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A PSEUDO-STEADY STATE APPROXIMATION FOR STOCHASTIC CHEMICAL KINETICS

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1. **Introduction.** Many quantitative investigations of biochemical reactions occurring in the cell are carried out "in vitro" using the pooled extracts from very many cells. Mathematically the chemical species are treated as continuous variables, i.e., concentrations, obeying ordinary differential equations. However, serious problems might arise in extrapolating this approach, and thus its conclusions, down to intracellular levels. For example, assuming the volume of an E. coli cell to be 10^{-15} liters, a 10^{-8} Molar solution represents about 6 molecules per cell. For this reason, and since chemical reactions are inherently probabilistic at the molecular level, it would seem more appropriate to use Markov chains to model the kinetics of intracellular substances.

Unfortunately, chemical reaction models are often non-linear, and non-linear stochastic models are even less tractable than non-linear deterministic models. Thus it is important to find good approximations to the behaviour of these stochastic models. One such approximation is a "law of large numbers" type result by Kurtz [8] which shows the relationship between stochastic and deterministic models.

A frequently used approximation for systems of non-linear rate equations arising in deterministic biochemical models is the so-called pseudo-steady-state hypothesis (see Rubinow [10]). This procedure was shown to be valid under "excess substrate" conditions by Heineken et al. [5]. In the simplest situation of this kind the use of this procedure leads to the well-known Michaelis-Menten equation.

Stochastic models for enzyme reactions have been studied before. For a review see Goel and Richter-Dyn [3]. Even in the simplest case, however, the equations arising are intractable. A natural question to ask, then, is whether this model simplifies under "excess substrate" conditions.

These conditions are satisfied by the photoreactivation system for pyrimidine dimers in E. coli. It has been shown that the total number of these photoreactivating enzymes in a given cell is quite small, probably 10–20 in normal cells, (see Harm, et al. [4]) whereas in a typical experiment there are hundreds or thousands of pyrimidine dimers, i.e., "substrate", per cell. In this case, indirect evidence indicates that the photo-

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reactivation of dimers follows Michaelis-Menten kinetics.

Thus it is possible that the Michaelis-Menten equation might be a good approximation for stochastic as well as deterministic enzyme kinetics under "excess substrate" conditions. In § 3 it is shown that this is true, and in fact that all such pseudo-steady-state approximations for biochemical reaction networks are, with high probability, good approximations under these same conditions. Also, a central limit theorem is derived, giving the fluctuations of the stochastic model about this approximation in terms of a Wiener integral whose covariance kernel is easily found from the infinitesimal parameters of the model.

2. **The Theorem.** A family $\{(X_t^n, Y_t^n)\}$ of bivariate Markov chains taking values in $Z^J \times S$, S a finite subset of Z^K (from now on X_t^n will be referred to as "large variables" and Y_t^n as "small variables") will be called density dependent in the large variables if there are continuous functions $q(x, \alpha; \ell, \beta)$; $x \in R^J$; $\ell \in Z^J$; $\alpha, \beta \in S$, so that the infinitesimal parameters for the (X_t^n, Y_t^n) process are given by:

$$\text{intensity of jump } (k, \alpha) \to (k + \ell, \beta) = n\, q\left(\frac{k}{n}, \alpha; \ell, \beta\right)$$

and so that

$$q(x, \alpha; 0, \alpha) = \sum_{(\ell,\beta)\neq(0,\alpha)} q(x, \alpha; \ell, \beta).$$

Now for $1 \leqq i \leqq J$, let $F_i(x, \alpha; \beta) = \sum_\ell \ell_i q(x, \alpha; \ell, \beta)$ and $F_i(x, \alpha) = \sum_{\beta \in S} F_i(x, \alpha; \beta)$. For $1 \leqq i, j \leqq J$, let $\sigma_{ij}^2(x, \alpha; \beta) = \sum_\ell \ell_i \ell_j q(x, \alpha; \ell, \beta)$ and then $\sigma_{ij}^2(x, \alpha) = \sum_{\beta \in S} \sigma_{ij}^2(x, \alpha; \beta)$. For $\alpha, \beta \in S$ let $Q(x, \alpha, \beta) = \sum_\ell q(x, \alpha; \ell, \beta)$. For fixed x, $Q(x, \cdot, \cdot)$ can be thought of as the infinitesmal matrix of a finite state Markov chain $Y(x, t)$, the "boundary layer" process. Assume that $Y(x, t)$ is irreducible. Then it is exponentially ergodic with stationary distribution $\pi(x, \cdot)$. Define $F_i(x) = \sum_{\alpha \in S} F_i(x, \alpha)\pi(x, \alpha)$ and $\sigma_{ij}^2(x) = \sum_{\alpha \in S} \sigma_{ij}^2(x, \alpha)\pi(x, \alpha)$.

Now since $\sum_\alpha (F_i(x, \alpha) - F_i(x))\pi(x, \alpha) = 0$ we can define

$$\eta(x, \alpha) = \int_0^\infty E^\alpha[F(x, Y(x, t)) - F(x)]\, dt,$$

and we have

$$\begin{cases} \sum_{\alpha \in S} \pi(x; \alpha)\eta_i(x, \alpha) = 0, \\ \sum_{\beta \in S} Q(x; \alpha, \beta)\eta_i(x, \beta) = F_i(x) - F_i(x, \alpha). \end{cases}$$

Define

$$\overline{\Gamma}_{ij}(x) = \frac{1}{2}\,\sigma_{ij}^2(x) + \sum_{\alpha\in S} \pi(x;\,\alpha)\,\eta_j(x,\,\alpha)(F_i(x,\,\alpha) - F_i(x)) + \sum_{\alpha\beta\in S} \pi(x;\,\alpha)F_i(x,\,\alpha;\,\beta)(\eta_j(x,\,\beta) - \eta_j(x,\,\alpha)).$$

Set $\Gamma(x) = \overline{\Gamma}(x) + (\overline{\Gamma}(x))^t$. By its definition $\Gamma(x)$ is symmetric, and it will be seen to be non-negative definite (it is *not* in general positive definite).

Now assume there is an open set $\Omega \subset \mathbf{R}^J$ for which the following conditions hold:

(C1) $\sigma_{ij}^2(x,\,\alpha;\,\beta)$ and $Q(x,\,\alpha;\,\beta)$ are $C^{(2)}$ functions of x in Ω and $F_i(x,\,\alpha;\,\beta)$ are $C^{(3)}$ functions of x in Ω.
(C2) $Y(x,\,t)$ is uniformly exponentially ergodic in $x \in \Omega$.
(C3) $\sup_{x\in\Omega} \sum_{|\ell|>d} |\ell_i\ell_j| q(x,\,\alpha;\,\ell,\,\beta) \to 0$ as $d \to \infty$.
(C4) $X(t,\,x_0)$ solves the differential equation

$$X(0,\,x_0) = x_0,$$

$$\frac{\partial X}{\partial t}(t,\,x_0) = F(X(t,\,x_0)) \text{ on } 0 \leqq t \leqq T, \text{ some } T > 0,\, T < \infty,$$

$$\{X(t,\,x_0) : 0 \leqq t \leqq T\} \subseteq \Omega.$$

Now suppose further that

$$Y_0^n \xrightarrow{D} \gamma,$$

$$\sqrt{n}\left(\frac{X_0^n}{n} - x_0\right) \xrightarrow{D} \xi,$$

where ξ is a finite valued random variable. Then:

THEOREM I. $\sqrt{n}\,((X_t^n/n) - X(t,\,x_0)) \to W_t$ *weakly in* $D_{\mathbf{R}^J}[0,\,T]$ *where* W_t *is a diffusion process satisfying the stochastic differential equation.*

$$W_0 = \xi,$$

$$dW_t = J(X(t,\,x_0)) \cdot W_t dt + C(X(t,\,x_0))\, dB_t.$$

Here J *and* C *are matrices given by* $J_{ij}(x) = \partial F_i/\partial x_j(x)$ *and* $C(x)$ *is a symmetric square root of* $\Gamma(x)$, *and* B_t *is a* J*-dimensional Brownian motion independent of* ξ.

Furthermore, $P(Y_t^n = \beta) \to \pi(X_t,\,\beta)$ *uniformly for* $t_0 \leqq t \leqq T$ *for any* $t_0 > 0$.

COROLLARY. *For any* $\epsilon > 0$, $P(\sup_{0 \leq s \leq t} |(X_s^n/n) - X(s, x_0)| > \epsilon) \to 0$ *that is, with high probability the sample paths of* X_t^n/n *lie close to the limit process* $X(t, x_0)$.

REMARK. The equation for W_t may be solved explicitly, yielding

$$W_t = \Phi(t)\xi + \int_0^t \Phi(t)\Phi^{-1}(s)\, C(X_s)\, dB_s,$$

where $\Phi(t)$ is the fundamental matrix for the equation

$$dW_i = \sum_j \frac{\partial F_i}{\partial x_j} (X(t, x_0))\, W_j\, dt$$

which is the equation of variations for initial value perturbations in the solution $X(t, x)$. Thus W_t is the sum of two terms, the first of which is the same as that gotten by analyzing the effect of small random perturbations of the initial value of the deterministic limit, and the second of which is a Gaussian process with independent increments, whose covariance matrix is easily computed in terms of Φ and Γ. The proof of Theorem I will be given in § 4 below after some preliminary results.

3. **Application to Enzyme Systems.** The result in § 2 is, as it stands, too difficult to apply easily, since it involves computing various functionals of the "boundary layer process". However, in the study of enzyme systems, substantial simplifications result from two assumptions which are valid for all kinetic schemes of which the author is aware. Throughout this section assume $S \subset \{(z_1, \cdots, z_k), z_i \in Z, z_i \geqq 0\}$.

ASSUMPTION I. $q(x, y; \ell, y + \gamma) = r(x; \ell, \gamma) + \sum_j y_j s_j(x; \ell, \gamma)$.

Now define

$$A_i(x) = \sum_\ell \sum_\gamma \ell_i\, r(x; \ell, \gamma) \qquad 1 \leqq i \leqq J,$$

$$B_{ij}(x) = \sum_\ell \sum_\gamma \ell_i s_j(x; \ell, \gamma) \qquad \text{for } 1 \leqq i \leqq J,\ 1 \leqq j \leqq K,$$

$$C_i(x) = \sum_\ell \sum_\gamma \gamma_i\, r(x; \ell, \gamma) \qquad 1 \leqq i \leqq K,$$

$$D_{ij}(x) = \sum_\ell \sum_\gamma \gamma_i\, s_j(x; \ell, \gamma) \qquad 1 \leqq i, j \leqq K,$$

$$G_i(x, y) = \sum_\ell \sum_\gamma \gamma_i q(x, y; \ell, y + \gamma) \qquad 1 \leqq i \leqq K$$

and notice that

$$F_i(x) = A_i(x) + \sum_j B_{ij}(x)y_j$$

and

$$G_i(x) = C_i(x) + \sum_j D_{ij}(x)y_j.$$

ASSUMPTION II. All eigenvalues of $D(x) = (D_{ij}(x))$ have negative real parts.

One can easily check that under Assumption I $E^y Y(x, t) = m(x, y, t)$ satisfies the differential equation $d/dt\ m(x, y, t) = G(x, m(x, y, t))$ which is the boundary layer equation in the Tikhonov theorem. Since $Y(x, t)$ is ergodic by assumption, this equation is asymptotically stable for all initial mean vectors generated by S and thus Assumption II nearly follows from Assumption I.

However, under Assumptions I and II the results of this section (and § 2) extend to the case where S is denumerably infinite.

Let $y = \phi(x)$ be the unique "stable" root of $G(x, y) = 0$. To state Theorem II we need to define $\Lambda(x, y)$.

$$\Lambda_{ij}(x, y) = \sigma_{ij}^2(x, y) = \sum_{\ell} \sum_{\gamma} \ell_i \ell_j q(x, y; \ell, y + \gamma) \qquad \text{for } 1 \leqq i \leqq J,\ 1 \leqq j \leqq J.$$

$$\Lambda_{i,J+k}(x, y) = \Lambda_{J+k,i}(x, y) = \sum_{\ell} \sum_{\gamma} \ell_i \gamma_k q(x, y, \ell, y + \gamma) \qquad \text{for } 1 \leqq i \leqq J,\ 1 \leqq k \leqq K.$$

$$\Lambda_{J+j,J+k}(x, y) = \sum_{\ell} \sum_{\gamma} \gamma_j \gamma_k q(x, y, \ell, y + \gamma) \qquad \text{for } 1 \leqq j \leqq K,\ 1 \leqq k \leqq K.$$

Let $H(x) = -B(x)D^{-1}(x)$. Then we have

THEOREM II. $F(x) = F(x, \phi(x))$ and

$$\Gamma(x) = (I, H(x))\Lambda(x, \phi(x))(I, H(x))^t$$

where I is the $J \times J$ identity matrix and $(I, H(x))$ is the $(J + K) \times (J + K)$ matrix

$$\begin{pmatrix} I & H(x) \\ 0 & 0 \end{pmatrix}.$$

PROOF. For the first identity we need only show $F_i(x, \phi(x)) = \sum_{y \in S} \pi(x, y)F_i(x, y)$. But

$$F_i(x, y) = A_i(x) + \sum_j B_{ij}(x)y_j$$

and

$$\sum_{j \in S} \pi(x, y)Y_j = m_j(x, y_0, \infty) = \phi_j(x)$$

so

$$\sum_{y \in S} \pi(x, y)F_i(x, y) = A_i(x) + \sum_j B_{ij}(x)\phi_j(x) = F(x, \phi(x)).$$

The same argument shows that

$$\sum_{y \in S} \pi(x, y)\, \Lambda_{ij}(x, y) = \Lambda_{ij}(x, \phi(x))$$

for $1 \leqq i \leqq K + J$, $1 \leqq j \leqq K + J$ and this takes care of the first term in $\Gamma(x)$.

Next we show that

$$\sum_{y \in S} \sum_{\gamma} \pi(x, y)F_i(x, y; y + \gamma)(\eta_j(x, y + \gamma) - \eta_j(x, y))$$
$$= - \sum_k (\Lambda_{i,J+k}(x, \phi(x))) \cdot (B(x)\, D^{-1}(x))^t_{kj}.$$

To see this, note that $F_i(x, y; y + \gamma) = \sum_\ell \ell_i q(x, y; \ell, y + \gamma)$ and since $F(x, y) - F(x) = B(x)(y - \phi(x))$ we have

$$\eta(x, y) = \int_0^\infty E^y B(x)(Y(x, t) - \phi(x)).$$

It is easy to check that $E^y(Y(x, t) - \phi(x)) = \exp(D(x)t)(y - \phi(x))$ and so $\eta(x, y) = -B(x)D^{-1}(x)(y - \phi(x))$. Thus $\eta(x, y + \gamma) - \eta(x, y) = -B(x)D^{-1}(x)\gamma$. So

$$\sum_{y \in S} \sum_{\gamma} \pi(x, y)F_i(x, y; y + \gamma)(\eta_j(x, y + \gamma) - \eta_j(x, y))$$
$$= - \sum_{y \in S} \sum_{\gamma} \sum_{\ell} \sum_{k} \pi(x, y)\ell_i q(x, y; \ell, y + \gamma)(B(x)D^{-1}(x))_{jk}\gamma_k$$
$$= - \sum_k \left(\sum_{y \in S} \pi(x, y)\Lambda_{i,J+k}(x, y) \right) (B(x)D^{-1}(x))^t_{kj}$$
$$= - \sum_k \Lambda_{i,J+k}(x, \phi(x))(B(x)D^{-1}(x))_{kj}.$$

Finally we show that

$$\sum_{y \in S} \pi(x, y)[\eta_i(x, y)(F_j(x, y) - F_j(x))$$
$$+ \eta_j(x, y)(F_i(x, y) - F_i(x))]$$
$$= \sum_m \sum_n (B(x)D^{-1}(x))_{im}$$
$$\cdot \Lambda_{J+m,J+n}(x, \phi(x))(B(x)D^{-1}(x))^t_{nj}.$$

Now

$$\sum_{y \in S} \pi(x, y)\eta_i(x, y)(F_j(x, y) - F_j(x))$$
$$= -(B(x)D^{-1}(x)V(x)B^t(x))_{ij}$$

where

$$V_{ij}(x) = \sum_{y \in S} \pi(x, y)(y_i - \phi_i(x))(y_j - \phi_j(x)).$$

Thus we have

$$\sum_{y \in S} \pi(x, y)[\eta_i(x, y)(F_j(x, y) - F_j(x))$$
$$+ \eta_j(x, y)(F_i(x, y) - F_i(x))]$$
$$= -(B(x)D^{-1}(x)V(x)B^t(x) + B(x)V(x)(B(x)D^{-1}(x))^t)_{ij}$$
$$= -(B(x)D^{-1}(x))[V(x)D^t(x) + D(x)V(x)](B(x)D^{-1}(x))^t)_{ij}.$$

Now let

$$V_{ij}(x, y_0, t) = E^{y_0}(Y_i(x, t)$$
$$- m_i(x, y_0, t))(Y_j(x, t) - m_j(x, y_0, t)).$$

It is easily checked that V satisfies the matrix differential equation

$$\frac{d}{dt} V_{ij}(x, y_0, t) = \Lambda_{J+i,J+j}(x, m(x, y_0, t))$$
$$+ (D(x)V(x, y_0, t) + V(x, y_0, t)D^t(x))_{ij}.$$

Letting $t \to \infty$ in this formula we get

$$-(D(x)V(x) + V(x)D^t(x)) = \Lambda_{J+i,J+j}(x, \phi(x))$$

and the proof of Theorem II is complete.

Now we apply Theorem II to the simple one-substrate and one-enzyme irreversible reaction scheme. The same methods should work on more complex schemes since under Assumptions I and II one comes up with the problem of solving the same linear algebraic equations encountered in the steady-state approximation to the deterministic model. This problem is discussed in Rubinow [10].

In the one-substrate, one-enzyme reaction scheme enzymes convert substrate into product in two steps: (1) the formation of an intermediate complex and (2) the dissociation of this complex, either into free enzyme plus product, or into free enzyme plus substrate. Schematically:

$$E + S \rightleftarrows E \cdot S \rightarrow E + P.$$

Note that the number of free enzymes plus the number of complexes remains constant throughout. Suppose that initially all enzymes are free and there is some large number of substrate molecules homogeneously distributed with respect to the different enzyme molecules.

Let X_t be the number of substrate molecules left at time t, and Y_t the number of free enzymes at time t. The number of complexes present at time t is then $Y_0 - Y_t$. In time $(t, t + h)$ the following elementary events can occur:

(a) one free enzyme and one substrate molecule can collide to form a complex with probability $\alpha X_t Y_t h + o(h)$,
(b) one complex can dissociate into free enzyme plus substrate with probability $\beta(Y_0 - Y_t)h + o(h)$,
(c) one complex can dissociate into free enzyme plus product with probability $\gamma\,(Y_0 - Y_t)h + o(h)$.

This setup leads to an intractable system of differential equations for the joint probabilities. However, intuitively, if the number of substrate molecules present greatly exceeds the total number of enzymes present, and the frequency of collisions is of the same order of magnitude as the frequency of dissociations, the number of enzymes present in complexed form can come to a statistical equilibrium with those present as free enzymes in a time interval during which the percentage change of substrate molecules is very little. Since the ratio of substrate to initial substrate is slowly changing, however, this is only a pseudo-steady-state.

We are requiring that the collision intensity be of the same order of magnitude as the dissociation intensity, i.e.,

$$\alpha X_t Y_t \approx (\beta + \gamma)(Y_0 - Y_t).$$

Since Y_t is of the same order of magnitude as $Y_o - Y_t$, we get that $(\beta + \gamma)/\alpha$ should be of the same order of magnitude as X_t. These considerations lead to a sequence of models $(X_t^n,\ Y_t^n)$ where $X_o^n \sim nX_0$,

$Y_0^n = Y_0$ and having the following transitions and associated intensities:

$$(x, y) \to (x-1, y-1) \text{ with intensity } n\,\alpha(x/n)y,$$
$$(x, y) \to (x+1, y+1) \text{ with intensity } n\,\beta(Y_0 - y),$$
$$(x, y) \to (x, y+1) \text{ with intensity } n\,\gamma(Y_0 - y).$$

This sequence easily satisfies (C1)–(C4) of § 2 with $\Omega = \{x > \alpha\}$, any $\alpha > 0$. Upon calculating $Q(x; y_1, y_2)$ and solving for $\pi(x, y)$ one sees that the pseudo-stationary distribution π is binomial with parameters Y_0 and $K/(K + x)$ where $K = (\beta + \gamma)/\alpha$ is the Michaelis-Menten constant. Since $F(x, y) = -\alpha xy + \beta(Y_0 - y)$ one sees that the degenerate system is given by:

$$\frac{d}{dt} X_t = -\frac{\gamma Y_0 X_t}{K + X_t}, \quad Y_t \sim \text{Bin}\left(Y_0, \frac{K}{K + X_t}\right).$$

In this case one can say something about the diffusion approximation. Since we have a one-dimensional situation, we may write

$$W_t = \exp \int_0^t J(X(u, x_0))\,du)$$
$$\cdot \left\{\xi + \int_0^t \exp - \int_0^s J(X(u, x_0)(du)\, C(X(s, x_0))\, dB_s\right\}.$$

This formula can be simplified somewhat by noting that X_t is monotone in t, so one can "change variables" in the integral $\int_0^t J(X(u, x_0))\,du$ by $du = (du/dx)\,dx = (F(x))^{-1}\,dx$, and use $J(x) = F'(x)$ to get

$$\int_0^t J(X(u, x_0))\,du = \int_{x_0}^{X(t, x_0)} \frac{F'(x)}{F(x)}\,dx$$
$$= \log\left(\frac{F(X(t, x_0))}{F(x_0)}\right)$$

so

$$W_t = \frac{F(X(t, x_0))}{F(x_0)}$$
$$\cdot \left\{\xi + \int_0^t \frac{F(x_0)}{F(X(s, x_0))}\, C(X(s, x_0))\, dB_s\right\}.$$

Thus

$$\operatorname{Var} W_t = \frac{F^2(X(t, x_0))}{F^2(x_0)}$$
$$\cdot \operatorname{Var} \xi + \int_0^t \frac{F^2(X(t, x_0))}{F^2(X(s, x_0))} \Gamma(X(s, x_0))\, ds.$$

Now using Theorem II we compute

$$\Gamma(x) = \frac{Y_0 x}{(K + x)^3} \left((K + x)^2 - 2 \frac{\gamma x}{\alpha} \right)$$

and changing variables again we get

$$\operatorname{Var} W_t = \frac{F^2(X(t, x_0))}{F^2(x_0)} \operatorname{Var} \xi$$
$$+ \frac{F^2(X(t, x_0))}{\gamma^2 Y_0^2} \Bigg[x_0 - X(t, x_0)$$
$$+ 2\beta/\alpha \ln \left(\frac{x_0}{X(t, x_0)} \right) + \left(\frac{x_0 - X(t, x_0)}{x_0 X(t, x_0)} \right) \Bigg] .$$

4. **Proof of Theorem I.** We first note that if condition (C4) holds, we may without loss of generality assume (C1)–(C3) hold for all x in $\mathbf{R}^J$. To see this, note that for some $\epsilon > 0$ the set $G_\epsilon = \{y \in \mathbf{R}^J : \inf_{0 \leqq t \leqq T} |y - x(t, x_0)| \leqq \epsilon\}$ is contained in Ω. Now G_ϵ is compact and Ω open so there is a C^∞ function $\psi(x)$ with bounded derivatives satisfying $0 \leqq \psi(x) \leqq 1$ $\psi(x) \equiv 1$ on G_ϵ and $\psi(x) \equiv 0$ outside of Ω.

Define new processes $(\overline{X}_t^n, \overline{Y}_t^n)$ having infinitesimal parameters $\bar{q}(x, \alpha; \ell, \beta) = \psi(x) q(x, \alpha; \ell, \beta)$ for $\ell \neq 0$, $\bar{q}(x, \alpha; 0, \beta) = \psi(x) q(x, \alpha; 0, \beta) + (1 - \psi(x))\overline{Q}(\alpha, \beta)$ where $\overline{Q}$ is a fixed ergodic intensity matrix on S. Then (C1)–(C4) hold for $(\overline{X}_t^n, \overline{Y}_t^n)$ for all x in $\mathbf{R}^J$ and since $(\overline{X}_t^n, \overline{Y}_t^n)$ agrees with (X_t^n, Y_t^n) up to the first exit for G_ϵ (for either one), it suffices to prove Theorem I for $(\overline{X}_t^n, \overline{Y}_t^n)$.

Lemma 1. $\Gamma(x)$ is non-negative definite.

Proof. Fix x and consider the chain (X_t, Y_t) with infinitesimal parameters given by

$$\text{intensity of jump } (k, \alpha) \rightarrow (k + \ell, \beta) = q(x, \alpha, \ell, \beta).$$

More general processes of this kind are studied in Ezhov and Skorokhod [1].

Define $P_u(\alpha, \beta) = P(Y_u = \beta \mid Y_0 = \alpha)$. Now for fixed t and n let $\delta = t/n$. Assume $Y_o \equiv 0$, and write

$$X_t - tF(x) = \sum_{m=0}^{n-1} (\Delta X(m) - \delta F(x))$$

where

$$\Delta X(m) = X_{(m+1)\delta} - X_{m\delta}.$$

Similarly write

$$\begin{aligned}(X_{ti} &- tF_i(x))(X_{tj} - tF_j(x)) \\ &= \sum_{m=0}^{n-1} (\Delta X_i(m) - F_i(x))(\Delta X_j(m) - F_j(x)) \\ &+ \sum_{m=0}^{n-2} (\Delta X_i(m) - \delta F_i(x)) \sum_{p=m+1}^{n-1} (\Delta X_j(p) - \delta F_j(x)) \\ &+ \sum_{m=0}^{n-2} (\Delta X_j(m) - \delta F_j(x)) \sum_{p=m+1}^{n-1} (\Delta X_i(p) - \delta F_i(x)) \\ &= S_1(n, t) + S_2(n, t) + S_3(n, t).\end{aligned}$$

Let π be the initial distribution $X \equiv 0$, $Y_0 \sim \pi(x)$.

It is easily seen that $\lim_{n\to\infty} E^{\pi} S_1(n, t) = t\sigma_{ij}^2(x)$. By conditioning on $\sigma\{X_s, Y_s, s \leqq (m+1)\delta\}$ for $0 \leqq m \leqq n-2$ we see that

$$\begin{aligned}\lim_{n\to\infty} & E^{\pi} S_2(n, t) \\ &= \int_0^t \sum_{\alpha,\beta,\gamma} \pi(x, \alpha) F_i(x, \alpha, \beta) \int_0^{t-s} P_u(\beta, \gamma)(F_j(x, \gamma) \\ &\quad - F_j(x))\, du\, ds \\ &\quad - \int_0^t \sum_{\alpha,\gamma} \pi(x, \alpha) F_i(x) \int_0^{t-s} P_u(\alpha, \gamma)(F_j(x, \gamma) \\ &\quad - F_j(x))\, du\, ds\end{aligned}$$

and therefore, examining $S_3(n, t)$ in the same way, we have

$$\lim_{t\to\infty} \frac{1}{t} E^{\pi}(X_{ti} - tF_i(x))(X_{tj} - tF_j(x)) = \Gamma_{ij}(x).$$

Therefore $\Gamma(x)$ is the limit of non-negative definite matrices and hence is non-negative definite. The principal tool needed in the proof of Theorem I is the following proposition which is an immediate corollary of Theorem 4.29 in Kurtz [9].

PROPOSITION. *Let Z_t be a Markov Process on $\mathbf{R}^m$ with semigroup T_t on $C_0(\mathbf{R}^m)$ and generator A and suppose Z_t has paths in $D_{\mathbf{R}^m}(0, \infty)$. Let Z_t^n be a sequence of Markov Processes on $\mathbf{R}^m \times S$, $S \subset \mathbf{R}^k$, with semigroups T_t^n and waek generators $\bar{A}_n$. Let $\theta : \mathbf{R}^m \times S \to \mathbf{R}^m$ be the natural projection, and for $f \in C_0(\mathbf{R}^m)$ let $\eta f = f \circ \theta$. Suppose $\theta \circ Z_t^n$ has paths in $D_{\mathbf{R}^m}(0, \infty)$. Now suppose*

$$\lim_{n\to\infty} E(\eta f(Z_0^n)) = Ef(Z_0)$$

and

$$(*) \qquad \lim_{n\to\infty} \sup_{y\in\mathbf{R}^m\times S} |T_t^n \eta f(y) - \eta T_t f(y)| = 0$$

for all $t \geqq 0$ and all $f \in C_0(\mathbf{R}^m)$. Then $\{\theta \circ Z_t^n\}$ converges weakly to Z_t. Let D be the set of $f \in \mathscr{D}(A)$ for which there exist $f_n \in \mathscr{D}(\bar{A}_n)$ with

$$\lim_{n\to\infty} \sup_{y\in\mathbf{R}^m\times S} |f_n(y) - f(\theta y)| = 0,$$

$$\lim_{n\to\infty} \sup_{y\in\mathbf{R}^m\times S} |\bar{A}^n f_n(y) - Af(\theta y)| = 0.$$

Then if D is a core for A, $(*)$ holds.

To use this result define

$$Z_t = (X_t, W_t),\ Z_t^n = \left(\frac{X_t^n}{n},\quad Y_t^n,\ \sqrt{n}\left(\frac{X_t^n}{n} - X_t\right)\right)$$

and

$$\theta(x, \alpha, w) = (x, w).$$

All conditions needed hold, except that it is difficult to find a core for the generator of Z_t. Were $\Gamma(x)$ uniformly positive definite, $C(x)$ would be twice continuously differentiable with bounded derivatives (Lemma 1.1.1 in Chapter 6 of Friedman [2]), and we could find a core to which we could apply the condition in the proposition. (See Lemmas 5 and 6). So we reduce to this case. The idea is to change X_t by adding "noise".

Let $X_t^{n,\epsilon}$ satisfy the equation

$$X_t^{n,\epsilon}(x_0) = x_0 + \int_0^t F(X_s^{n,\epsilon}(x_0))\, ds + \frac{\epsilon}{\sqrt{n}} \int_0^t dB_s,$$

where B_t is J-dimensional Brownian motion independent of Z_t^n, Z_t for all n, for all $t \geqq 0$. Noting that F has bounded first derivatives we have by Gronwall's inequality

$$E|X_t^{n,\epsilon}(x_0) - X_t(x_0)| \leqq \frac{\epsilon}{\sqrt{n}} A e^{Bt}$$

for some A and B and all x_0, $0 \leqq t \leqq T$.

Now define

$$Z_t^{n,\epsilon} = \left(\frac{x_t^n}{n}, \quad Y_t^n, \sqrt{n} \left(\frac{X_t^n}{n} - X_t^{n,\epsilon} \right)\right)$$

and denote its semi-group by $T_t^{n,\epsilon}$. To compare $T_t^{n,\epsilon}$ with T_t^n we first make some definitions. Let

$$\overline{Z}_t^n = \left(\frac{X_t^n}{n}, Y_t^n, X_t \right) \text{ and } \overline{Z}_t^{n,\epsilon} = \left(\frac{X_t^n}{n}, Y_t^n, X_t^{n,\epsilon} \right)$$

with respective semigroups S_t^n and $S_t^{n,\epsilon}$, and define $\theta_n : \mathbf{R}^{2J+K} \longrightarrow \mathbf{R}^{2J+K}$ by $\underline{\theta_n}(x, \alpha, v) = (x, \alpha, \sqrt{n}\,(x\,v))$. Then $Z_t^n = \theta_n \circ \overline{Z}_t^n$, $Z_t^{n,\epsilon} = \theta_n \circ \overline{Z}_t^{n,\epsilon}$ and so

$$T_t^n \phi(x, \alpha, w) = S_t^n(\phi \circ \theta_n)(\theta_n^{-1}(x, \alpha, w))$$

and

$$T_t^{n,\epsilon}\phi(x, \alpha, w) = S_t^{n,\epsilon}(\phi \circ \theta_n)(\theta_n^{-1}(x, \alpha, w)).$$

If P_t^n is the transition probability for the $(X_t^n/n, Y_t^n)$ process, we get

$$T_t^n \phi(x, \alpha, w) = \sum_{l,\beta} P_t^n(x, \alpha; x + \frac{l}{n}, \beta)\phi$$

$$\circ\theta_n\left(x + \frac{l}{n}, \beta, X_t \left(x - \frac{w}{\sqrt{n}}\right)\right)$$

and

$$T_t^{n,\epsilon}\phi(x, \alpha, w) = \sum_{l,\beta} P_t^n\left(x, \alpha, x + \frac{l}{n}, \beta\right)E\phi$$

$$\circ\theta_n\left(x + \frac{l}{n}, \beta, X_t^{n,\epsilon}\left(x - \frac{w}{\sqrt{n}}\right)\right)$$

for $\phi \in C_0(\mathbf{R}^{2J} \times S)$. We have

Lemma 2. *Let $\phi \in C_0(\mathbf{R}^{2J} \times S)$ be uniformly Lipschitz in x and w with constant k. Then*

$$\sup_{x,\alpha,w} |T_t^{n,\epsilon}\phi(x, \alpha, w) - T_t^n\phi(x, \alpha, w)| \leqq \epsilon A_1 K e^{B_1 t}.$$

PROOF.

$$|T_t^{n,\epsilon}\phi(x, \alpha, w) - T_t^n\phi(x, \alpha, w)|$$
$$\leqq \sum_{\ell,\beta} P_t^n\left(x, \alpha; x + \frac{\ell}{n}, \beta\right) E\left|\phi \circ \theta_n \left(x + \frac{\ell}{n}, \beta, X_t^{n,\epsilon}\left(x - \frac{w}{\sqrt{n}}\right)\right) - \phi \circ \theta_n \left(x + \frac{\ell}{n}, \beta, X_t\left(x - \frac{w}{\sqrt{n}}\right)\right)\right|$$
$$\leqq \sqrt{n} K \sum_{\ell,\beta} P_t^n\left(x, \alpha; x + \frac{\ell}{n}, \beta\right) E\left|X_t^{n,\epsilon}\left(x - \frac{w}{\sqrt{n}}\right) - X_t\left(x - \frac{w}{\sqrt{n}}\right)\right| \leqq \epsilon A k e^{Bt}.$$

Now let $\mathrm{I}^\epsilon(x) = \Gamma(x) + \epsilon^2 I$. Notice $\mathrm{I}^\epsilon(x)$ is uniformly positive definite and so it has a $C^{(2)}$ symmetric square root $C^\epsilon(x)$.

Let $Z_t^\epsilon = (X_t, W_t^\epsilon)$ satisfy the equations

$$X_t = x_0 + \int_0^t F(X_s)\, ds,$$

$$W_t^\epsilon = w_0 + \int_0^t J(X_s)\, W_s\, ds + \int_0^t C^\epsilon(X_s)\, dB_s^*$$

and recall

$$W_t = w_0 + \int_0^t E(X_s) \cdot W_s\, ds + \int_0^t C(X_s)\, dB_s^*,$$

so

$$W_t^\epsilon = \Phi(t) w_0 + \int_0^t \Phi(t)\Phi^{-1}(s) C^\epsilon(X_s)\, dB_s^*$$

and

$$W_t = \Phi(t) w_0 + \int_0^t \Phi(t)\Phi^{-1}(s) C(X_s)\, dB_s^*.$$

By arguing as in the proof of Freidlin's theorem (Theorem 6.1.2 in Friedman [2]), one sees that for a subsequence $\epsilon_m \downarrow 0$ $C^{\epsilon_m}(x) \longrightarrow C(x)$ uniformly on $\mathbf{R}^J$, and letting $B_m = \sup_x |C^{\epsilon_m}(x) - C(x)|$ we get $E|Z_t^{\epsilon_m} - Z_t| \leqq A_2 B_m$ for some A_2 and all x_0, w_0, $0 \leqq t \leqq T$. Thus we have

LEMMA 3. *If T_t^ϵ, T_t are the semigroups for Z_t^ϵ and Z_t respectively and $\phi \in C_0(\mathbf{R}^{2J})$ is Lipschitz in x, w with constant K then*

$$|T_t^{\epsilon_m} \phi(x, w) - T_t\phi(x, w)| \leqq A_2 K B_m.$$

Here $B_m \to 0$.

LEMMA 4. *Suppose for each $\epsilon > 0$ and $\phi \in C_0(\mathbf{R}^{2J})$ $T_t^{n,\epsilon}(\eta\phi)(x, \alpha, w) \to \eta(T_t^\epsilon\phi)(x, \alpha, w)$ uniformly in x, α, w and $0 \leqq t \leqq T$. Then $T_t^n(\eta\phi)(x, \alpha, w) \to \eta(T_t\phi)(x, \alpha, w)$ uniformly in x, α, w and $0 \leqq t \leqq T$.*

PROOF. Let ϕ_j be Lipschitz $C_0(\mathbf{R}^{2J})$ functions, with Lipschitz constants K_j converging to ϕ. Then

$$\begin{aligned}|T_t^n(\eta\phi)(x, \alpha, w) - \eta T_t\phi(x, \alpha, w)|& \\ \leqq 2\|\phi - \phi_j\| + \epsilon_m A_1 K_j e^{B_1 t} + A_2 K_j B_m& \\ + |T_t^{n,\epsilon_m}(\eta\phi)(x, \alpha, w) - \eta T_t^{\epsilon_m}\phi(x, \alpha, w).&\end{aligned}$$

So for any δ, first choose j so large that $\|\phi - \phi_j\| < \delta/8$, then m so large that $\epsilon_m A_1 K_j e^{B_1 T} \leqq \delta/4$ and $A_2 K_j B_m \leqq \delta/4$, and finally n so large that the last factor is less than $\delta/4$.

Now let $D = \{\phi \in C_0;\ \phi$ has two continuous derivatives which vanish at infinity, and $|w|^2\ |\partial\phi/\partial w_k| \leqq M$ for all x, w, k and some $M\}$ and let A^ϵ be the generator for Z_t^ϵ.

LEMMA 5. *D is a core for A^ϵ.*

PROOF. It suffices to show $T_t^\epsilon(D) \subseteq D$.

The fact that $T_t\,(x_0, w_0)$ is twice continuously differentiable in x_0, w_0 follows from Theorem 5.5 in Chapter 5 of Friedman [2].

Write

$$\begin{aligned}W_t^\epsilon(x_0, w_0) &= \Phi(t)w_0 + \int_0^t \Phi(t)\Phi^{-1}(s)\, C^\epsilon\,(X_s(x_0))\, dB_s^* \\ &= U_t(x_0, w_0) + V_t^\epsilon(x_0).\end{aligned}$$

For any t there exist $0 < \rho < 1$ and A so that $|U_t(x_0, w_0)| \geqq \rho w_0$ and $P(|V_t^\epsilon(x_0)| > k) \leqq A/k^2$ for all x_0, w_0, k. Therefore

$$P\left(\ |W_t^\epsilon(x_0, w_0)| \leqq \frac{\rho}{2}\,|w_0|\ \right) \leqq \frac{4}{\rho^2}\,\frac{A}{|w_0|^2}\,.$$

Now

$$\frac{\partial}{\partial w_j}\,(T_t^\epsilon\phi)(x_0, w_0)$$

$$= \sum_i E \frac{\partial \phi}{\partial w_i}(X_t(x_0), W_t^\epsilon(x_0, w_0)) \frac{\partial W_{t_i}^\epsilon}{\partial w_j}(x_0, w_0).$$

Since $(\partial W_{t_i}^\epsilon/\partial w_j)(x_0, w_0) = \Phi_{ij}(t)$ and so is bounded, in order to show $|w_0|^2|(\partial/\partial w_j)(T^\epsilon\phi)(x_0, w_0)|$ is bounded it suffices to show $|w_0|^2\ |E(\partial\phi/\partial w_i)(X_t(x_0), W_t^\epsilon(x_0, w_0)|$ bounded. Split the expectation into the sets on which $|W_t(x_0, w_0)| \leqq \rho/2\, w_0$ and for which $|W_t(x_0, w_0)| > \rho/2\, w_0$. The first term is bounded by $4/\rho^2 A \sup_{x,w}|(\partial\phi/\partial w_i)(x, w)|$ and the second by $4/\rho^2 \sup_{x,w}|w|^2|(\partial\phi/\partial w_i)(x, w)|$.

To show that the first two derivatives of $T_t^\epsilon\phi$ vanish at infinity one uses similar arguments.

LEMMA 6. *If $\phi \in D$, there exist $\phi_n \in \mathscr{D}(A^{n,\epsilon})$ so that $|\phi_n(x, \alpha, w) - \eta\phi(x, \alpha, w)| \to 0$ uniformly in x, α, w and $|A^{n,\epsilon}\phi_n(x, \alpha, w) - \eta A^\epsilon\phi(x, \alpha, w)| \to 0$ uniformly in x, α, w.*

REMARK. The essential technique used in the proof of this lemma is due to Kurtz (example 1 of [7]).

PROOF. Supposed for fixed α, $\phi(x, \alpha, w)$ is in D as a function of x and w. Then $\phi \in \mathscr{D}(A^{n,\epsilon})$ and

$$\begin{aligned} A^{n,\epsilon}\phi(x, \alpha, w) = {} & \sum_{\ell,\beta} \left(\phi \left(x + \frac{\ell}{n}, \beta, w + \frac{\ell}{\sqrt{n}} \right) \right. \\ & \left. + \phi(x, \beta, w) \right) \eta q(x, \alpha; \ell, \beta) \\ & - \sqrt{n} \sum_i F_i \left(x - \frac{w}{\sqrt{n}} \right) \frac{\partial\phi}{\partial w_i}(x, \alpha, w) \\ & + \frac{1}{2}\epsilon^2 \sum_i \frac{\partial^2\phi}{\partial w_i^2}(x, \alpha, w) \\ & + n \sum_\beta Q(x; \alpha, \beta)\phi(x, \beta, w). \end{aligned}$$

Now, using the uniform continuity and boundedness of the first two derivatives of ϕ and the boundedness of $w_i w_j(\partial\phi/\partial w_k)$ (x, α, w) in x and w, together with 2nd order Taylor expansions with integral remainder whenever possible, we can rewrite this expression as

$$\begin{aligned} A^{n,\epsilon}\phi(x, \alpha, w) = {} & \sum_i \sum_\beta \frac{\partial\phi}{\partial x_i}(x, \beta, w) F_i(x, \alpha, \beta) \\ & + \sum_{i,k} \frac{\partial F_i}{\partial x_k}(x) w_k \frac{\partial\phi}{\partial w_i}(x, \alpha, w) \end{aligned}$$

$$+ \sqrt{n} \sum_{\beta} \sum_{i} \frac{\partial \phi}{\partial w_i}(x, \beta, w) F_i(x, \alpha, \beta)$$

$$- \sqrt{n} \sum_{i} \frac{\partial \phi}{\partial w_i}(x, \alpha, w) F_i(x)$$

$$+ \frac{1}{2} \sum_{\beta} \sum_{i,j} \sigma_{ij}^2(x, \alpha, \beta) \frac{\partial^2 \phi}{\partial w_i \partial w_j}(x, \beta, w)$$

$$+ \frac{1}{2} \epsilon^2 \sum_{i} \frac{\partial^2 \phi}{\partial w_i^2} (x, \alpha, w) + n \sum_{\beta} Q(x, \alpha, \beta)(x, \beta, w)$$

$$+ R_n(x, \alpha, w)$$

where $R_n \to 0$ as $n \to \infty$ uniformly in x, α, w. Now suppose $\psi = \eta g$, $g \in D$. Then

$$A^{n,\epsilon}\psi(x, \alpha, w) = \sum_{i} \frac{\partial g}{\partial x_i}(x, w) F_i(x, \alpha)$$

$$+ \sum_{i,k} \frac{\partial F_i}{\partial x_k}(x) w_k \frac{\partial g}{\partial w_i}(x, w)$$

$$+ \sqrt{n} \sum_{i} \frac{\partial g}{\partial w_i}(x, w)(F_i(x, \alpha) - F_i(x))$$

$$+ \frac{1}{2} \sum_{i,j} (\sigma^2(x, \alpha) + \sigma^2 I)_{ij} \frac{\partial^2 g}{\partial w_i \partial w_j} + R_n(x, \alpha, w),$$

$$= \sum_{i} \frac{\partial g}{\partial x_i} (x, w) F_i(x) + \sum_{i,k} \frac{\partial F}{\partial x_k}(x) w_k \frac{\partial g}{\partial w_i}(x, w)$$

$$+ \frac{1}{2} \sum_{i,j} (\sigma^2(x) + \epsilon^2 I)_{ij} \frac{\partial^2 g}{\partial w_i \partial w_j}$$

$$+ \sum_{i} \frac{\partial g}{\partial x_i}(x, w)(F_i(x, \alpha) - F_i(x))$$

$$+ \sqrt{n} \sum_{i} \frac{\partial g}{\partial w_i}(x, w)(F_i(x, \alpha) - F_i(x))$$

$$+ \frac{1}{2} \sum_{i,j} \frac{\partial^2 g}{\partial w_i \partial w_j}(\sigma_{ij}^2(x, \alpha) - \alpha_{ij}^2)x))$$

$$+ R_n(x, \alpha, w).$$

Now let $\eta_i(x, \alpha)$ be defined as before so that

$$\sum_\alpha \pi(x, \alpha)\eta_i(x, \alpha) = 0,$$

$$\sum_\beta Q(x; \alpha, \beta)\eta_i(x, \beta) = F_i(x) - F_i(x, \alpha),$$

and similarly find $\gamma_{ij}(x, \alpha)$ so that

$$\sum_\alpha \pi(x, \alpha)\gamma_{ij}(x, \alpha) = 0,$$

$$\sum_\beta Q(x;\alpha, \beta)\gamma_{ij}(x, \beta) = \sigma^2_{ij}(x) - \sigma^2_{ij}(x, \alpha),$$

and finally find $\delta_{ij}(x, \alpha)$ so that

$$\sum_\alpha \pi(x, \alpha)\delta_{ij}(x, \alpha) = 0$$

and

$$\sum_\beta Q(x, \alpha, \beta)\delta_{ij}(x, \alpha)$$

$$= \sum_\alpha \pi(x, \alpha) \cdot \left(\sum_\beta (F_j(x, \alpha, \beta)\eta_i(x, \beta) - \eta_i(x, \alpha)F_j(x) \right)$$

$$- \sum_\beta (F_j(x, \alpha, \beta)\eta_i(x, \beta) - \eta_i(x, \alpha)F_j(x)).$$

Notice that η_i, γ_{ij}, and δ_{ij} are in D as functions of x. In fact they have compact support since F and σ^2 do. Let e_i be the unit vector in the i^{th} direction in $\mathbf{R}^J$. Define

$$a_j(x, \alpha, w) = \left(g \left(x + \frac{e_j}{n}, w \right) - g(x, w) \right) \eta_j(x, \alpha),$$

$$b_j(x, \alpha, w) = \left(g \left(x, w + \frac{e_j}{\sqrt{n}} \right) - g(x, w) \right) \eta_j(x, \alpha),$$

$$c_{ij}(x, \alpha, w) = \frac{1}{2}\left(g \left(x, w + \frac{e_i}{\sqrt{n}} + \frac{e_j}{\sqrt{n}} \right) - g(x, w + \frac{e_i}{\sqrt{n}} \right)$$

$$-\left(g \left(x, z \frac{e_j}{\sqrt{n}}\right) + g(x, w) \right) \cdot \gamma_{ij}(x, \alpha),$$

$d_{ij}(x, \alpha, w)$

$$= \left[g\left(x, w + \frac{e_i}{\sqrt{n}} + \frac{e_j}{\sqrt{n}}\right) - g\left(x, w + \frac{e_i}{\sqrt{n}}\right) - g\left(x, w + \frac{e_j}{\sqrt{n}}\right) + g(x, w) \right] \cdot \delta_{ij}(x, \alpha),$$

and finally

$$h_{ii}(x, \alpha, w) = \frac{1}{2}\left[g\left(x, w + \frac{2e_i}{\sqrt{n}}\right) - 2g\left(x, w + \frac{e_i}{\sqrt{n}}\right) + g(x, w) \right] \eta_i(x, \alpha),$$

and let

$$g_n(x, \alpha, w) = g(x, w) + \sum_i a_i(x, \alpha, w) + \sum_i b_i(x, \alpha, w) + \sum_{i,j} C_{ij}(x, \alpha, w) + \sum_{i,j} d_{ij}(x, \alpha, w) + \sum_i h_{ii}(x, \alpha, w).$$

Then for fixed α, $g_n(x, \alpha, w)$ is in D as a function of x, w and

$$|g_n(x, \alpha, w) - \eta g(x, \alpha, w)| \to 0$$

uniformly in x, α, w and

$$A^{n,\epsilon} g_n(x, \alpha, w) \to \sum_i \frac{\partial g}{\partial x_i}(x, w) F_i(x) + \sum_{i,k} \frac{\partial F_i}{\partial x_k}(x) w_k \frac{\partial g}{\partial w_i}(x, w) + \frac{1}{2} \sum_{i,j} \Gamma^{\epsilon}_{ij}(x) \frac{\partial^2 g}{\partial w_i \partial w_j}(x, w)$$

$$= \eta A^{\epsilon} g(x, \alpha, w)$$

uniformly in x, α, w. Here $\Gamma^{\epsilon}(x) = \Gamma(x) + \epsilon^2 I$.

Thus the proof of Lemma 6 is finished.

To finish the proof of Theorem I we have

LEMMA 7. *Under the assumptions of the theorem we have:* $P(Y_t^n = \beta) \to \pi(X(t, x_0), \beta)$ *uniformly in* $t_0 \leqq t \leqq T$ *for any* $t_0 > 0$, *as* $n \to \infty$.

PROOF. Let

$$P_t^n(x, \alpha; z, \beta) = P(Y_t^n = \beta, X_t^n = x \mid X_0^n = x, Y_0^n = \alpha)$$

and

$$\overline{P}_t^n(x, \alpha; \beta) = \sum_z P_t^n(x, \alpha; z, \beta).$$

It suffices to show $\overline{P}_t^n(x; \alpha, \beta) \to \pi(X(t, x), \beta)$ uniformly in $t_0 \leqq t \leqq T$, $t_0 > 0$. We can write

$$\frac{d}{dt} \overline{P}_t^n(x, \alpha; \beta) = n \sum_z \sum_\gamma P_t^n(x, \alpha; z, \gamma) Q(z, \gamma; \beta)$$

$$= n \left[\sum_\gamma \overline{P}_t^n(x, \alpha; \gamma) Q(X(t, x), \gamma, \beta) + K(x, \alpha, t, n) \right].$$

Now this last system of equations, together with the equation

$$\frac{d}{dt} X(t, x) = F(X(t, x))$$

constitute a simplified version of the singularly perturbed initial value problem. Notice that the solutions $P_t^*(x; \alpha, \gamma)$ to the boundary layer equations

$$\frac{d}{dt} P^*(x; \alpha, \gamma) = \sum_\beta P^*(x, \alpha, \beta) Q(x, \beta; \gamma)$$

are uniformly asymptotically stable uniformly in $x \in \Omega$ by (C3) and that

$$K(x, \alpha, t, n) = \sum_z \sum_\gamma P_t^n(x, \alpha; z, \gamma)[Q(z, \gamma; \beta) - Q(X(t, x), \gamma, \beta)]$$

converges to zero uniformly in $x \in \Omega$, $0 \leqq t \leqq T$, as $n \to \infty$ by uniform continuity of $Q(x, \alpha; \beta)$ together with convergence in probability of X_t^n to $X(t, x)$ uniformly with respect to initial point x in Ω.

We may therefore apply the main theorem of [6] for bounded time intervals to conclude the proof.

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