Nonlinear Conformation Response in the Finite Channel: Existence of a Unique Solution for the Dynamic PNP Model

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Abstract

The standard PNP model for ion transport in channels in cell membranes has been widely studied during the previous two decades; there is a substantial literature for both the dynamic and steady models. What is currently lacking is a generally accepted gating model, which is linked to the observed conformation changes on the protein molecule. In [SIAM J. Appl. Math. 61 (2000), no.3, 792–802], C.W. Gardner, the author, and R.S. Eisenberg suggested a model for the net charge density in the infinite channel, which has connections to stochastic dynamical systems, and which predicted rectangular current pulses. The finite channel was analyzed by these authors in [J. Theoret. Biol. 219 (2002), no. 3, 291–299]. The finite channel cannot, in general, be analyzed by a traveling wave approach. In this paper, a rigorous study of the initial-boundary value problem is carried out for the deterministic version of the finite channel; an existence/uniqueness result, with a weak maximum principle, is derived on the space-time domain under assumptions on the inital and boundary data which confine the channel to certain states. A significant open problem for the finite channel is the study of phase plane orbits, as exists for the infinite channel. Another open problem is the derivation of comparable existence/uniqueness results, under assumptions on the given data which allow for the complete set of states for the channel.

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1 Introduction

The model considered in this article is based upon the finite channel gating model discussed and simulated in [9]. The infinite channel model was introduced earlier in [8]. In both of these articles, rectangular current pulses–the analog of gating–were obtained, via the implementation of a nonlinear charge response. The form of this was derived in [8] via a Boltzmann factor. In the case of the infinite channel, reduction via the use of a change of variable, based on a traveling wave ansatz, reduces the system to a pure initial value problem (cf. [24] for the use of this idea for the analogous semiconductor model). The deterministic model for the infinite channel has a fundamental drawback, since it allows the channel to remain permanently in a stationary state, corresponding to a fixed point, which is not observed for this class of voltage-gated channels. Accordingly, a stochastic forcing term (noise) was utilized in [8], allowing for the use of traditional methods in stochastic dynamical systems [23]. For general deterministic dynamical systems, the biophysical case corresponds to bifurcation from a line of fixed points, a situation considered in [5, 6](cf. [17] for a study of a class of symmetric perturbations). In the case of the finite channel, it is the time dependent boundary conditions which preclude the system from occupying a permanent state corresponding to a fixed point. In this article, we treat the model as deterministic, and traveling wave reductions are excluded because of the boundary conditions. The critical term which separates this model from the standard PNP model is the nonlinear representation for the charge density of the protein, expressed as a function of mobile positive ion concentration p and electric field E. This incorporates the characterization of the protein as undergoing a conformation change, permitting the gating of the channel. The derivation was carried out in [8, pp. 794–795]. The ensuing model presents analytical difficulties not previously encountered with time dependent Poisson-Nernst-Planck systems (PNP). There is a growing, and already rich literature for the standard PNP system, which would be difficult to summarize here. A noteworthy aspect of current research is that studies have moved beyond questions of existence and uniqueness, and have advanced to asymptotic issues, particularly incorporating geometry. An interesting recent study is given in [18]. General questions of existence for the steady [14] and dynamic [21, 15] self-consistent drift diffusion systems were already considered in the context of the analogous semiconductor model in the 1980s. Since that time, topics of uniqueness/non-uniqueness [1], stochastics [4], and singular perturbations [3] have been studied, in addition to many others. The model adopted here, for the existence and uniqueness theory, and the derivation of a weak maximum principle, closely follows the original article [9].

For readers wishing to understand the biophysics of ion channels, the treatise of Hille [12] is highly recommended. An interesting biochemical interpretation of gating is given in terms of binding and unbinding of ions, producing current fluctuations [22]. A major impetus to the study of ion channels was the discovery of the patch clamp [19], making single channel voltage/current recordings experimentally possible.

The existence/uniqueness theory which we present places a restriction on the relative size of the initial and boundary data for the ionic concentration; it cannot exceed a certain benchmark parameter, called $\bar{p}$ in the following sections. This is made explicit in section 1.1. Because of the Gauss equation for the electric field, this has the effect of considering only those states corresponding to the increase of the electric field. Among the open problems discussed at the conclusion of the article is that of extending the analysis to the corresponding states when the electric field decreases.

1.1 The mathematical description of the IBVP

We will consider the following initial-boundary value problem (IBVP) on an interval $[a, b]$, which represents the actual channel, typically of length on the order of a nanometer, during a time interval $[0, T]$. The positive ions are selected as K^+ ions in [8]. The first equation (1) of the following system is a conservation equation for the positive ion concentration p. The second equation (2) is the Gauss equation for the electric field E. The current density is described by (3), the boundary conditions by (4), and the initial condition by (5). We have:

$$\frac{\partial p}{\partial t} + \frac{1}{e}\frac{\partial j}{\partial x} = 0, \tag{1}$$

$$\frac{\partial}{\partial x}(\varepsilon E) = e(p - N) = \rho(p, E), \tag{2}$$

$$j(p, E) = e\mu p E - eD\frac{\partial p}{\partial x}, \tag{3}$$

$$p(a, t) = p_a(t),\ p(b, t) = p_b(t),\ E(a, t) = E_a(t),\ \phi(b, t) = \phi_b(t), \tag{4}$$

$$p(x, 0) = p_0(x). \tag{5}$$

The relation of E and ϕ is: $E(x) = -\phi'(x)$. Here, ϕ represents the usual electrostatic potential. Note that the right end of the channel has a prescribed potential, varying in time. In (2), the net charge density term $e(p - N)$, combining the mobile ions with the charge on the protein, was expressed by:

$$\rho(p, E) = -ce(p - \bar{p})\left|\frac{E}{\bar{E}} - 1\right|, \tag{6}$$

where $c, \bar{p}, \bar{E}$ are positive constants. Here, $\bar{p}, \bar{E}$ are interpreted as reference levels. The positive constants μ and D represent the mobility and diffusion coefficients, respectively, and are assumed to satisfy the Einstein relation:

$$D = U_{T_0}\mu,\ U_{T_0} = k_B T_0/e.$$

The constant U_{T_0} is known as the thermal voltage, expressed in terms of Boltzmann's constant k_B, the constant ambient temperature T_0, and the charge modulus e. The sign in (6) is critical for gating. Simulations show that rectangular pulses are not observed if $\rho \mapsto -\rho$ for positive ions [7]; there is a type of mirror symmetry for negative charges, and in this case one obtains rectangular pulses for $\rho \mapsto -\rho$ and negative $\bar{E}$ [7]. The results depend strongly on the derivation of invariant region principles. The following hypothesis is directly tied to this fact.

Assumptions on Initial and Boundary Data
The boundary value functions p_a, p_b are assumed in $C^1[0,T]$, and to be *nonnegative*. The initial ion concentration $p_0 \geq 0$ is assumed in $H^1(a,b)$, and the boundary value functions E_a, ϕ_b are assumed in $C[a,b]$. *It is assumed that the supremum norms of p_a, p_b, p_0 do not exceed $\bar{p}$.*

Remark 1.1. *The paper establishes that $\bar{p}$ is a bound for p when the data satisfy this condition. This corresponds to the channel state when the field is increasing.*

1.2 Weak solutions and general approach

The objective of this study is to demonstrate the existence of a unique weak solution of the system defined in section 1.1. A weak maximum principle is derived, and is integral to the mathematical arguments. The precise definition of weak solution is given in Definition 4.1, via equations (15,16). Note that equation (16) is expressed in terms of ϕ, rather than E. Our approach is based on Rothe's method, as developed in the author's monograph [13]. This involves a thorough analysis of semidiscrete problems, carried out in the following sections 2 and 3. Section 4 discusses the compactness issues on the space-time domain, and convergence to a weak solution, which is shown to be unique. The main theorems of the paper are expressed as Theorems 4.1 and 4.2. We have included two appendices in order to maintain an appropriate flow of the mathematical exposition.

2 The Semidiscretization

The definitions associated with the semidiscrete system (7, 8) below are presented formally at the outset. The remainder of section 2 deals with the fixed point arguments required for this recursive nonlinear system.
We employ the method of horizontal lines. Given $N > 0$, and a terminal time T, we define $\Delta t = T/N$. Inductively, assume that p_ℓ is defined for $\ell < k$, and ϕ_ℓ is defined for $1 \leq \ell < k$ where $k > 0$. Define p_k and E_k by:

$$\frac{p_k - p_{k-1}}{\Delta t} + \frac{1}{e}\frac{\partial j(p_k, E_k)}{\partial x} = 0, \tag{7}$$

$$\frac{\partial}{\partial x}(\varepsilon E_k) = \rho(p_k, E_k), \quad E_k = -\phi_k', \tag{8}$$

where the boundary conditions at time $t_k = k\Delta t$ must be adjoined. This is a coupled nonlinear system, and requires a fixed point analysis.

2.1 Semidiscretization map

Given a fixed $k > 0$, we define a mapping P from $C[a,b]$ into itself as follows. For $p \in C[a,b]$, solve

$$\frac{\partial}{\partial x}(\varepsilon E) = \rho(p, E), \quad E(a) = E_a(t_k)$$

uniquely for $E = E(p)$. This is possible in the classical sense by use of Theorem B.1 stated and proved in appendix B. Next, given $E \in C^1[a,b]$, use Theorem A.1 in appendix A to solve the linear problem:

$$\frac{Pp - p_{k-1}}{\Delta t} + \frac{1}{e}\frac{\partial j(Pp, E)}{\partial x} = 0, \tag{9}$$

with boundary conditions adjoined, uniquely for Pp. This solution is initially defined as a weak solution, as discussed in appendix A and interpreted below as (11). We observe that a fixed point p of this map, coupled with the associated function $E = E(p)$, form a solution pair of the semidiscrete system (7, 8).

2.2 Equivalence of weak solutions

Because of the use of weak solutions for the p-equation (9), we introduce the necessary ideas at this time. There are actually three equivalent interpretations of weak solution, each with its own usefulness at appropriate stages of the analysis. We choose one of them as the definition, the obvious and expected choice, and proceed to the equivalences.

Definition 2.1. *For E given in $C^1[a, b]$, the function $Pp \in H^1(a, b)$ is a weak solution of (9) if, $\forall \psi \in H_0^1(a, b)$, the relation,*

$$\int_a^b \left[\frac{Pp - p_{k-1}}{\Delta t}\right] \psi \, dx - \frac{1}{e}\int_a^b j(Pp, E)\left(\frac{d\psi}{dx}\right) dx = 0, \tag{10}$$

holds, together with the boundary conditions specified by p_a, p_b at $x = a, b$, resp., for $t = t_k$.

Lemma 2.1. *The characterization (10) is equivalent to the following for $\alpha = e^2 D$, $\omega \in H_0^1(a, b)$, and $E = -\phi'$:*

$$\int_a^b \left[\frac{Pp - p_{k-1}}{\Delta t}\right] \omega e^{\phi/U_{T_0}} \, dx + \frac{1}{\alpha}\int_a^b j(Pp, E) j(\omega, E) e^{\phi/U_{T_0}} \, dx = 0. \tag{11}$$

Proof. It is a straightforward calculation to see that the two relations are connected by the reversible transformation:

$$\omega = \psi e^{-\phi/U_{T_0}}.$$

For example, to see that (10) implies (11), write:

$$\frac{d\psi}{dx} = \frac{d(e^{\phi/U_{T_0}}\omega)}{dx} = \left(\frac{-1}{e\mu U_{T_0}}\right) j(\omega, E) e^{\phi/U_{T_0}},$$

so that the second terms in (10) and (11) are equal. Since the first terms are equal under the transformation, we have verified one of the implications. The other simply reverses this argument. □

Lemma 2.2. *Introduce the Slotboom transformation, $Pp = e^{-\phi/U_{T_0}} W$, for $-\phi' = E$. Then (10) is equivalent to:*

$$\int_a^b e^{-\phi/U_{T_0}} W \psi \, dx + D\Delta t \int_a^b e^{-\phi/U_{T_0}} \frac{dW}{dx}\frac{d\psi}{dx} \, dx = \int_a^b p_{k-1}\psi \, dx. \tag{12}$$

Proof. This follows by a direct differentiation, analogous to that used in the proof of the previous lemma:

$$\frac{dW}{dx} = \frac{d(e^{\phi/U_{T_0}} Pp)}{dx} = \left(\frac{-1}{e\mu U_{T_0}}\right) j(Pp, E) e^{\phi/U_{T_0}}.$$

Substitution into (10) and simplification give (12). The transformation is reversible, so that (10) can be obtained from (12). □

The actual existence of a weak solution is expressed via (11), as proven in Appendix A, Theorem A.1.

2.3 Essential properties of P

These are stated and proved in anticipation of an application of the Leray-Schauder fixed point theorem, required to establish the well-posedness of the semidiscretization.

2.3.1 Relative compactness of the range of P

In the following, $C[a, b]$ denotes the Banach space of real continuous functions on $[a, b]$ with the supremum norm, and $H^1(a, b)$ denotes the Hilbert space of absolutely continuous real functions with square integrable derivatives, with inner product, $(u, v)_{H^1} = \sum_{i=0}^{1} \int_a^b u^{(i)}(x) v^{(i)}(x)\, dx$.

Lemma 2.3. *P is bounded from $C[a, b]$ into $H^1(a, b)$. In particular, P is compact as a mapping from $C[a, b]$ into itself.*

Proof. We use the characterization (12). By writing $W = \omega + \ell$, where ω vanishes at $x = a, x = b$, and where ℓ is the linear interpolant of W, one obtains:

$$\int_a^b e^{-\phi/U_{T_0}} \omega\psi\, dx + D\Delta t \int_a^b e^{-\phi/U_{T_0}} \frac{d\omega}{dx}\frac{d\psi}{dx}\, dx =$$

$$\int_a^b e^{-\phi/U_{T_0}} (p_{k-1} e^{\phi/U_{T_0}} - \ell)\psi\, dx - D\Delta t \int_a^b e^{-\phi/U_{T_0}} \frac{d\ell}{dx}\frac{d\psi}{dx}\, dx.$$

The selection $\psi = \omega$ leads to

$$\frac{1}{2}\int_a^b e^{-\phi/U_{T_0}} \omega^2\, dx + \frac{D\Delta t}{2}\int_a^b e^{-\phi/U_{T_0}} \left(\frac{d\omega}{dx}\right)^2 dx \le$$

$$\frac{1}{2}\int_a^b e^{-\phi/U_{T_0}} |p_{k-1} e^{\phi/U_{T_0}} - \ell|^2\, dx + \frac{D\Delta t}{2}\int_a^b e^{-\phi/U_{T_0}} \left(\frac{d\ell}{dx}\right)^2 dx,$$

where integrand products have been expressed as sums of squares. Now, as p ranges over a bounded set in $C[a, b]$, the range of ϕ and the range of $\phi' = -E$ both lie in bounded intervals (see Theorem B.1 of appendix B). It is also the case that the linear interpolants, together with their (constant) derivatives, are pointwise bounded. The H^1 boundedness for ω follows if one makes appropriate replacements for ϕ in terms of maximum and/or minimum values. It follows that W, and Pp, lie in a bounded set in H^1. □

2.3.2 Continuity of P

Lemma 2.4. *The mapping P is continuous from $C[a,b]$ into $H^1[a,b]$. In particular, P is continuous as a mapping from $C[a,b]$ into itself.*

Proof. We use the Slotboom variables; for distinct p_1, p_2, write $Pp_i = \exp(-\phi_i/U_{T_0})W_i, i = 1, 2$. As above, this permits the rewriting of the difference of the weak forms of (12):

$$\int_a^b e^{-\phi_1/U_{T_0}}(W_1 - W_2)^2\, dx + D\Delta t \int_a^b e^{-\phi_1/U_{T_0}} \left[\frac{d(W_1 - W_2)}{dx}\right]^2 dx =$$

$$\int_a^b [e^{-\phi_2/U_0} - e^{-\phi_1/U_{T_0}}] W_2(W_1 - W_2)\, dx +$$

$$D\Delta t \int_a^b [e^{-\phi_2/U_0} - e^{-\phi_1/U_{T_0}}] \frac{dW_2}{dx} \frac{d(W_1 - W_2)}{dx}\, dx.$$

Now hold p_1 fixed. As $p_2 \to p_1$, one knows that ϕ_2 converges uniformly to ϕ_1 from Corollary B.1. We also know from Lemma 2.3 that W_2 is H^1-bounded in any ball centered at the fixed H^1 function W_1. The above estimate implies the conclusion of Lemma 2.4. □

2.4 Existence of a fixed point for P

In order to apply the version of the Leray-Schauder theorem suitable for the system (7, 8), we require a uniform bound for homotopy fixed points. This property is stated and verified in the following lemma. We begin with a definition of a bound for the invariant interval for the p-equation.

Definition 2.2. *Define B by*

$$B = \max(\bar{p}, \sup_{0 \le t \le T} p_a(t), \sup_{0 \le t \le T} p_b(t), \sup_{a \le x \le b} p_0(x)).$$

Remark 2.1. *The principal hypothesis of this article, stated with the set of assumptions in section 1.1, is the assumption that*

$$B = \bar{p}. \tag{13}$$

With the choice of the sign of ρ in (6), we have not been able to extend the results to the case when $B > \bar{p}$. Simulations carried out by Carl Gardner [7], show that p first increases significantly, and then settles down to a pattern of rectangular waves in the regime where $B > \bar{p}$. If $\rho \mapsto -\rho$, then the arguments of this paper imply that existence and uniqueness hold for this case. However, it is not the physically appropriate case; this is borne out by the derivation cited from [8], as well as by simulations carried out, again, by Carl Gardner, which show very different behavior from that of rectangular waves.

Lemma 2.5. *Suppose that $p_* = tPp_*$, for some $t, 0 \le t \le 1$. Then, there is a uniform $C[a,b]$ bound M for the fixed points p_*. In fact, $M = \bar{p}$ holds for each t. This bound holds recursively with respect to k.*

Proof. Assume, inductively, that $0 \leq p_{k-1} \leq \bar{p}$, and suppose that p_* satisfies the fixed point property. We may assume that $t > 0$. Set $\tau = \frac{1}{t}$ for $0 < t \leq 1$. Denote the corresponding electric field by E_* and the integral of $-E_*$, satisfying the boundary condition at b, by ϕ_*. In particular, E_* satisfies the equation:

$$\frac{\partial}{\partial x}(\varepsilon E_*) = \rho(p_*, E_*) = -ce(p_* - \bar{p})\left|\frac{E_*}{\bar{E}} - 1\right|. \quad (14)$$

There are two parts to the proof. For the first part, we use (11):

$$\frac{1}{\alpha}\int_a^b j(\tau p_*, E_*) j(\psi, E_*) e^{\phi_*/U_{T_0}}\, dx + \int_a^b \frac{\tau p_* \psi}{\Delta t} e^{\phi_*/U_{T_0}}\, dx =$$
$$\int_a^b \frac{p_{k-1}\psi}{\Delta t} e^{\phi_*/U_{T_0}}\, dx, \ \forall \psi \in H_0^1.$$

In order to show that $p_* \geq 0$, we select $\psi = p_*^-$, where $u^- = u, u \leq 0$, and is zero otherwise. Note that $\psi(a) = \psi(b) = 0$. If this definition of ψ is inserted in the weak formulation, then

$$\frac{\tau}{\alpha}\int_a^b |j(p_*^-, E_*)|^2 e^{\phi_*/U_{T_0}}\, dx + \tau \int_a^b \frac{(p_*^-)^2}{\Delta t} e^{\phi_*/U_{T_0}}\, dx =$$
$$\int_a^b \frac{p_{k-1} p_*^-}{\Delta t} e^{\phi_*/U_{T_0}}\, dx \leq 0.$$

Since the left hand side is the product of τ and a constant times the squared norm of p_*^-, as defined in the appendix, we conclude that $p_*^- \equiv 0$. We now verify that $p_* \leq \bar{p}$ by showing that $\psi = (p_* - \bar{p})^+ \equiv 0$, where $u^+ = u, u \geq 0$, and u is zero otherwise. We employ ψ as a test function in the weak formulation (10) (note the change in the formulation from the previous case), to obtain:

$$\frac{\tau}{\Delta t}\int_a^b (p_* - \bar{p})(p_* - \bar{p})^+\, dx + \tau D \int_a^b [(d/dx)(p_* - \bar{p})^+]^2\, dx$$
$$-\frac{1}{\Delta t}\int_a^b (p_{k-1} - \tau\bar{p})(p_* - \bar{p})^+\, dx = \tau\mu \int_a^b p_* E_* (d/dx)(p_* - \bar{p})^+\, dx.$$

We show that the right hand side term is nonpositive. The left hand side is nonnegative by inspection. This requires the inequality $\tau \geq 1$, and the induction hypothesis $p_{k-1} \leq \bar{p}$. We write, via the short hand notation $R(p_*, E_*)$,

$$R(p_*, E_*) = \tau\mu \int_a^b p_* E_* (d/dx)(p_* - \bar{p})^+\, dx =$$
$$\frac{\tau\mu}{2}\int_a^b E_*(d/dx)[(p_* - \bar{p})^+]^2\, dx + \ \tau\mu\bar{p}\int_a^b E_*(d/dx)(p_* - \bar{p})^+\, dx,$$

and integrate each of these terms by parts. By use of the differential equation (14), one obtains

$$R(p_*, E_*) = \frac{-\tau\mu}{2\varepsilon}\int_a^b \rho[(p_* - \bar{p})^+]^2\, dx - \frac{\tau\mu\bar{p}}{\varepsilon}\int_a^b \rho(p_* - \bar{p})^+\, dx.$$

On the set where $(p_* - \bar{p})^+$ is nonzero, it is seen that $\rho \geq 0$. We conclude that $(p_k - \bar{p})^+ \equiv 0$. □

Theorem 2.1. *The system (7, 8), with boundary conditions defined by* p_a, p_b, E_a*, has a solution pair in the following sense:* p_k *satisfies a weak form of its equation and hence a strong (classical) form;* E_k *satisfies a strong form. Furthermore,* p_k *satisfies the invariant region principle:* $\|p_k\|_{C[a,b]} \leq \bar{p}$*. Also,* $p_k \geq 0$*.*

Proof. The version of the Leray-Schauder fixed point theorem used is stated and proven in [10]. The hypotheses of continuity, compactness, and a uniform bound for homotopy fixed points have been demonstrated within the Banach space $C[a, b]$. The mapping P has been constructed so that fixed points define solution pairs. The function p_k is a distribution solution and hence a classical solution [11, chapter 8] in the sense that p_k has continuous derivatives of order two, and satisfies its equation pointwise. □

3 Uniqueness of Semidiscrete Solutions

We demonstrate uniqueness of the solutions derived in Theorem 2.1 under a size restriction on Δt. We begin the analysis with a relation between differences in E and differences in p.

Lemma 3.1. *Suppose that* p_*, E_* *and* p_{**}, E_{**} *are solution pairs in the sense of Theorem 2.1, where* p_*, p_{**} *are bounded by* $\bar{p}$*. Then*

$$\int_a^b (E_* - E_{**})^2 \, dx \leq C \int_a^b (p_* - p_{**})^2 \, dx,$$

for some constant $C = C(c, \bar{p}, \bar{E}, a, b, E_a)$*.*

Proof. Theorem B.1 yields an electric field bound, $E_0 = E_0(c, \bar{p}, \bar{E}, a, b, E_a)$, when the p-bound $\bar{p}$ is given. Define the function of s:

$$g(s) = \frac{1}{2}[E_*(s) - E_{**}(s)]^2,$$

and differentiate. After use of the defining differential equation (14), and an addition and subtraction, one obtains the identity,

$$\left(\frac{\varepsilon}{e}\right) g' = (E_* - E_{**})[\rho(p_*, E_*) - \rho(p_*, E_{**})] +$$

$$(E_* - E_{**})[\rho(p_*, E_{**}) - \rho(p_{**}, E_{**})].$$

Recall that ρ is Lipschitz continuous in each argument. If we set

$$h(s) = [p_*(s) - p_{**}(s)]^2,$$

and utilize the standard inequality $rs \leq \frac{1}{2}(r^2 + s^2)$, we obtain, via the derived bounds,

$$g'(s) \leq c_1 g(s) + c_2 h(s).$$

Here, c_1, c_2 are positive constants. After solving this inequality by an integrating factor, and then integrating over $[a, b]$, one obtains the result. In solving the inequality, the use of $g(a) = 0$ is employed. This completes the proof. □

Theorem 3.1. *There exists a positive constant δ such that, if $\Delta t < \delta$, solutions of the system (7, 8), in the sense of Theorem 2.1, are unique.*

Proof. Suppose that p_*, E_* and p_{**}, E_{**} are solution pairs in the sense of Theorem 2.1, where p_*, p_{**} are bounded by $\bar{p}$. Both p_* and p_{**} are fixed points of P; we use this in the weak formulation (10). If the equations are subtracted, and the substitution,

$$\psi = p_* - p_{**},$$

is utilized, one has:

$$\int_a^b (p_* - p_{**})^2 \, dx = \frac{\Delta t}{e} \int_a^b (j(p_*, E_*) - j(p_{**}, E_{**})(p'_* - p'_{**}) \, dx.$$

If the current density expressions j are expanded, one has, after simplification,

$$\int_a^b (p_* - p_{**})^2 \, dx + D\Delta t \int_a^b (p'_* - p'_{**})^2 \, dx = \mu \Delta t \int_a^b E_*(p_* - p_{**})(p'_* - p'_{**}) \, dx +$$

$$\mu \Delta t \int_a^b p_{**}(E_* - E_{**})(p'_* - p'_{**}) \, dx.$$

Use of the inequality,

$$rs \leq \frac{1}{2}\left(\frac{2r^2}{U_{T_0}} + \frac{U_{T_0} s^2}{2}\right),$$

as applied to the integrands of both right hand side terms, gives

$$\int_a^b (p_* - p_{**})^2 \, dx + \frac{D\Delta t}{2} \int_a^b (p'_* - p'_{**})^2 \, dx \leq$$

$$c_1 \Delta t \int_a^b (p_* - p_{**})^2 \, dx \; + c_2 \Delta t \int_a^b (E_* - E_{**})^2 \, dx,$$

for positive constants c_1, c_2. Use of Lemma 3.1 gives

$$\int_a^b (p_* - p_{**})^2 \, dx + \frac{D\Delta t}{2} \int_a^b (p'_* - p'_{**})^2 \, dx \leq \frac{\Delta t}{\delta} \int_a^b (p_* - p_{**})^2 \, dx$$

for a positive constant δ. This is the constant in the statement of the theorem. This implies that $p_* - p_{**} = 0$, and the uniqueness follows. □

4 Space-Time Domain Analysis

We begin with the definition of weak solution adopted in this article. $\mathcal{D}$ denotes the space-time domain $(a, b) \times (0, T)$. The function spaces used are consistent with those employed in the basic reference [13].

Definition 4.1. *The pair $[p, \phi]$ is said to be a weak solution of the system (1, 2) if p satisfies the specified Dirichlet boundary conditions and the initial condition in the sense of the Sobolev trace theorems, if ϕ satisfies the Dirichlet boundary condition pointwise, and, in addition, $p \in \mathcal{X} := H^1((0,T); L^2(a,b)) \cap L^2((0,T); H^1(a,b))$, $\phi \in C([0,T]; H^1(a,b))$ and the following conditions hold:*

$$\int_{\mathcal{D}} \left[\frac{\partial p}{\partial t}\omega_p + D\frac{\partial p}{\partial x}\frac{\partial \omega_p}{\partial x} + \left(\frac{D}{U_{T_0}}\right) p \frac{\partial \phi}{\partial x}\frac{\partial \omega_p}{\partial x} \right] dxdt = 0, \tag{15}$$

$$\int_{\mathcal{D}} \frac{\partial \phi}{\partial x}\frac{\partial \omega_\phi}{\partial x}\, dxdt = \frac{1}{\varepsilon}\int_{\mathcal{D}} \rho(p,E)\omega_\phi\, dxdt + \int_0^T L_t(\omega_\phi)dt, \tag{16}$$

for test functions $\omega_p \in C^\infty(\bar{\mathcal{D}})$, which vanish at $x = a, x = b$ and test functions $\omega_\phi \in C^\infty(\bar{\mathcal{D}})$, vanishing at $x = b$. Here, $L_t(\omega_\phi) = E_a(t)\omega_\phi(a,t)$ defines the linear functional which incorporates the Neumann boundary condition for ϕ at $x = a$.

A method was introduced in [13] for constructing weak solutions, in the sense of Definition 4.1, from the semidiscrete solutions defined by Rothe's method, by a compactness principle, applied to piecewise linear sequences on $\mathcal{D}$. We continue with the definitions of these approximation sequences.

Definition 4.2. *We recall the previous notation. For each N and $\Delta t = T/N$, set $t_k = k\Delta t, k = 0, \dots, N$. Select the solution pair for the semidiscrete system (7, 8), for each $k = 1, \dots, N$. Define piecewise linear (in t) sequences built on the p_k as follows. For $t_{k-1} \le t \le t_k$,*

$$P^N(\cdot\,, t) = p_k + \frac{(t - t_k)(p_k - p_{k-1})}{\Delta t}.$$

For $0 \le t \le T$, define $E^N(\cdot\,, t)$ to be the unique solution of the differential equation,

$$\frac{\partial}{\partial x}(\varepsilon E^N(\cdot\,,t)) = \rho(P^N(\cdot\,,t), E^N),$$

augmented by the time dependent boundary condition: $E^N(a,t) = E_a(t)$.

4.1 Properties of the approximation sequences

We begin with a lemma.

Lemma 4.1. *The sequences $\{P^N\}$ and $\{E^N\}$ are uniformly bounded on the space-time domain $\mathcal{D}$. There is a constant C, depending only on the given data of the IBVP, such that*

$$\int_{\mathcal{D}} [E^N(x,t) - E^M(x,t)]^2\, dxdt \le C \int_{\mathcal{D}} [P^N(x,t) - P^M(x,t)]^2\, dxdt.$$

In particular, the existence of any L^2-convergent subsequence $\{P^{N_i}\}$ of $\{P^N\}$ implies the corresponding convergence of $\{E^{N_i}\}$.

Proof. We note that

$$|P^N(x,t)| \le \bar{p},\ \forall (x,t) \in \mathcal{D},$$

as follows from the invariant interval property, and the piecewise linear definition of P^N. The boundedness of E^N follows from Theorem B.1. This was discussed previously. The remainder of the argument follows a pattern similar to the proof of Lemma 3.1, but is summarized here because of the significant contextual differences. Define, for fixed M, N, t, the function of s:

$$g_t(s) = \frac{1}{2}[E^N(s,t) - E^M(s,t)]^2,$$

and differentiate. After use of the defining differential equation, and an addition and subtraction, one obtains the identity,

$$\left(\frac{\varepsilon}{e}\right) g_t' = (E^N - E^M)[\rho(P^N, E^N) - \rho(P^N, E^M)] +$$

$$(E^N - E^M)[\rho(P^N, E^M) - \rho(P^M, E^M)].$$

Recall that ρ is Lipschitz continuous in each argument. If we set

$$h_t(s) = [P^N(s,t) - P^M(s,t)]^2,$$

we obtain, via the derived bounds,

$$g_t'(s) \le c_1 g_t(s) + c_2 h_t(s), \ g_t(a) = 0,$$

for positive constants c_1, c_2. After solving this inequality and integrating over $\mathcal{D}$, one obtains the result. This completes the proof. □

We continue with a statement regarding the sequence P^N.

Lemma 4.2. *The sequence P^N satisfies the following boundedness properties in the indicated spaces:*

$$\left\{\frac{\partial P^N}{\partial t}\right\} \subset L^2(\mathcal{D}) \text{ is bounded;}$$

$$\left\{P^N\right\} \subset L^\infty((0,T); H^1) \text{ is bounded.}$$

Proof. The second property is immediate from the uniform H^1 bound for p_k, via a direct estimate of the norm of P^N in $L^\infty((0,T); H^1)$. The first property is more complicated. It suffices to show that

$$\int_{\mathcal{D}} \left(\frac{\partial P^N}{\partial t}\right)^2 dxdt \le C,$$

where C does not depend on N. By direct calculation, this is equivalent to the inequality:

$$\left(\frac{1}{\Delta t}\right) \sum_{k=1}^{N} \|p_k - p_{k-1}\|_{L^2}^2 \le C. \tag{17}$$

We will establish this inequality. For each $k = 1, \ldots, N$, let ℓ_k denote the linear function satisfying $\ell_k(a) = p_a(t_k), \ell_k(b) = p_b(t_k)$. Use the weak form (10) of (7) with test function:

$$\psi = (p_k - p_{k-1}) - (\ell_k - \ell_{k-1}).$$

Following an integration by parts, this gives the following identity:

$$\frac{1}{\Delta t}\int_a^b [p_k - p_{k-1}]^2 \, dx + D\int_a^b \frac{dp_k}{dx}\frac{d(p_k - p_{k-1})}{dx} \, dx \; =$$

$$\frac{1}{\Delta t}\int_a^b (p_k - p_{k-1})(\ell_k - \ell_{k-1}) \, dx + D\int_a^b \frac{dp_k}{dx}\frac{d(\ell_k - \ell_{k-1})}{dx} \, dx$$

$$+\mu\int_a^b \frac{d(E_k p_k)}{dx}(p_k - p_{k-1}) \, dx - \mu\int_a^b \frac{d(E_k p_k)}{dx}(\ell_k - \ell_{k-1}) \, dx.$$

We now estimate each term after the first in this equation by replacing integrand products by sums of squares. Altogether, this gives the following:

$$\frac{1}{2\Delta t}\int_a^b [p_k - p_{k-1}]^2 \, dx + \frac{D}{2}\int_a^b \left(\frac{dp_k}{dx}\right)^2 \, dx - \frac{D}{2}\int_a^b \left(\frac{dp_{k-1}}{dx}\right)^2 \, dx \le$$

$$\frac{1+\mu/2}{\Delta t}\int_a^b (\ell_k - \ell_{k-1})^2 \, dx + \frac{D\Delta t}{2}\int_a^b \left(\frac{dp_k}{dx}\right)^2 \, dx$$

$$+\frac{D}{2\Delta t}\int_a^b \left(\frac{d(\ell_k - \ell_{k-1})}{dx}\right)^2 \, dx + (\mu^2 + \mu/2)\Delta t\int_a^b \left(\frac{d(E_k p_k)}{dx}\right)^2 \, dx.$$

One now sums on k and uses the telescoping property of the left hand side terms:

$$\left(\frac{1}{2\Delta t}\right)\sum_{k=1}^{N}\int_a^b [p_k - p_{k-1}]^2 \, dx + \frac{D}{2}\int_a^b \left(\frac{dp_N}{dx}\right)^2 \, dx - \frac{D}{2}\int_a^b \left(\frac{dp_0}{dx}\right)^2 \, dx \le$$

$$\frac{1+\mu/2}{\Delta t}\sum_{k=1}^{N}\int_a^b (\ell_k - \ell_{k-1})^2 \, dx + \frac{D}{2\Delta t}\sum_{k=1}^{N}\int_a^b \left(\frac{d(\ell_k - \ell_{k-1})}{dx}\right)^2 \, dx \; + C.$$

We have used the fact that each derivative, $\frac{d(E_k p_k)}{dx}$, has a uniformly bounded L^2 norm. The terms involving the interpolants and their derivatives are bounded by the assumed regularity, in t, of the functions p_a, p_b. For example, a direct calculation shows that

$$\frac{1}{\Delta t}\int_a^b (\ell_k - \ell_{k-1})^2 \, dx \le \left(\frac{1}{\Delta t}\frac{b-a}{2}\right)(A_k^2 + B_k^2),$$

where

$$A_k = p_a(t_k) - p_a(t_{k-1}), \; B_k = p_b(t_k) - p_b(t_{k-1}).$$

By the standard mean value theorem for derivatives, one has

$$A_k^2 \le \max_{0 \le t \le T} |p_a'(t)|^2 (\Delta t)^2, B_k^2 \le \max_{0 \le t \le T} |p_b'(t)|^2 (\Delta t)^2.$$

This gives the bound,

$$\frac{1}{\Delta t}\int_a^b (\ell_k - \ell_{k-1})^2 \, dx \le \left(\frac{b-a}{2}\right)(\max_{0 \le t \le T} |p_a'(t)|^2 + \max_{0 \le t \le T} |p_b'(t)|^2)\Delta t,$$

so that summation is bounded. Similarly, one estimates,

$$\frac{1}{\Delta t}\int_a^b \left(\frac{d(\ell_k - \ell_{k-1})}{dx}\right)^2 \, dx \le \left(\frac{1}{\Delta t}\frac{2}{b-a}\right)(A_k^2 + B_k^2),$$

for A_k, B_k defined above. Again, summation is bounded. This completes the proof. □

4.2 Convergence

Proposition 4.1. *There are subsequences, denoted P^{N_i}, and functions $p \in \mathcal{X} = H^1((0,T); L^2(a,b)) \cap L^2((0,T); H^1(a,b))$, $E \in L^2(\mathcal{D})$ such that:*

1. $$P^{N_i} \rightharpoonup p \text{ weakly in } \mathcal{X},$$

2. $$P^{N_i} \to p \text{ in } L^2(\mathcal{D}).$$

3. $$E^{N_i} \to E \text{ in } L^2(\mathcal{D}).$$

The function p satisfies $0 \le p \le \bar{p}$ a.e. on $\mathcal{D}$.

Proof. The Aubin lemma ([2], [13, p.158]) implies that the space $\mathcal{X}$, as defined above, is compactly embedded in $L^2(\mathcal{D})$. Thus, the limit in (1), which exists by weak compactness, leads to (2). In this connection, recall that a compact mapping (injection) maps weakly convergent sequences onto strongly convergent sequences. The limit in (3) follows from (2) and Lemma 4.1. Since, for each i, $0 \le P^{N_i} \le \bar{p}$ a.e., this property is inherited by the limit function p. □

Remark 4.1. *This is sufficient to derive the existence of a weak solution. For readers not familiar with this methodology, we indicate the steps involved.*

We introduce a step function sequence as an auxiliary tool.

Definition 4.3. *For $t_k < t \le t_{k+1}$, and $0 \le k \le N-1$, we define*

$$P_S^N(x,t) = p_{k+1}(x), \; x \in [a,b].$$

Lemma 4.3. *By relabeling if necessary, we may assume, without loss of generality, that the sequence $\{P_S^{N_i}\}$ converges weakly in $L^2((0,T); H^1(a,b))$ and strongly in $L^2(\mathcal{D})$.*

Proof. That the weak limit may be taken to be p follows from (1) and (17) (see [13, Lemma 5.2.6]). Here, we have relabeled. A direct calculation shows that the strong convergence is implied by (2) when (17) holds. □

Theorem 4.1. *Suppose the pair (p, E), is constructed as a limiting pair in the sense of Proposition 4.1. Then $p \in \mathcal{X}$ and $E \in C([0,T]; L^2(a,b))$. If ϕ is constructed from E via $E = -\phi'$, and $\phi(b,t) = \phi_b(t)$, then the pair (p, ϕ) defines a solution in the sense of Definition 4.1. The function p satisfies the weak maximum principle, $0 \le p \le B$. The boundary conditions and the initial condition for p are satisfied in the sense of the trace theorem. The boundary condition for ϕ is satisfied pointwise.*

Proof. We begin with equation (15) in Definition 4.1. By choosing for the test functions in the semidiscrete equations (10), the functions

$$\int_{t_{k-1}}^{t_k} \omega_p(x,t)\, dt,$$

and summing on $k = 1, \ldots, N$, we obtain the following.

$$\int_{\mathcal{D}} \left[\frac{\partial P^{N_i}}{\partial t} \omega_p + D \frac{\partial P_S^{N_i}}{\partial x} \frac{\partial \omega_p}{\partial x} - \left(\frac{D}{U_{T_0}} \right) P_S^{N_i} E^{N_i} \frac{\partial \omega_p}{\partial x} \right] dx dt = 0.$$

We can take limits in this equation to obtain (15). Indeed, the limits of the first and second terms follow from the weak convergence in $\mathcal{X}$. The limit of the third term follows from the L^2 convergence of both sequences. We now verify (16). This is quite straightforward. One begins with the differential equation for E^N as stated in Definition 4.2 at any time t. Multiply by the indicated test function, integrate by parts over $[a, b]$, and then integrate with respect to t. Taking limits gives the stated relation with ϕ' replaced by $-E$. However, $E \in C([0, T]; L^2(a, b))$, as follows from the corresponding property for p augmented by the proof of Lemma 4.1. This permits the construction of $\phi(\cdot\,, t)$ for each t. The weak maximum principle for p and the trace boundary conditions are standard results for the regularity class satisfied by p. □

4.3 Uniqueness

In this section, we establish the uniqueness of solutions in the sense of Definition 4.1.

Theorem 4.2. *There exists a unique solution in the stated regularity class of Definition 4.1 satisfying (15, 16). It follows that the full sequences* $\{P^N\}$ *and* $\{E^N\}$ *are convergent.*

Proof. Suppose p, E_p and q, E_q are solution pairs for the system. Substitute the difference, $p - q$ as test function in (15). Note that this is possible via simple limits of the smooth test functions. By the use of an approach which uses elements of the proof of Theorem 3.1, we obtain the estimate, for some positive constant C, and each $0 < t < T$,

$$\frac{1}{2} \|p(\cdot\,, t) - q(\cdot\,, t)\|_{L^2}^2 + \frac{D}{2} \int_0^t \|\partial p/\partial x - \partial q/\partial x\|_{L^2}^2 \, ds \leq$$

$$C \int_0^t \|p - q\|_{L^2}^2 \, ds.$$

Uniqueness for the p-equation follows from this estimate by the Gronwall inequality. This in turn implies that the associated electric fields are identical, hence the associated potentials.

The second statement follows now from the proof of existence: every subsequence of the pair (P^N, E^N) has a (further) subsequence, convergent to a weak solution pair. Uniqueness implies convergence of the entire sequence. □

5 Summation

The gating modeling of the finite channel lies at the intersection of analysis, dynamical systems, and, of course, the biophysical sciences. The first model to address the formation of pulses, i.e., rectangular waves, was the model introduced in [8] for the infinite channel. This case, analyzed by traveling waves, was ideal for compatibility with stochastic dynamical systems. In [9], by the selection of boundary conditions compatible with the traveling wave solutions, it was also shown that 'quasi-rectangular waves' are derivable from the model. However, a general numerical study was not carried out for arbitrary boundary conditions in [9]. More recently [7], Carl Gardner augmented the study of [9] to support the conclusion of rectangular waves, and to demonstrate the significance of the sign of the effective charge ρ. In this article, we have formulated the fully deterministic initial-boundary value problem on a bounded interval for arbitrary finite time, and have demonstrated the existence of a unique solution within a Sobolev space regularity class in the case where the electric field is increasing. The model closely follows [9], with a modification of an endpoint boundary condition for carrier concentration. Our approach is based upon Rothe's method, which is very close to the design of numerical methods. In fact, the fixed point map employed at each time step is a decoupling map, and is well suited to approximation.
It is of interest how much of the rich structure of dynamical systems carries over to the case of the finite channel. For example, the reader can refer to the phase plane heteroclinic orbits of [8]. A significant question is how much of this theory remains for general boundary conditions. Analytical support for rectangular waves would represent progress in explaining the link between conformation change and gating.
Another question pertains to the exact form we have selected for the net charge ρ. We have made use of the following properties of this form:

- There is a sign reversal when the ion concentration crosses a benchmark value $\bar{p}$ from negative to positive.
- The function ρ is separately Lipschitz continuous in each of its arguments p, E.

Another open question relates to the number of ion species. This model uses exactly one, chosen to be a cation carrier. Clearly, if the model is to be further developed, multiple species, of differing parity, must be included. The final question relates to the extension of the results to the case when the electric field is decreasing, which is made possible by boundary/initial data specified in the range exceeding the benchmark parameter $\bar{p}$.

Appendices

A Analysis of the p-Equation

We collect here a few facts related to the existence of solutions of the boundary value problem for the discretized p-equation (7). We introduce the inner product,

$$(u,v) = \frac{1}{\alpha}\int_a^b [j(u,E)j(v,E) + \alpha c^2 uv] e^{\phi/U_{T_0}}\, dx, \tag{18}$$

where ϕ is a fixed smooth function, c^2 is a positive constant, and

$$\alpha = e^2 D.$$

Lemma A.1. *The norm defined by the inner product* (18) *is equivalent to the usual* H^1 *norm.*

Proof. It is clear that $H^1(a,b)$ is a real inner product space with respect to (18). By the open mapping theorem, it suffices to show:

1. H^1 is complete in the associated norm.
2. The inequality,
$$\|u\| \leq C\|u\|_{H^1},$$
holds for some constant $C = C(\phi, c^2)$.

The first step uses the completeness of L^2 and H^1. If f_j is a Cauchy sequence, one uses the Slotboom transformation to write, $f_j = e^{-\phi/U_{T_0}} w_j$, and

$$\|f_j - f_k\|^2 = D\int_a^b \left|\frac{d(w_j - w_k)}{dx}\right|^2 e^{-\phi/U_{T_0}}\, dx + c^2 \int_a^b |w_j - w_k|^2 e^{-\phi/U_{T_0}}\, dx.$$

This identity establishes that $\{w_j\}$ is a Cauchy sequence in the Hilbert space $H^1(a,b)$, with weighted inner product/norm. We may take the limit as $k \to \infty$ on the right hand side, to obtain a limit function w in this weighted H^1 space. It follows that $f = e^{-\phi/U_{T_0}} w$ is the left hand side limit. This proves the completeness. The second step is a direct estimate. We may choose

$$C^2 = \frac{\lambda}{\alpha}\left[2e^2 D^2 + 2e^2\mu^2\gamma^2 + \alpha c^2\right],$$

where

$$\lambda = e^{\phi_{\max}/U_{T_0}},\ \gamma = \max|\phi'|.$$

□

Theorem A.1. *With* $(\cdot\,,\cdot), \|\cdot\|$ *defined above, the quadratic minimization problem,*

$$\min\{\|u\|^2 - 2(u,f) : u \in U\},$$

where U *is the flat in* H^1 *consisting of functions* u *satisfying*

$$u(a) = p_a(t_k),\ u(b) = p_b(t_k),$$

has a unique minimizer u_0*. If* $f = c^2 p_{k-1}$*, where* $c^2 = \frac{1}{\Delta t}$*, then this minimizer satisfies (11) if we identify* u_0 *with* Pp*:*

$$\frac{1}{\alpha}\int_a^b j(Pp,E)j(\psi,E)e^{\phi/U_{T_0}}\, dx + \int_a^b \frac{Pp - p_{k-1}}{\Delta t}\psi e^{\phi/U_{T_0}}\, dx = 0. \tag{19}$$

Here, $\psi \in H_0^1(a,b)$*.*

Proof. If we select an element $v_0 \in H^1$ which is the Riesz representer of the continuous linear functional, (u, f), then the minimization problem becomes,

$$\min\{\|u - v_0\|^2 - \|v_0\|^2\},$$

over U. Geometrically, this amounts to determining the unique element in U which is closest to v_0. Since U is a closed flat in the Hilbert space H^1, this can be done. The characterization (19) is the Hilbert space characterization that u_0 is closest to v_0. □

B Analysis of the IVP

The following global existence/uniqueness theorem is required for the paper, particularly regarding the Gauss equation for E. We were not able to identify this in the literature, in the form we need. We provide the relatively short proof. The corollary to follow is also necessary.

Theorem B.1. *Let $f : [a, b] \times R^m \to R^m$ be a continuous vector function, which is uniformly Lipschitz in its second argument and uniformly bounded in its first argument. Specifically, we assume:*

$$\|f(\cdot\,, r) - f(\cdot\,, s)\|_{R^m} \leq C\|r - s\|_{R^m},\ \forall r, s \in R^m, C > 0;$$

$$\|f(x, u_a)\|_{R^m} \leq C_0,\ \forall x \in [a, b].$$

Then the initial value problem,

$$u' = f(\cdot\,, u),\ u(a) = u_a,$$

has a unique C^1 solution defined on $[a, b]$. The bound for u depends only upon C, C_0, a, b, u_a.

Proof. We define the mapping,

$$Ku(x) = u_a + \int_a^x f(s, u(s))\, ds,$$

of $Z = C[a, b]$ into itself. Here, we denote by $C[a, b]$ the normed vector space of continuous vector-valued functions v, where $\|v\|_{C[a,b]} = \max\{\|v(s)\|_{R^m} : a \leq s \leq b\}$. We observe that K is continuous and compact, i. e., K maps bounded sequences in Z into sequences which allow extraction of convergent subsequences. The compactness is a direct consequence of the Arzela-Ascoli theorem [20, p. 179], which asserts that every equicontinuous, uniformly bounded sequence on a compact set has a uniformly convergent subsequence.

By a version of the Leray-Schauder theorem [10] the mapping K has a fixed point u, for which $Ku = u$, provided there is a constant M such that every homotopy fixed point v, satisfying $v = tKv$, $0 \leq t \leq 1$, lies in the open ball of radius M. Thus, suppose that

$$v = tKv,\ 0 \leq t \leq 1.$$

Upon differentiation, we have

$$v'(s) = tf(s, v(s)),\ a \leq s \leq b.$$

If we take the dot product of both sides with $v(s) - v(a)$, we obtain the equation,

$$\frac{1}{2}\frac{d}{ds}\|v(s) - v(a)\|^2_{R^m} = t[f(s, v(s)) - f(s, v(a))]\cdot (v(s) - v(a)) +$$

$$t[f(s, v(a)) - f(s, u_a)]\cdot (v(s) - v(a)) + t[f(s, u_a) - f(a, u_a)]\cdot (v(s) - v(a)) +$$
$$tf(a, u_a)\cdot (v(s) - v(a)).$$

Note that $v(a) = tu_a$. We now use the Lipschitz property of f. Upon setting

$$h(s) = \frac{1}{2}\|v(s) - v(a)\|^2_{R^m},$$

we obtain, for positive constants A and B,

$$h'(s) \leq Ah(s) + B,\ h(a) = 0,$$

after an appropriate use of $cd \leq \frac{1}{2}(c^2 + d^2)$. Direct integration now gives

$$h(s) \leq \frac{B}{A}(e^{A(s-a)} - 1) \leq \frac{B}{A}(e^{A(b-a)} - 1).$$

This estimate allows the direct construction of M. In particular, a fixed point exists, which represents a solution of the initial-value problem with the stated bounds. To prove uniqueness, suppose that u, v are solutions of the IVP, and set

$$g(s) = \frac{1}{2}\|v(s) - u(s)\|^2_{R^m}.$$

One shows directly that

$$g'(s) \leq Cg(s),\ a \leq s \leq b.$$

This implies that g is constant, hence the zero function, since $g(a) = 0$. It follows that the solution is unique. □

Corollary B.1. *Suppose that $f(\cdot, u)$ is given as in the theorem, with the additional property that f is also Lipschitz continuous with respect to its first argument. More precisely, if the second argument is confined to a fixed element in a bounded set in $\mathbf{R}^m$, the resulting function is globally Lipschitz continuous with respect to the first argument. Suppose that $q \in C[a, b]$ is fixed and and $\|p - q\|_{C[a,b]} \leq \delta$. Suppose further that u_q and u_p are solutions of the initial value problem of the theorem, corresponding to $f_q(x, u) = f(q(x), u), f_p(x, u) = f(p(x), u)$, resp. Then the continuous dependence estimate holds:*

$$\|u_p - u_q\|_{C[a,b]} \leq C\delta.$$

Here, C depends upon q, but not upon p.

Proof. The proof contains elements of the proof of the preceding theorem. Define, for u_q and u_p as stated in the hypotheses,

$$g(s) = \frac{1}{2}\|u_q(s) - u_p(s)\|^2_{R^m}.$$

Note that $g(a) = 0$. One shows directly that

$$g'(s) \leq (2C_q + C_1)g(s) + \frac{C_1}{2}|q(s) - p(s)|^2, \qquad (20)$$

where C_q is the Lipschitz constant of f_q, and C_1 is the local Lipschitz constant of f in its first argument, where the second argument lies in a ball of fixed radius, independent of δ. Use of the upper bound of δ^2 for $|q(s) - p(s)|^2$ implies the result, by integration. □

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