definition needed before we give the modified definition of a simple C-slow exit point.

Definition 5.1. Let $\{\varphi^\lambda\}_{\lambda\in\Lambda}$ be a continuous family of flows. Let K be a compact invariant set under φ^{λ_0}, and let a neighborhood U of $\mathcal{R}(K)$ be given. A *simple chain recurrent set neighborhood and* ε *collection* (*a simple* CRSNE *collection*) *of* K *relative to* U is a collection $\{V, W, \varepsilon\}$ such that (a) V is an open neighborhood of $\mathcal{R}(K)$ and $V \subset U$, (b) W is an open neighborhood of K, and (c) for all λ with $d(\lambda, \lambda_0) < \varepsilon$, if $x \in V$, then either:

1. $\varphi^\lambda(x, [0, \infty)) \subset U$ or

2. there exists a $t_0 > 0$ such that $\varphi^\lambda(x, [0, t_0]) \subset U$ and $\varphi^\lambda(x, t_0) \in U \setminus W$.

Remark 5.1. Clearly we can take the neighborhoods V of $\mathcal{R}(K)$ and W of K smaller and take $\varepsilon > 0$ smaller and still retain a simple CRSNE collection of K relative to U.

Remark 5.2. This definition takes the "main lemma" of Conley in [**5**], simplifies it (by avoiding *Morse decompositions*), and turns it into a definition. Conley's point was that simple CRSNE collections can always be found in a theoretical sense. The point of this definition is that, in applications, one may want to find simple CRSNE collections by actually constructing them from the details of the flow. This can make application of Conley's ideas more direct [**12**].

Now we come to the modified definition of a simple C-slow exit point. The context for this definition is for a flow φ^ε defined by the differential equation $\dot{x} = f_0(x) + \varepsilon f_1(x)$, where f_0 and f_1 are smooth and $x \in \mathbf{R}^n$. A function g defined on $S = \operatorname{Inv}(N, \varphi^0)$ is said to have *strictly positive averages* on S if the limit of the set of numbers $\{1/T \int_0^T g(\varphi^0(x,s))\, ds \mid x \in S\}$ has closure in the interval $(0, \infty)$.

Definition 5.2. A point $x \in S_\partial$ is called a *simple C-slow exit point* if there exists a compact set $K_x \subset S$ which is invariant under φ^0, a bounded neighborhood U_x of the chain recurrent set $\mathcal{R}(K_x)$, and a differentiable function $\ell_0 : cl(U_x) \to \mathbf{R}$ such that the following conditions are satisfied.

(a) $\omega(x, \varphi^0) \subset K_x$

(b) Let $g_0(z) = \nabla \ell_0(z) \cdot f_0(z)$ and $g_1(z) = \nabla \ell_0(z) \cdot f_1(z)$. Then $g_0 \equiv 0$ on U_x and g_1 has strictly positive averages on $\mathcal{R}(K_x)$.

(c) There exists a number $\bar{\varepsilon} > 0$, an open neighborhood V_x of $\mathcal{R}(K_x)$, and an open neighborhood W_x of K_x such that (i) $\{V_x, W_x, \bar{\varepsilon}\}$ is a simple CRSNE collection for K_x relative to U_x, (ii) $\ell_0|_{V_x} > -\delta$ for some $\delta > 0$, and (iii) $\ell_0|_{cl(U_x \cap (S \setminus W_x))} < -m\delta$ for some $m > 1$.

(d) If U_x' is a neighborhood of $\mathcal{R}(K_x)$ with $U_x' \subset U_x$, then there exists an open neighborhood V_x' of $\mathcal{R}(K_x)$ and an open neighborhood W_x' of K_x such that (i) $\{V_x', W_x', \bar{\varepsilon}\}$ is a simple CRSNE collection for K_x relative to U_x', (ii) $\ell_0|_{V_x'} > -\eta$ for some $\eta > 0$ and (iii) $\ell_0|_{\mathrm{cl}\,(U_x' \cap (S \setminus W_x'))} < -n\eta$ for some $n > 1$.

Remark 5.3. It is shown in [**12**] that this definition is easier to use than it may appear.

Remark 5.4. We can, of course, define the dual notion of a simple C-slow entrance point and we can also define a strict simple C-slow entrance point. The analogs of Theorems 3.11, 3.12 and 3.13 are also true in this context.

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P.O. Box 95, Bethel University, St. Paul, MN 55112
Email address: b-kinney@bethel.edu