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SMALL RANDOM PERTURBATIONS OF DYNAMICAL SYSTEMS WITH APPLICATIONS IN POPULATION GENETICS

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Small random perturbations of dynamical systems with applications in population genetics*)

by

J. Grasman

SUMMARY

This paper deals with the approximation of the stationary solution of the Fokker-Planck equation for dynamical systems with small random perturbations acting upon the state variables as well as the parameters. This singularly perturbed boundary value problem is solved by using its variational formulation.

KEY WORDS & PHRASES: *Fokker-Planck equation, elliptic singular perturbations, variational problems, random perturbations, exit problems.*

*) This report is submitted for publication elsewhere

1. INTRODUCTION

The state of a deterministic dynamical system at time t is given by a vector $x(t) = (x_1(t),\ldots,x_n(t))$ satisfying a differential equation of the type

$$\dot{x} = b(x). \tag{1.1}$$

It is assumed that the set of admissable states forms a bounded domain $\chi \subset \mathbb{R}_n$ and that for every point $x_0 \in \bar{\chi}$ the system (1.1) with $x(0) = x_0$ tends to the only stationary point $x = 0 \in \chi$ as $t \to \infty$ without leaving χ. The dynamics of such a system is well understood, particularly, when b(x) denotes a gradient field. The above equation is used to model real world problems such as the stability of elastic structures, chemical reactions and the distribution of genotypes in a population. In all these problems there is another

factor we did not include in (1.1), that is the influence of random perturbations. Let us assume that these perturbations are small and of a type known as Gaussian white noise. Then (1.1) changes into a stochastic differential equation

$$(1.2) \qquad dx_\varepsilon = b(x_\varepsilon)dt + \varepsilon\sigma(x_\varepsilon)dw, \qquad 0 < \varepsilon << 1,$$

where w(t) is a n-dimensional Wiener process and σ the diffusion matrix of Brownian motion. From probability theory it is known that x_ε leaves χ with probability 1. The time t_e needed to reach $\partial\chi$ depends on the starting point x_0 and ε. For $\varepsilon \to 0$ we have that $t_e \to \infty$ which is consistent with the dynamics of the deterministic system. In this paper we will concentrate on the question where the system leaves χ. We will present a method that computes the probability density of leaving χ at a point $x \in \partial\chi$, if at $t = 0$ the system was in a state $x_0 \in \chi$. Our analysis of this problem has its starting-point in the Fokker-Planck equation related with (1.2). This equation for the transition probability density of x_ε has the form

$$(1.3) \qquad \frac{\partial\Phi}{\partial t} = \varepsilon^2 \sum_{i,j=1}^{n} a_{ij}(x) \frac{\partial^2\Phi}{\partial x_i \partial x_j} + \sum_{i=1}^{n} b_i(x) \frac{\partial\Phi}{\partial x_i},$$

with

$$a_{ij}(x) = \frac{1}{2}[\sigma(x)\sigma^*(x)]_{ij},$$

where σ^* denotes the adjoint of σ, see [4]. Let $p_\varepsilon(x,x_0)$ denote the probability density of leaving χ the first time at $x \in \partial\chi$ when starting at $x_0 \in \chi$. Then the following relation is known to be valid.

$$(1.4) \qquad \int_{\partial\chi} p_\varepsilon(x,x_0)h(x)ds = \Phi(x_0;\varepsilon),$$

where ds is a positive measure on $\partial\chi$ and Φ is a stationary solution of (1.3) satisfying the boundary condition $\Phi = h$ on $\partial\chi$, see [10]. Finally, we will also consider systems containing a set of parameters $(p_1,\ldots,p_m)$

$$(1.5) \qquad \dot{x} = b(x,p)$$

and study the influence of small random perturbations acting upon x as well as p, so that (1.2) changes into

$$(1.6) \qquad d\begin{pmatrix} x_\varepsilon \\ p_\varepsilon \end{pmatrix} = \begin{pmatrix} b(x_\varepsilon,p_\varepsilon) \\ 0 \end{pmatrix} dt + \begin{pmatrix} \sigma_{x1}(x_\varepsilon,p_\varepsilon) & \sigma_{x2}(x_\varepsilon,p_\varepsilon) \\ \sigma_{p1}(x,_\varepsilon p_\varepsilon) & \sigma_{p2}(x_\varepsilon,p_\varepsilon) \end{pmatrix} dw,$$

where w(t) is a (n+m)-dimensional Wiener process.

The central problem we deal with is the construction of an asymptotic solution of the stationary Fokker-Planck equation (1.3) for $\varepsilon \to 0$. In this paper we will use a variational method as given in [6, p.590] with a slightly different functional. It is noted that this modification of the functional means a considerable reduction of the computational work. Employing formula (1.4) we are able to compute the probability that the system leaves a bounded domain of the (x,p)-space at a specified part of the boundary.

2. ONE DIMENSIONAL SYSTEMS

2.1 The resonant turning point problem

Let a function $\Phi(x;\varepsilon)$ satisfy the time-independent Fokker-Planck equation for a one-dimensional dynamical system with state-independent random perturbations

$$(2.1a) \qquad \varepsilon^2 \frac{d^2\Phi}{dx^2} + b(x) \frac{d\Phi}{dx} = 0, \qquad 0 < \varepsilon << 1,$$

for the interval $\chi = (0,1)$ with boundary values

$$(2.1b) \qquad \Phi(0;\varepsilon) = A, \qquad \Phi(1;\varepsilon) = B.$$

It is assumed that $b'(x)$ is strictly negative throughout the interval $[0,1]$ and that $b(\gamma) = 0$ for some $0 < \gamma < 1$. The exact solution for this problem reads

$$(2.2a) \qquad \Phi(x;\varepsilon) = \frac{(B-A)V(x;\varepsilon)+AV(1;\varepsilon)-BV(0;\varepsilon)}{V(1;\varepsilon)-V(0;\varepsilon)}$$

with

$$(2.2b) \qquad V(x;\varepsilon) = \int_{\gamma}^{x} \exp\{-\frac{1}{\varepsilon^2}\int_{\gamma}^{y} b(z)dz\}dy.$$

The asymptotic behaviour of Φ as $\varepsilon \to 0$ can be derived from (2.2). However, for higher dimensional systems we are not always in the position to obtain an explicit expression for the solution, we then have to look for suitable implicit asymptotic methods by which the behaviour of Φ as $\varepsilon \to 0$ can be derived directly from the differential equation. As an illustrative example we also approach this problem by an implicit method.

The problem (2.1) is a so-called singular perturbation problem. Substitution of $\varepsilon = 0$ in (2.1a) yields the reduced equation $b\Phi_0' = 0$ having the solution

$$(2.3) \qquad \Phi_0(x) = k.$$

For problems with b not changing sign on the interval (0,1), it can be shown that k must have the value A for $b > 0$ or B for $b < 0$. For x fixed and $\varepsilon \to 0$, Φ tends to Φ_0. In an ε-interval near the end-point where the boundary value differs from Φ_0, the solution changes from the value k to this boundary value; as $\varepsilon \to 0$ the solution steepens in this ε-interval and forms a so-called boundary layer.

For the present problem it is not clear what value has to be taken for k. This problem was noticed first by ACKERBERG and O'MALLEY [1] for the equation

$$(2.4) \qquad \varepsilon^2 \frac{d^2\Phi}{dx^2} + b(x)\frac{d\Phi}{dx} + c(x)\Phi = 0$$

with b as in (2.1). For the solution of the corresponding reduced equation one has

$$(2.5) \qquad \Phi_0(x;\varepsilon) = k \exp\{-\int_{\gamma}^{x} \frac{c(\bar{x})}{b(\bar{x})} d\bar{x}\}.$$

They found that for

(2.6) $\quad -c(\gamma)/b(\gamma) = 0,1,2,\ldots$

the value of k is in general different from zero; k can be determined by various methods, see [2, 6 and 9]. In the other cases k has to be taken zero as otherwise higher order terms of the asymptotic expansion for the solution become singular; for these problems boundary layers arise at both end-points. For the so-called resonant cases satisfying (2.6) a boundary layer is found at one of the end-points depending on the sign of

$$(2.7) \qquad I = \int_0^1 b(x)dx.$$

and at both sides if (2.7) vanishes.

For the asymptotic solution of the resonant problem (2.1) we follow [6], as this method also applies to partial differential equations. Utilizing the standard method of matched asymptotic expansions we expect the formal asymptotic solution of (2.1) to have the form

$$(2.8) \qquad \Phi_{as}(x;\varepsilon) = k + (A-k)\exp\{-b(0)x/\varepsilon^2\} + (B-k)\exp\{b(1)(1-x)/\varepsilon^2\}.$$

Apparently, we lost information in the standard approach, as k is undetermined. This information is recovered by submitting (2.8) to a variation constraint. Multiplying equation (2.1a) with $\exp\{\Psi(x;\varepsilon)\}$ we obtain

$$(2.9) \qquad \frac{d}{dx}\left(\exp\Psi\frac{d\Phi}{dx}\right) = 0,$$

if

$$(2.10) \qquad \Psi(x;\varepsilon) = \frac{1}{\varepsilon^2}\int_0^x b(y)dy.$$

In the corresponding variational problem one considers the functional

$$(2.11) \qquad J(\Phi) = \frac{1}{2}\int_0^1 \left(\frac{d\Phi}{dx}\right)^2 \exp\Psi(x;\varepsilon)dx.$$

Taking (2.8) as a restricted class of admissible functions we choose k such that the functional (2.11) is stationary in the first order asymptotic

approximation. Ignoring relatively exponentially small terms we obtain

$$(2.12)\qquad J(\Phi_{as}) = \frac{b(0)^2(A-k)^2}{2\varepsilon^4}\int_0^1 \exp\{-\frac{2b(0)x}{\varepsilon^2} + \Psi(x;\varepsilon)\}dx +$$

$$+ \frac{b(1)^2(B-k)^2}{2\varepsilon^4}\int_0^1 \exp\{\frac{2b(1)(1-x)}{\varepsilon^2} + \Psi(x;\varepsilon)\}dx,$$

The first integral has its largest contribution from an ε^2-interval near $x = 0$ and the second from an interval near $x = 1$:

$$J(k) \approx \frac{b(0)(A-k)^2}{2\varepsilon^2}\exp\Psi(0;\varepsilon) - \frac{b(1)(B-k)^2}{2\varepsilon^2}\exp\Psi(1;\varepsilon).$$

For the value of k at the stationary point satisfying $dJ/dk = 0$ we need to distinguish three cases

$$(2.13a)\qquad k = A \qquad (I > 0),$$

$$(2.13b)\qquad k = B \qquad (I < 0),$$

$$(2.13c)\qquad k = \frac{A\,b(0)-B\,b(1)}{b(0)-b(1)} \qquad (I = 0).$$

2.2. The one-locus problem in population genetics

For an introduction in the mathematics of population genetics we refer to CROW and KIMURA [3]. The application we deal with concerns the one-locus problem for a diploid population. Let there be two alleles A and a at this locus. Then the population is divided into three genotypes AA, Aa and aa, which may have different fitness (ability to survive and to reproduce). The relative fitness is parameterized by the selection coefficient s and the measure of dominance h. If p is the total frequency of allele A, we can characterize the genotypes as follows.

genotype	AA	Aa	aa
frequency	p^2	$2p(1-p)$	$(1-p)^2$
rel. fitness	1-s	1-hs	1

Table 2.1

The average fitness of the population is

$$w = (1-s)p^2 + 2(1-hs)p(1-p) + (1+p)^2 = 1 - sp\{p + 2h(1-p)\},$$

while the average fitness of genotypes containing allele A equals

$$w_A = \{(1-s)p^2 + (1-hs)p(1-p)\}p^{-1} = 1 - s\{p + h(1-p)\}.$$

The change of frequency p over large time intervals satisfies

$$\dot{p} = p(w_A - w)/w. \tag{2.14}$$

For s small we have

$$\dot{p} = sp(1-p)\{-h + (2h-1)p\}. \tag{2.15}$$

In case of selection favouring the hetrozygote ($h < 0$) there exists a non-homogeneous stationary distribution with $p = p_s = h/(2h-1)$, which is stable as we see from figure 2.1.

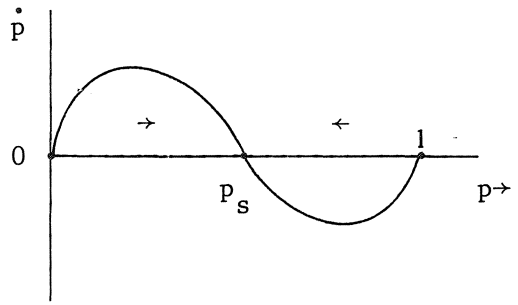

Fig. 2.1

We now introduce random mating. Besides a drift of the expected value p given by (2.15), there will be small random perturbations with variance $p(1-p)/N$ in the change of p (N is the size of the population). This stochastic problem is described by the Fokker-Planck equation (also indicated as Kolmogorov backward equation)

$$(2.16) \qquad \frac{\partial \Phi}{\partial t} = \frac{p(1-p)}{N} \frac{\partial^2 \Phi}{\partial p^2} + sp(1-p)\{h + (1-2h)p\} \frac{\partial \Phi}{\partial p} ,$$

where Φ is the transition probability density of p at time t. Assuming $Ns >> 1$ we see that a time-independent solution of (2.16) will satisfy the singularly perturbed two-point boundary value problem

$$(2.17a) \qquad \varepsilon \frac{d^2 \Phi}{dp^2} + \{h + (1-2h)p\} \frac{d\Phi}{dp} = 0, \qquad \varepsilon = (Ns)^{-1},$$

$$(2.17b) \qquad \Phi(0;\varepsilon) = A, \qquad \Phi(1;\varepsilon) = B.$$

Let us set $A = 0$, $B = 1$. According to (2.13a), $\Phi(x;\varepsilon) \to 0$ as $\varepsilon \to 0$ for x fixed. Thus, using (1.4) we find that p reaches the value 1 with probability zero. Setting $A = 1$ and $B = 0$ we conclude that p reaches the value 0 with probability 1.

In this problem we see the drastic influence of (even small) random perturbations: the seemingly stable state with $p = p_s$ with a heterogeneous population will disappear and the allele A will become extinct with probability 1.

3. SMALL RANDOM PERTURBATIONS OF GRADIENT SYSTEMS

3.1. The variational characterization

We consider the dynamical system (1.1) with one stationary state, $x = 0$, which is assumed to be asymptotically stable. The set of admissable states forms a bounded domain $\chi \subset \mathbb{R}_n$ satisfying

$$(3.1) \qquad \chi = \{x \mid 0 \le r < \bar{r}\ (\theta_1, \theta_2, \ldots, \theta_{n-1})\},$$

where (r,θ) denote the spherical coordinates for the point x. The vector $b(x)$ is directing to the inside of the domain χ and forms a gradient field

$$(3.2) \qquad b(x)\cdot\nu(x) < 0 \quad \text{for} \quad x \in \partial\chi \quad \text{and} \quad b(x) = \nabla \Psi(x)$$

where $\nu(x)$ is the outward normal at $\partial\chi$. We restrict ourselves to the case that the random perturbations are state-independent. A stationary solution of the Fokker-Planck equation will satisfy the following partial differential equation with boundary values

$$\varepsilon^2\Delta\Phi + \sum_{i=1}^{n} b_i(x)\,\frac{\partial\Phi}{\partial x_i} = 0 \quad \text{in } \chi, \tag{3.3a}$$

$$\Phi = h(\theta) \quad \text{on } \partial\chi. \tag{3.3b}$$

The method of matched asymptotic expansions suggests an asymptotic solution of the form

$$\Phi_{as}(x;\varepsilon) = k + \{h(\theta)-k\}\exp\{q(\theta)(\bar{r}(\theta)-r)/\varepsilon^2\}, \tag{3.4}$$

with

$$q(\theta) = \frac{1}{r}\sum_{i=1}^{n} x_i b_i(\bar{r}(\theta),\theta).$$

As in section 2.1 we determine the constant k by formulating the corresponding variational problem. The constant k has to be chosen such that for the class of functions (3.4) the following functional is stationary in the first order approximation

$$J(\Phi) = \frac{1}{2}\int_{\chi}\sum_{i=1}^{n}\left(\frac{\partial\Phi}{\partial x_i}\right)^2\exp\left(\frac{\Psi(x)}{\varepsilon^2}\right)dx. \tag{3.5}$$

3.2. Exit problems for two-dimensional systems

Let us consider the Dirichlet problem (3.3) with χ being the unit circle in $\mathbb{R}_2$ and with $b_i(x) = -x_i$, see figure 3.1. Then the asymptotic solution will be of the form

$$\Phi_{as}(x;\varepsilon) = k + \{h(\theta)-k\}\exp\{-(1-r)/\varepsilon^2\}, \tag{3.6}$$

and so

$$(3.7)\qquad \frac{\partial \Phi_{as}}{\partial x_i} = \{h(\theta)-k\}\exp\{-(1-r)/\varepsilon^2\}\{\frac{x_i}{\varepsilon^2 r} + O(1)\}.$$

Substitution in (3.5) gives

$$J(\Phi_{as}) = \{\frac{1}{2\varepsilon^2} + O(1)\}\int_0^1 \exp\{-\frac{(r-2)^2}{2\varepsilon^2}\}dr \int_0^{2\pi} \{h(\theta)-k\}^2 d\theta.$$

The condition dJ/dk = 0 yields

$$(3.8)\qquad k = \frac{1}{2\pi}\int_0^{2\pi} h(\theta)d\theta.$$

If the starting-point x_0 is taken in the outer region of χ (outside the boundary layer of thickness $O(\varepsilon^2)$), then according to formula (1.4) the probability density of leaving χ at a point of the boundary equals $1/2\pi$. Thus, all boundary points may be point of exit with equal probability.

Next we consider the same problem for a slightly different domain with $\bar{r}(0) = 1$, $1 < \bar{r}(\theta) < 2$ for $\theta \neq 0$ and $\bar{r}(\theta) \approx 1 + \alpha^2\theta^2$ for $|\theta| << 1$ and α some positive constant, see figure 3.2b. Then we have

$$J(\Phi_{as}) = \{\frac{1}{2\varepsilon^2} + O(1)\}\int_0^{2\pi} \{h(\theta)-k\}^2 \int_0^{\bar{r}(\theta)} \exp\{-\frac{2(\bar{r}(\theta)-r)}{\varepsilon^2} - \frac{r^2}{2\varepsilon^2}\}dr d\theta.$$

Integration over r gives

$$J(\Phi_{as}) = \{\frac{1}{4} + O(\varepsilon^2)\}\int_0^{2\pi} \{h(\theta)-k\}^2 \exp\{-\frac{\bar{r}^2(\theta)}{2\varepsilon^2}\}d\theta,$$

while the main contribution in the integration over θ comes from an ε-neighbourhood of the value $\theta = 0$,

$$J(\Phi_{as}) = \{\frac{\sqrt{\pi}\varepsilon}{4\alpha} + O(\varepsilon^2)\}\exp\{\frac{-1}{2\varepsilon^2}\}\{h(0)-k\}^2.$$

This expression is minimal for

$$k = h(0).$$

If we choose $0 \le h(\theta) \le 1$ with $h(0) = 1$ and $h(\theta) = 0$ for $|\theta| \ge \delta > 0$ with δ

arbitrary small but independent of ε, we have the following inequality

$$(3.9) \qquad \int_{-\delta}^{\delta} p_\varepsilon(\theta,x_0)d\theta \geq \int_{-\delta}^{\delta} p_\varepsilon(\theta,x_0)h(\theta)d\theta = \Phi(x_0,\varepsilon).$$

For a starting point $x_0 \in \chi$ bounded away from $\partial\chi$, $\Phi(x_0;\varepsilon) \to k$ as $\varepsilon \to 0$, so that the system leaves the domain χ near the point $(r,\theta) = (1,0)$ with probability 1.

Finally, we take a domain with $\bar{r}(0) = \bar{r}(\pi) = 0$, $1 < \bar{r}(\theta) < 2$ for $\theta \neq 0,\pi$ and

$$(3.10a) \qquad \bar{r}(\theta) \approx 1 + \alpha^2\theta^2 \qquad (|\theta| << 1),$$

$$(3.110b) \qquad \bar{r}(\theta) \approx 1 + \beta^2(\theta - \pi)^2 \qquad (|\theta-\pi| << 1).$$

Then we have

$$J(\Phi_{as}) = \frac{\sqrt{\pi}\varepsilon}{4} \exp\{\frac{-1}{2\varepsilon^2}\}\{\frac{(h(0)-k)^2}{\alpha} + \frac{(h(\pi)-k)^2}{\beta}\}\{1 + O(\varepsilon)\},$$

so that

$$k = \{\beta h(0) + \alpha h(\pi)\}/(\alpha + \beta).$$

From the estimate (3.9) we compute the probability of exit at the point (1,0) and in a similar way the probability of exit at (-1,0), see figure 3.3.

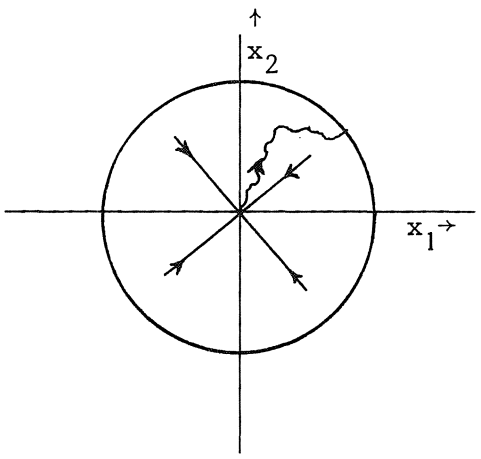

Fig. 3.1. All boundary points have equal probability of being exit point.

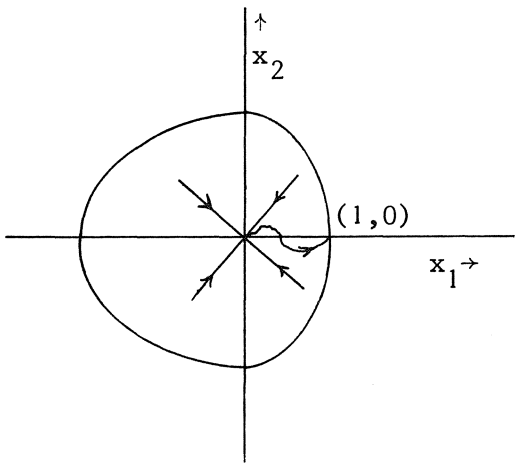

Fig. 3.2. The point (1,0) is exit point with probability 1.

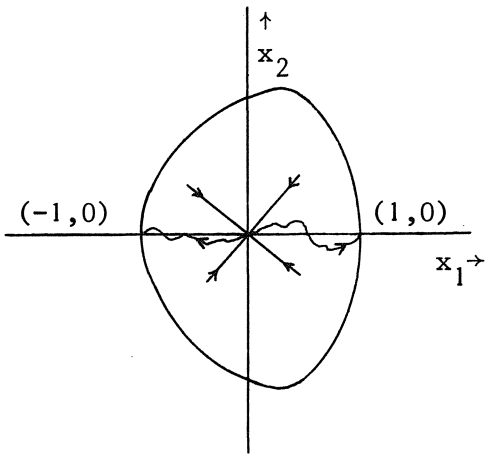

Fig. 3.3. The point (1,0) is exit point with probability $\beta/(\alpha+\beta)$ and (-1,0) with probability $\alpha/(\alpha+\beta)$, see formula (3.10).

4. DYNAMICAL SYSTEMS CONTAINING A PARAMETER VECTOR

4.1. The effect of random perturbations in the parameter vector

For the system (1.6) the set of admissable states x and parameter values p forms a bounded domain $\Omega \subset \mathbb{R}_k$ $(k = m+n)$,

$$\Omega = \{(x,p),\ x \in \chi(p),\ p \in \Gamma\}, \tag{4.1}$$

where Γ is a bounded domain in $\mathbb{R}_m$. For p fixed $\chi(p)$ has the form (3.1), b(x,p) is assumed to satisfy condition (3.2a) and the inequality

$$\sum_{i=1}^{n} b_i(x,p)x_i \le -L\,x^2 \quad \text{in } \bar{\Omega}. \tag{4.2}$$

The Fokker-Planck equation for (1.6) reads

$$\frac{\partial \Phi}{\partial t} = \varepsilon^2 L_2\Phi + L_1\Phi, \tag{4.3}$$

$$L_2 \equiv \sum_{i,j=1}^{n} \alpha_{ij} \frac{\partial^2}{\partial x_i \partial x_j} + 2\sum_{i=1}^{n}\sum_{j=1}^{n} \beta_{ij} \frac{\partial^2}{\partial x_i \partial p_j} + \sum_{i,j=1}^{m} \gamma_{ij} \frac{\partial^2}{\partial p_i \partial p_j},$$

$$L_1 \equiv \sum_{i=1}^{n} b_i \frac{\partial}{\partial x_i},$$

with symmetric coefficient matrices

$$\{\alpha_{ij}\}_{n\times n} = \sigma_{x1}\sigma_{x1}^{*} + \sigma_{x2}\sigma_{x2}^{*},\quad \{\gamma_{ij}\}_{m\times m} = \sigma_{p1}\sigma_{p1}^{*} + \sigma_{p2}\sigma_{p2}^{*}$$

and with

$$\{\beta_{ij}\}_{n\times m} = \sigma_{x1}\sigma_{p1}^{*} + \sigma_{x2}\sigma_{p2}^{*}.$$

A stationary solution of (4.3) is found as the solution of an elliptic equation with boundary values

$$\varepsilon^2 L_2\Phi + L_1\Phi = 0, \quad \text{in } \Omega, \tag{4.4a}$$

$$\Phi = h(x,p) \quad \text{on } \partial\Omega. \tag{4.4b}$$

Standard perturbation methods yield an asymptotic solution of the form

$$\Phi_{as}(x,p) = k(p) + \{h(\theta,p)-k(p)\}\exp\{q(\theta,p)(\bar{r}(\theta)-r)/\varepsilon^2\}. \tag{4.5}$$

Multiplying equation (4.4a) with $\varepsilon^{-2}\exp\Psi(x,p;\varepsilon)$ we obtain

$$\begin{aligned}\sum_{i,j=1}^{n} \frac{\partial}{\partial x_i}\left(\alpha_{ij}e^{\Psi}\frac{\partial\Phi}{\partial x_j}\right) + 2\sum_{i=1}^{n}\sum_{j=1}^{m}\frac{\partial}{\partial p_j}\left(\beta_{ij}e^{\Psi}\frac{\partial\Phi}{\partial x_i}\right) + \\ + \sum_{i,j=1}^{m}\frac{\partial}{\partial p_i}\left(\gamma_{ij}e^{\Psi}\frac{\partial\Phi}{\partial p_j}\right) + \sum_{i=1}^{n}\{\varepsilon^{-2}b_i e^{\Psi} - \sum_{j=1}^{n}\frac{\partial}{\partial x_j}(\alpha_{ij}e^{\Psi}) - \\ - 2\sum_{j=1}^{m}\frac{\partial}{\partial p_j}(\beta_{ij}e^{\Psi})\}\frac{\partial\Phi}{\partial x_i} - \sum_{i=1}^{m}\frac{\partial}{\partial p_i}(\gamma_{ij}e^{\Psi})\frac{\partial\Phi}{\partial p_j} = 0.\end{aligned} \tag{4.6}$$

Clearly, this equation is selfadjoint, if

$$\sum_{j=1}^{n}\frac{\partial}{\partial x_j}(\alpha_{ij}e^{\Psi}) + 2\sum_{j=1}^{m}\frac{\partial}{\partial p_j}(\beta_{ij}e^{\Psi}) = \varepsilon^{-2}b_i e^{\Psi}, \quad i = 1,\ldots,n, \tag{4.7a}$$

$$\sum_{i=1}^{m}\frac{\partial}{\partial p_i}(\gamma_{ij}e^{\Psi}) = 0, \quad j = 1,\ldots,m, \tag{4.7b}$$

for some function Ψ. Under these conditions the problem can be reformulated as the variational problem for the functional

$$(4.8)\qquad J(\Phi) = \frac{1}{2}\int_{\Omega} \sum_{i,j=1}^{n} \{\alpha_{ij} \frac{\partial\Phi}{\partial x_i}\frac{\partial\Phi}{\partial x_j} + 2 \sum_{i=1}^{n}\sum_{j=1}^{m} \beta_{ij} \frac{\partial\Phi}{\partial x_i}\frac{\partial\Phi}{\partial p_i} +$$

$$+ \sum_{i,j=1}^{m} \gamma_{ij} \frac{\partial\Phi}{\partial p_i}\frac{\partial\Phi}{\partial p_j}\} e^{\Psi} dxdp.$$

From (4.2) and (4.7a) it follows that Ψ is a function of the order $O(|x|^2/\varepsilon^2)$. Substitution of (4.5) into (4.8) gives an expression with leading term

$$(4.9)\qquad J_0(k) = \frac{1}{2}\int_{\Gamma} \sum_{i,j=1}^{m} \gamma_{ij}(0,p) \int_{-\infty}^{+\infty} \exp\Psi_0(\xi,p)d\xi \frac{\partial k}{\partial p_i}\frac{\partial k}{\partial p_j}\, dp,$$

where

$$\Psi_0(\xi,p) = \lim_{\varepsilon\to 0} \Psi(\xi_1\varepsilon,\ldots,\xi_n\varepsilon,\ p_1,\ldots,p_m;\varepsilon).$$

The corresponding Euler-Lagrange equation for (4.9) is an elliptic differential equation for $k(p)$ holding in the domain $\Gamma \subset \mathbb{R}_m$

$$(4.10a)\qquad \sum_{i,j=1}^{m} \frac{\partial}{\partial p_i}\Big(\gamma_{ij}(0,p) \int_{-\infty}^{\infty} \exp\Psi_0(\xi,p)d\xi \frac{\partial k}{\partial p_j}\Big)dp = 0.$$

Using (4.7b) we can reduce this equation to

$$(4.11a)\qquad \sum_{i,j=1}^{m} \gamma_{ij}(0,p) \frac{\partial^2 k}{\partial p_i \partial p_j} = 0.$$

We are still in the position to impose boundary conditions upon $k(p)$. Holding the view that a formal procedure must be of such a nature that it avoids spurious boundary layers we choose as boundary values

$$(4.11b)\qquad k(p) = h(x,p) \quad \text{with } x = 0 \quad \text{and} \quad p \in \partial\Gamma.$$

Since (4.5) augmented with (4.11) produces a unique asymptotic solution, it is worth to concentrate on the necessity of the selfadjointness condition (4.7). This problem has been investigated in [5], where a rigorous

proof of the validity of (4.5) and (4.11) has been given without using conditions (4.7).

Let us consider the boundary value problem with $0 \le h(\theta,p) \le 1$, $h = 1$ $p \in \partial\Gamma$ and $h = 0$ outside a δ-neighbourhood of $\partial\Gamma$, then $k = 1$ and according to (1.4) the system (1.6) leaves Ω in a δ-neighbourhood of a point (x,p) with $x = 0$ and $p \in \partial\Gamma$ as $\varepsilon \to 0$, because

$$(4.12) \qquad \int_{\substack{\partial\Omega \\ |x|\le\delta}} p_\varepsilon(x,x_0)ds \ge \int_{\substack{\partial\Omega \\ |x|\le\delta}} p_\varepsilon(x,x_0)h(x)ds = \Phi(x_0;\varepsilon)$$

and $\Phi(x_0,\varepsilon) \to 1$ as $\varepsilon \to 0$ when x_0 belongs to the outer region of Ω. Thus, the system will leave the admissable set of, state- and parameter values, because of the random perturbations in the parameters. Note that the value of p at $\partial\Gamma$ where (x,p) leaves Ω depends only $\gamma_{ij}(0,p)$ and the starting value p_0.

4.2. The two-locus problem in population genetics

A population of N diploid individuals, each characterized by its genotype with respect to two loci and with two alleles at each locus, is described by the fractions of gametes of types AB, Ab, aB and ab. Let these fractions be denoted by q_i, $i = 1,2,3,4$. For a population with random mating the following Fokker-Planck equation can be derived (see [3, 8])

$$(4.13) \qquad \frac{\partial\Phi}{\partial t} = \sum_{i=1}^{3} \frac{q_i(1-q_i)}{4N} \frac{\partial^2\Phi}{\partial q_i^2} - \sum_{i=1}^{2} \sum_{j=i+1}^{3} \frac{q_iq_j}{2N} \frac{\partial^2\Phi}{\partial q_i \partial q_j} +$$

$$- \mu\{q_1(1-q_1-q_2-q_3) - q_2q_3\}\left(\frac{\partial\Phi}{\partial q_1} - \frac{\partial\Phi}{\partial q_2} - \frac{\partial\Phi}{\partial q_3}\right)$$

in a domain $S = \{(q_1,q_2,q_3) \mid q_i > 0,\ q_1 + q_2 + q_3 < 1\}$. Substitution of

$$(4.14) \qquad q_1 = p_1p_2 + x, \quad q_2 = p_1(1-p_2) - x, \quad q_3 = (1-p_1)p_2 - x$$

transforms the equation for the stationary problem into

$$(4.15)\qquad \varepsilon\Big[\sum_{i=1}^{2}\{p_i(1-p_i)\frac{\partial^2\Phi}{\partial p_i} + 2x(1-2p_i)\frac{\partial^2\Phi}{\partial p_i\partial x} + 2x\frac{\partial^2\Phi}{\partial p_1\partial p_2} +$$

$$+ \{p_1p_2(1-p_1)(1-p_2) + x(1-2p_1)(1-2p_2) - x^2\}\frac{\partial^2\Phi}{\partial x^2} - x\frac{\partial\Phi}{\partial x} = 0,$$

$$\varepsilon = 1/(2+4N\mu),$$

while the domain S transforms into a domain Ω of the type (4.1). We consider the Dirichlet problem of (4.15) with $0 < \varepsilon << 1$ for a subdomain $\Omega_\eta \subset \Omega$ with $\partial\Omega_\eta$ bounded away from $\partial\Omega$. In the way as carried out in the foregoing section one can prove that for $\varepsilon \to 0$ the two-locus system, if starting in the outer region of Ω, tends to linkage equilibrium ($x = 0$) along the subcharacteristic of L_1 by choosing a domain Ω_η as in figure 4.1 with η arbitrary small but independent of ε.

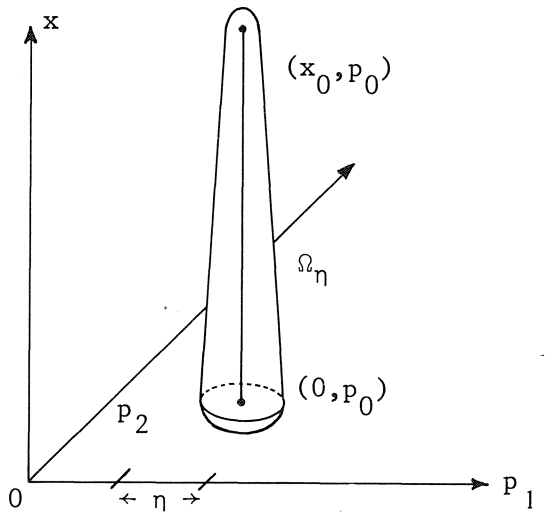

Fig. 4.1

5. SOME REMARKS

In our presentation we have emphasized the variational approach of singularly perturbed boundary value problems with resonant turning-point

behaviour. We gave applications in the theory of dynamical systems with small random perturbations referring, in particular, to problems in population genetics. However, we did not formulate the mathematical problems in their most general form, nor did we treat some extensions of the method. It was merely our aim to give the reader an impression how we arrived at this method of solving asymptotically the above class of singular perturbation problems. For example, in section 4.1 we already mentioned that the self-adjointness condition (4.7) could be dropped. However, this part forms the key to the asymptotic solution of the problem. Without this it would not be understandable how one arrives at the result (4.11a). Likewise the method of section 3.1 can be extended to non-gradient systems, see MATKOWSKY and SCHUSS [10]. The case where the dynamical system has more than one stationary point has been worked out in [11].

LITERATURE

[1] ACKERBERG, R.C. & R.E. O'MALLEY, *Boundary layer problems exhibiting resonance*, Studies in Appl. Math. 49, 277-295 (1970).

[2] COOK, PAMELA & W. ECKHAUS, *Resonance in a boundary value problem of singular perturbation type*, Studies in Appl. Math. 52, 129-139 (1973).

[3] CROW, J.F. & M. KIMURA, *An introduction to population genetics theory*, Harper and Row, New York (1970).

[4] FRIEDMAN, A., *Stochastic differential equations and applications*, vol. 2, Acad. Press, New York (1976).

[5] GRASMAN, J., *On a class of elliptic singular perturbations with applications in population genetics*, Math. Centre Report TW 184 (1978), to appear in Math. Methods in the A-pl. Sci.

[6] GRASMAN, J. & B.J. MATKOWSKY *A variational approach to singularly perturbed boundary value problems for ordinary and partial differential equations with turning points*, SIAM J. Appl. Math. 32 588-597 (1977).

[7] LITTLER, R.A., *Linkage disequilibrium in two-locus, finite, random mating models without selection or mutation*, Theor. Pop. Biol. 4, 259-275 (1973).

[8] MARUYAMA, T., *Stochastic problems in population genetics*, Lecture Notes in Biomath. 17, Springer-Verlag, Berlin (1977).

[9] MATKOWSKY, B.J., *On boundary layer problems exhibiting resonance*, SIAM Rev. 17, 82-100 (1975).

[10] MATKOWSKY, B.J. & Z. SCHUSS, *The exit problem for randomly perturbed dynamical systems*, SIAM J. Appl. Math. 33, 365-382 (1977).

[11] SCHUSS, Z. & B.J. MATKOWSKY, *The exit problem: A new approach to diffusion across potential barriers*, Northwestern Univ. Appl. Math. Techn. Report 7706 (1977).