A STOCHASTIC MODEL FOR OVIDUCTAL EGG TRANSPORT

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ABSTRACT   A mathematical description of ovum transport based on Langevin's diffusion equation is presented. The proposed model is deduced from qualitative features of this phenomenon, not induced from numerical fitting of experimental data. We demonstrate that egg transport in the ampulla of the rabbit oviduct can be represented as a one-dimensional random walk in a field of external force. The application of the model to describe isthmic ovum and sperm transport on the basis of simple random walk process is also discussed. The present formulation identifies and characterizes the forces involved in the motions of the ovum and predicts specific alternatives for physiological regulation of egg transport in the oviduct.

INTRODUCTION

Both acceleration and delay of oviductal egg transport can interfere with reproduction in mammals. Therefore, much effort has been directed to its study in the hope of obtaining basic information leading to the development of new and more reliable contraceptive methods. The mechanism that moves the egg from the ovary to the uterus has been cryptic and elusive when approached deterministically. However, the concept that oviductal egg transport is a stochastic process which can be characterized with a probabilistic approach (Verdugo et al., 1976) has simplified the understanding of this phenomenon. This concept has been pursued by several investigators who have demonstrated the heuristic value of such an approach (Portnow et al., 1977a, b; Hodgson and Talo, 1978; Talo and Hodgson, 1978). The aim of this report is to formulate a general stochastic model for oviductal egg transport, to test its validity, and to explicate some of the predictions implied in it.

Species variations in ovum transport complicate the development of a general descriptive model. Nevertheless, the following functional features are similar in all mammalian tubal transport and are considered as specific constraints for our formulation: (a) the total time required for the egg to move from the ostium of the oviduct to the uterus, although varying in different mammals, is consistent within each species (Croxatto and Ortiz, 1975); (b) the average velocity of egg transport is markedly different in various segments of the oviduct. In the rabbit, for example, after the freshly ovulated egg is captured by the fimbria and enters the ostium, it takes only a few minutes (~0.2% of the total transit time) to travel throughout the length of the ampulla, which is about one half of the total transit distance. The egg remains in the ampullo-isthmic junction for 15–25 h, and finally travels through the remaining isthmic half of the tube in 40 h (Greenwald, 1961; Harper, 1966; Boling and Blandau, 1971a; Pauerstein et al., 1974); (c) characteristic "to and fro" motions of the ovum and ovum surrogates have been observed in the various segments of mammalian oviducts and,

despite the overall timed sequence of ovum transport, such "spurts" are apparently random (Verdugo et al., 1976); (*d*) two mechanical effectors, smooth muscle of the wall and ciliated epithelium of the lumen lining, are present in the oviducts of mammals, the relative amount of each varying according to the species, the segment of the oviduct, and the hormonal influences (Blandau, 1969). Although it has been assumed that muscle contractions of the oviduct cause the pendular motions of the ovum, only recently has experimental evidence unequivocally supporting this argument been available (Halbert et al., 1976; Hodgson et al., 1977).

Black and Asdell's (1958) suggestion that the net pro-uterine transport of the egg in the oviduct might be due to "a gentle but persistent propulsive force" generated by cilia was not given much consideration at the time. However, more recently, two different but complementary lines of evidence have emerged to support the idea that cilia can generate sufficient force to transport the ovum along the rabbit ampulla. Stochastic analysis of experimental data indicate that egg motions in the ampulla of the rabbit have the characteristic features of a random process superimposed on a continuous nonperiodic process. The probability density function of velocities of ovum movements resembles a normal distribution with the mean value shifted 100–200 μm/s in a prouterine direction. This statistical pattern can be interpreted as the result of two-egg-driving forces: random muscle contractions responsible for the erratic pendular motions of the egg, and the continuous ciliary action responsible for driving the egg in a slow but consistent direction (Verdugo et al., 1977).

In another approach, by blocking muscle contractions with isoproterenol, Halbert et al. (1976) demonstrated that in the rabbit, ciliary force is sufficient to transport the egg in a continuous and unidirectional (pro-uterine) pattern at a rate of 100–150 μm/s. This finding is consistent with the velocity that can be inferred from the probabilistic studies, and further supports the idea that ciliary force might be most important in rabbit ampullary egg transport.

Peristaltic waves observed in oviductal smooth muscle are propagated for short distances, and their direction alternates in time, inducing the characteristic "to and fro" random motions of intratubal material. The stochastic nature of oviductal muscle contractions in the rabbit oviduct has been well documented (Verdugo et al, 1977; Talo and Hodgson, 1978; Hodgson and Talo, 1978). On the other hand, depending upon the species, ciliary activity may have different orientations in different segments of the oviduct but is continuous and unidirectional (Blandau, 1969; Gaddum-Rosse and Blandau 1973, 1976). Although the relative importance of these two effectors in egg transport is not well established, the formulation presented here will distinguish and characterize, according to their different statistical structure, both muscle and ciliary influences in gamete transport.

STOCHASTIC MODEL OF OVUM TRANSPORT

Using Langevin's equation, we have deduced from qualitative characteritics of tubal ovum transport a generic stochastic formulation to represent the relationship between random and nonrandom forces in oviductal egg transport. In this model we will consider the interaction of three forces which might operate differently in the various mammalian species and which, we submit, are the driving forces involved in the movements of the egg: (*a*) the forces generated by contractions of smooth muscle of the wall, which are discrete in time and space and which, in regard to direction of egg movement, can be considered random or pseudorandom (Verdugo

et al., 1977; Talo and Hodgson, 1978); (*b*) the continuous forces generated by ciliary activity, which may be pro-uterine or pro-ovarian or even absent, depending on the species and the segment of the oviduct (Gaddum-Rosse and Blandau, 1976); and (*c*) the frictional forces generated by the movement of the ovum in the oviduct. Although these are complex forces, for the purpose of the mathematical description we will represent each one as a single force factor.

Depending upon the relative directions of ciliary force and ovum transport, three general instances can be distinguished in the interaction of muscle-generated force, ciliary force, and egg transport: (*a*) when ciliary force is in the same direction as the net ovum transport, as in the oviduct of most mammals that have been studied (Gaddum-Rosse and Blandau, 1973); (*b*) when ciliary force is in the opposite direction of net ovum transport, as in the isthmus of the rabbit and the pig (Gaddum-Rosse and Blandau, 1973), and (*c*) when ciliary force cannot be assumed to account for movements of the ova owing to the high viscosity of luminal secretions (Jansen, 1978) or the scarcity of ciliated cells, as in the isthmus the guinea pig (Gaddum-Rosse and Blandau, 1976).

When ciliary force is in the same direction as ovum transport, it can impose direction on egg transport; the direction of the muscular egg-driving force can either be random (i.e., equal probability to move the egg in pro-ovarian or pro-uterine directions) or pseudorandom (i.e., the probability to move the egg in a pro-uterine direction is higher than in a pro-ovarian direction). If the ciliary force is thrust in the opposite direction of egg transport, the muscular force must be pseudorandom to overcome ciliary force and move the ovum toward the uterus. If the ciliary force is not acting, the egg is driven only by muscular force which can be pseudorandom or even truly random if appropriate boundary conditions exist (Portnow et al., 1977*a*).

Ovum transport in the rabbit ampulla was chosen to verify the validity of the present stochastic model because it provides the only instance in which detailed measurement of egg movements can be obtained and the sufficiency of the ciliary force to move the egg has been well established (Halbert et al., 1976). Also, since in the rabbit ampulla both muscle and cilia interact to produce egg transport, it represents a better experimental model to test our general formulation. It should be emphasized, however, that with very few specific changes the proposed mathematical description can also be applied to describe a variety of patterns of egg transport having different modes of interaction between muscle and cilia.

Based on our previous studies (Verdugo et al., 1976), we will assume that muscular force in the rabbit ampulla is random. The validity of this assumption, as well as the validity of the formulation itself, will be further verified by comparing predictions of the model with experimental results.

Transport of the ovum will be described as a one-dimensional random walk in a field of external force. The ampulla is represented by a straight line and the eggs are transported from the fimbriated end ($x = x_0$) to the ampullo-isthmic junction (AIJ) ($x = 0$). The motion of the egg can be described by Langevin's equation:

$$m \frac{\mathrm{d}v}{\mathrm{d}t} = -fv + A(t) + F_0 \tag{1}$$

where v is the velocity of the egg. The influence of the surrounding medium on the motion of

the egg has been divided into three variable assignments: first, a frictional force coefficient f (force/unit velocity), which is related to the size, shape, and surface properties of eggs as well as to the surface properties of the luminal wall, the pressure of the wall against the egg, and the viscosity of the luminal fluid; second, a fluctuating force $A(t)$ generated by the muscular activity of the ampulla which, in regard to the direction of the egg movements it produces, will be considered to be random; third, F_0, a continuous and unidirectional force acting on the egg and produced by ciliary activity.

Rather than formulating a random walk analysis of individual eggs, we shall seek a description of ovum transport in terms of the probability distribution of egg position at different times starting from a given initial distribution. The description of this process, based on Langevin's equation, was shown by Chandrasekhar (1943) to have the general form of the Fokker-Planck equation:

$$\frac{\partial P}{\partial t} = D \frac{\partial^2 P}{\partial x^2} + \frac{1}{f} \frac{\partial (F_0 P)}{\partial x} \tag{2}$$

where $P = P(x, t)$ is the probability of finding the egg at time t and position x, and the diffusion coefficient D defined as:

$$D = n \langle \ell^2 \rangle / 2 \tag{3}$$

where n is the frequency and $\langle \ell^2 \rangle$ is the mean square length of the discrete random movements or spurts of the egg in the oviduct.

Ciliary-driven egg transport rate in the ampulla has been measured in the absence of muscle force, and although it can vary among different rabbits, in each individual oviduct it is remarkably uniform (Halbert et al., 1976). Therefore F_0 may be considered as a constant, and Eq. 2 can be rewritten as:

$$\frac{\partial P}{\partial t} = D \frac{\partial^2 P}{\partial x^2} + u \frac{\partial P}{\partial x} \tag{4}$$

where $u = F_0/f$ and corresponds to the average transport velocity.

The boundary conditions for ampullary transport are defined by:

$$P(x, t) \rightarrow \delta(x - x_0) \text{ as } t \rightarrow 0 \tag{5}$$

and

$$D - \frac{\partial P}{\partial x} + uP = 0 \text{ at } x = 0 \text{ for all } t > 0. \tag{6}$$

Eq. 5 describes the initial condition at the ostial end of the ampulla, i.e., at time zero the probability of finding the egg in any location but the ostium is zero since the Dirac delta function $\delta(x - x_0)$ is:

$$\delta(x - x_0) = 0 \text{ if } x \neq x_0 \text{ and } \int_{-\infty}^{\infty} \delta(x) dt = 1. \tag{7}$$

Eq. 6 accounts for the long delay of the egg at the AIJ (i.e., at $x = 0$), and it establishes that when either of the arguments is null the other must also be zero.

In case the first argument in Eq. 6 is null, i.e., the muscle egg-driving force is absent at the AIJ, (i.e., $D = 0$) then, to explain a detention of the egg at this site, the model prescribes that $uP = 0$, and, since P is finite, $u = 0$. Since $u = F_0/f$, then $u = 0$ implies that either the ciliary force is null ($F_0 = 0$) or that the frictional coefficient f is very much increased. Ciliary force could be null because it is absent, because it is cancelled out, or because the viscosity of luminal secretions impair ciliary motions. Although a limited number of species have been studied, absence of ciliated epithelium at the AIJ has not yet been demonstrated in mammals. However, cancellation of ciliary force may indeed exist in the oviduct of some species. For instance, Gaddum-Rosse and Blandau (1973) observed that in rabbits and pigs ciliary activity is pro-uterine in the ampulla and pro-ovarian in the isthmus with, the site of confluence at AIJ. Hormonal-dependent changes of the physical properties of luminal secretions, which could indirectly affect ciliary activity, have also been postulated in the rabbit oviduct (Jansen, 1978). The frictional coefficient f could be increased by the existence of a functional sphincter at the AIJ (Greenwald, 1961; Brundin, 1964; Black and Asdell, 1958); by the presence of edema of the intratubal mucosa (Asdell, 1961; Hodgson, 1978); or by an increase in the viscosity of the luminal secretions.

If the second argument uP in Eq. 6 became null by one or several of the above-mentioned mechanisms, this boundary condition prescribes that the first argument should also be zero. Within the framework of our model this could occur either by inhibition of contractile activity or by a decoupling of muscle contraction and egg movements at the AIJ. In either case the muscle egg-driving force should be absent. According to Eq. 3, this implies that the size (ℓ) and/or the frequency (n) of the pendular motions of the egg be null.

To solve Eq. 4 subject to conditions of Eqs. 5 and 6, we make a transformation of variables:

$$P(x, t) = W(x, t) \exp\left[-\frac{u}{2D}(x - x_0) - \frac{u^2}{4D}t\right]. \tag{8}$$

With this transformation, Eq. 4 is reduced to:

$$\frac{\partial W}{\partial t} = D\frac{\partial^2 W}{\partial x^2} \tag{9}$$

and the boundary conditions are changed to:

$$W(x, t) \rightarrow \delta(x - x_0) \quad \text{as} \quad t \rightarrow 0 \tag{10}$$

$$D\frac{\partial W}{\partial x} + \frac{uW}{2} = 0 \quad \text{at} \quad x = 0 \quad \text{for all} \quad t > 0. \tag{11}$$

The solution to Eq. 9 with boundary conditions 10 and 11 is given in standard treatments of heat conduction (Mathews and Walker, 1964) and the final solution of Eq. 4 takes the form:

$$P(x, t) = \frac{1}{2(\pi Dt)} \frac{1}{2}\left\{\exp\left[-(x - x_0)^2/4Dt\right] + \exp\left[-(x + x_0)^2/4Dt\right]\right.$$

$$\left.\exp\left[-\frac{u}{2D}(x - x_0) - \frac{u^2}{4D}t\right] + \frac{u}{2D}\exp\left(-\frac{u}{D}x\right)E(x')\right\}, \tag{12}$$

where $E(x')$ is defined as:

$$E(x') = 1 - \text{erf}\,(x') = \frac{2}{\pi^{1/2}} \int_{x'}^{\infty} e^{-y^2}\,dy \qquad (13)$$

with $x' = (x + x_0 - ut)/2(Dt)^{1/2}$.

$$(14)$$

If muscle force is random and its interaction with ciliary and frictional force does have the form of Eq. 1, then the probability of finding the ovum at any position along the ampulla at any time after egg transport has been initiated should be predicted by Eq. 12.

EXPERIMENTAL EVIDENCE FOR THE STOCHASTIC MODEL

We have verified the present formulation by comparing the predictions of the stochastic model with measurements of ampullary egg transport in the rabbit. Records of the position of the egg along the rabbit ampulla as a function of time have been published by Verdugo et al. (1976). These data, as well as data from six new experiments, were used to validate the stochastic model.

MATERIALS AND METHODS

Experiments to record directly ovum transport through the ampulla were performed in six New Zealand White rabbits following the procedure introduced by Harper (1961) and developed further by Blandau (1971). Briefly, the animals were laporatomized under 1% halothane anesthesia. The oviduct was exposed and positioned in a small chamber affixed to the abdomen of the rabbit and filled with Hanks' solution thermoregulated at 37°C. Ovulation was induced in the experimental and in the egg-donor rabbits by a single i.v. dose of 100 μg of luteinizing hormone administered 10 h before the experiment. Eggs in cumulus were recuperated by flushing the donor's oviducts. To achieve proper ovum-to-background contrast during the cinematographic recording of ovum transport inside the oviduct of the experimental rabbit, the cumulus egg masses of the donor rabbit were stained with 2% methylene blue Hanks' solution. Motion pictures of the displacements of the stained ova from the ostium to the ampullo-isthmic junction were obtained at an optical magnification of ×2 and a sampling rate of 8 frames/s.

The distance from the ostium to the instantaneous location of the egg along the ampulla was measured and stored every 250 ms from the cinematographic pictures using a standard film digitizer. Computer plots of egg position along the ampulla versus time were then generated from the data stored on magnetic tape.

RESULTS

A typical plot of egg position vs. time is illustrated in the horizontal plane in Fig. 1. Note the oscillations in the x,t plane, corresponding to the characteristic pendular motions of the ovum and the approximately linear relationship of time and distance in the transit of the egg through the ampulla.

Predictions of the stochastic model in terms of the probability of finding the egg in a particular position along the rabbit ampulla at a particular time, $P(x,t)$, were computed from Eq. 12 and compared with the corresponding experimental measurements (see Table I).

According to Eq. 12 the parameters to be computed from the egg transport data to calculate $P(x,t)$ are the diffusion coefficient D, the average transport velocity u, and the
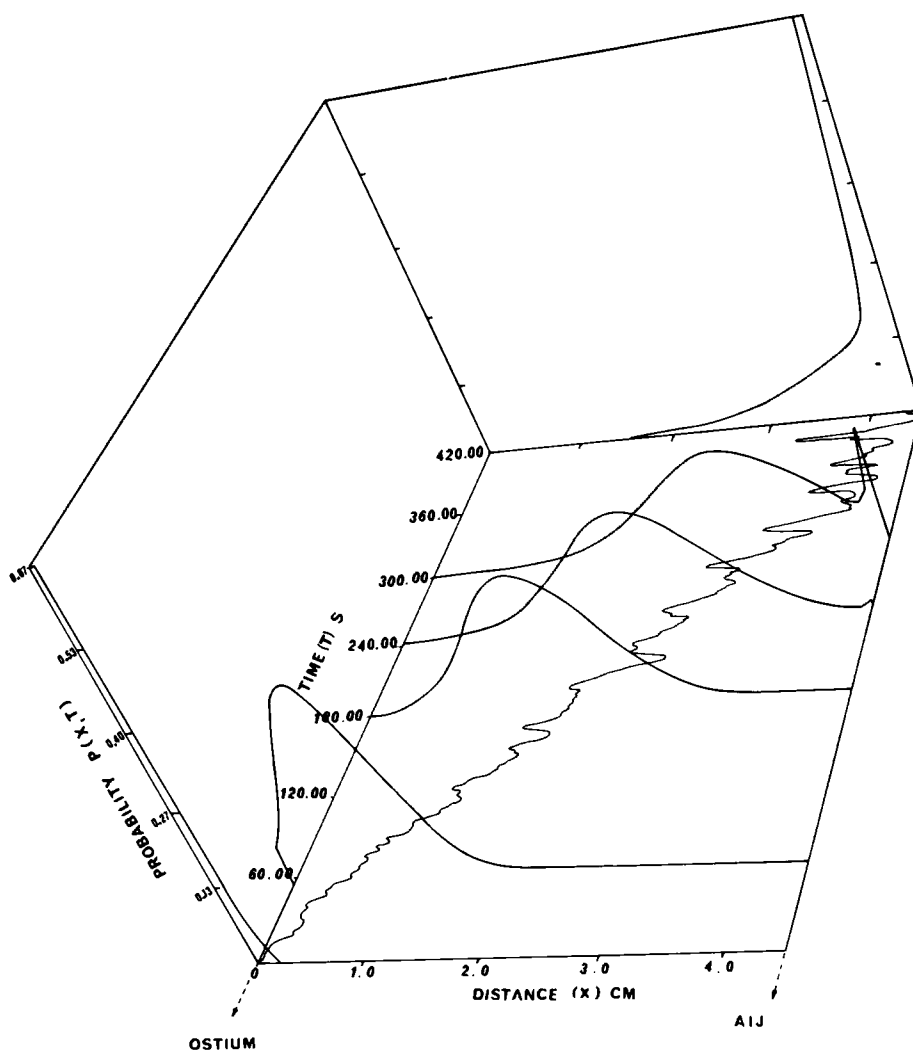
FIGURE 1 The egg position v/r time plot is in the horizontal plane and the vertical plane shows the probability distribution $P(x, t)$ of Eq. 12 along the ampulla at various times during egg transport. If an egg is at the fimbriated end, at the beginning, it appears to be stationary owing to the narrow distribution of $P(x, t_0)$. However, the ciliary activity soon affects the motion, and the peak of the distribution function begins to move toward the ampullo-isthmic junction with a velocity u. Concurrently, the variance of the distribution $P(x, t)$ becomes broader owing to the random motions induced in the egg by the muscle activity. After an extending period of time ($t \gg 0$) the equilibrium distribution is obtained. $P(x, t \gg 0) = (u/D) \exp(-ux/D)$ and the maximum probability is for the egg to be found in the AIJ.

length of ampulla where transport has been measured (see Table I). D can be computed according to Eq. 3 where the mean square length of the discrete pendular movements is:

$$\langle \ell^2 \rangle = \sum \ell_i^2 \, p(\ell_i), \tag{15}$$

and u is simply computed by dividing the transit time by the transit distance. Fig. 1 illustrates the relationship between predictions of the model and the experimental data in a rabbit under

COMPARISON BETWEEN PREDICTIONS OF THE STOCHASTIC MODEL AND EXPERIMENTAL MEASUREMENTS OF EGG TRANSPORT IN THE RABBIT OVIDUCT

Rabbit	Conditions	Transp. distance (from-to)	Transp. time	Av. vel. →	D		Position of the ovum at:							
							60 s	120 s	180 s	240 s	300 s	360 s	420 s	480 s
		cm	s	(cm/s)	(cm²/s)		cm	cm	cm	cm	cm	cm	cm	cm
4148	12 h post LH	1.3–3.4	180	1.1×10^{-2}	8.8×10^{-4}	Exp.	1.9	2.7	3.4					
						Pred.	1.9 ± 0.3	2.5 ± 0.4	3.2 ± 0.5					
4154-1	Estrous	0.9–3.7	540	5.1×10^{-3}	9.0×10^{-4}	Exp.	1.2	1.6	1.7	1.9	2.1	2.7	2.9	3.6
						Pred.	1.2 ± 0.3	1.5 ± 0.4	1.8 ± 0.5	2.4 ± 0.7	2.4 ± 0.7	2.7 ± 0.7	3.1 ± 0.8	3.4 ± 0.8
4154-2	Estrous	0.6–3.1	300	8.4×10^{-3}	7.1×10^{-4}	Exp.	1.1	1.7	2.3	3.1				
						Pred.	1.1 ± 0.3	1.5 ± 0.0	2.5 ± 0.6	3.1 ± 0.6				
4162	12 h post LH	0.0–1.3	240	5.3×10^{-3}	1.6×10^{-3}	Exp.	0.5	0.6	1.1	1.3				
						Pred.	0.3 ± 0.3	0.6 ± 0.5	0.9 ± 0.7	1.3 ± 0.8				
4167	Cl-628	0.0–2.6	300	8.9×10^{-3}	9.5×10^{-4}	Exp.	0.5	0.6	1.4	1.8	2.6			
						Pred.	0.6 ± 0.3	1.1 ± 0.5	1.6 ± 0.5	2.1 ± 0.5	2.7 ± 0.6			
4176	Cl-628	0.7–2.6	180	1.2×10^{-2}	9.2×10^{-4}	Exp.	1.5	2.2	2.7					
						Pred.	1.5 ± 0.3	2.2 ± 0.5	2.9 ± 0.5					
4178	12 hr post LH	1.1–2.6	300	5.1×10^{-3}	7.1×10^{-4}	Exp.	1.4	1.8	2.3	2.4	2.7			
						Pred.	1.4 ± 0.2	1.7 ± 0.3	2.1 ± 0.5	2.3 ± 0.5	2.6 ± 0.6			
4206-1	Estrous	1.7–4.7	420	6.8×10^{-3}	9.5×10^{-4}	Exp.	2.0	2.7	3.4	3.6	3.7	4.1	4.7	
						Pred.	2.2 ± 0.3	2.6 ± 0.4	3.0 ± 0.5	3.4 ± 0.6	3.8 ± 0.7	4.2 ± 0.7	4.7 ± 0.8	
4206-2	Estrous isop.	1.5–5.8	420	1.0×10^{-2}	1.89×10^{-3}	Exp.	1.9	2.8	3.5	4.3	5.0	5.5	5.8	
						Pred.	2.1 ± 0.4	2.7 ± 0.6	3.4 ± 0.7	4.0 ± 0.9	4.6 ± 0.9	5.2 ± 1.0	5.9 ± 1.2	

estrogen dominance. Note the agreement of the predicted position corresponding to the peak value of the probability density of function and the actual location of the egg at different times during transit along the ampulla.

Table I compares the observed position of the egg at several time intervals during ampullary egg transport in eight rabbits with the corresponding position predicted by the stochastic model. Note that although there is considerable variation in transport rate among experiments the agreement of observed and calculated position of the egg is within 7.7 ± 1.3 SEM.

DISCUSSION

The close agreement of predictions of the stochastic model with the experimental data indicate that the ampullary egg transport in the rabbit can indeed be described as a one-dimensional random walk in a field of external force, i.e., that the interaction of random muscle force and nonrandom ciliary force can be well defined by the form and the parameters of Langevin's equation (1).

The leading role of ciliary force in determining the fast ovum transport rate observed in the rabbit ampulla can be easily appreciated if we consider that even if the appropriate boundary conditions exist the ampullary transport driven only by random muscle contractions (without the intervention of ciliary force) should last for ~40 h. This estimation is based on Eq. 19 taking into consideration the length of the ampulla and the actual diffusion coefficient of the egg in the ampulla which can be calculated according to Eq. 3 from our measurement of frequency and magnitude of random egg motions. Therefore, the regulation of egg transport in the rabbit ampulla must be principally dependent upon hormonal or neurohormonal influences affecting ciliary activity. Indications that oviductal cilia might be under hormonal control have been reported in the past (Borell et al., 1957; Rumery and Eddy, 1974; Verdugo

et al., 1976; Critoph and Dennis, 1977; Westrom et al., 1977). However, available evidence is still insufficient to provide even a limited understanding of the physiological mechanisms of regulation of oviductal ciliary activity.

Although, in the particular case of the rabbit, muscular force seems to play a secondary role in determining the ampullary transport rate, there may be other species and/or other segments of the oviduct where contractile activity is the major driving force in the transport of the ovum. The present model indicates two mechanisms for the regulation of ovum transport rate, each dependent upon the control of tubal contractile activity. One, hormonal or neurohormonal influences could derandomize muscle contraction so that they preferentially move the egg in the direction of the uterus. In this regard it has been shown that the probability density function of velocities of a collection of egg movements in the ampulla of rabbits under estrogen withdrawal is skewed in a pro-uterine direction, suggesting a certain degree of derandomization of egg motion (Verdugo et al., 1976). In such conditions ampullary transit time has been observed to be shortened (Boling and Blandau, 1971a,b). Indications that progesterone might derandomize oviductal muscle activity have also been reported by Hodgson and Talo (1978). Two, a truly random pattern of muscle contractions could also change egg transport rate by increasing the spurt size (ℓ) and/or the frequency of pendular displacements (n). For instance, in the rabbit ampulla, ciliary force determines a rather fast ovum transport; however, when the random pendular movements induced by muscle contractions increase in magnitude (ℓ) and/or frequency (n), there exists a finite probability that the egg may arrive even earlier at the AIJ than if it were transported solely by ciliary force. The increase in ℓ or n will increase the magnitude of the diffusion coefficient D. The higher the value of D, the broader the variance and the faster the spreading of the probability distribution $P(x, t)$, i.e., the higher the probability of early arrival of the egg at the AIJ (see Fig. 1). Conversely, the smaller the spurt size, the narrower the probability distribution and the more dependent on ciliary force will be the transport of the egg. At the limit, where the muscular force is not involved in egg transport (e.g., when muscle contractions are pharmacologically inhibited), the fluctuating force $A(t)$ disappears from Eq. 1 and the solution of Langevin's equation is simple:

$$x = x_0 - ut, \tag{16}$$

where u is the egg transport velocity having the same definition as in Eq. 4, that is, F_0/f.

In the special case of random muscular activity without contribution of ciliary force, no unidirectional force acts on the egg and its motion may be described as a one-dimensional random walk with a probability distribution function $P(x, t)$ that satisfies the diffusion equation:

$$\frac{\partial P}{\partial t} = D \frac{\partial^2 P}{\partial x^2}, \tag{17}$$

i.e., the total egg transport time is proportional to the square of the length of the transport distance according to Einstein's relation:

$$\langle (x_0 - x)^2 \rangle = 2Dt \tag{18}$$

A description of purely random ovum transport based on a one-dimensional random walk

has been formulated by Portnow et al. (1977a). Obviously this formulation ignores the role of nonrandom ciliary force in moving the egg. However, its validation was based on measurements of transport time in the rabbit ampulla where it has been demonstrated that ciliary activity is the leading driving force in transporting the egg. In fact, the figures of ovum transport rate reported by Portnow et al. (1977a) are very similar to the rates of ciliary-driven egg transport in the absence of oviductal muscle contractions (Halbert et al., 1976). Because detailed measurements of egg motions were not conducted, the diffusion coefficient was assumed and adjusted for each experiment to fit a quadratic relationship between ovum transport time and transport distance as predicted by Einstein's equation. Closing a circular argument is the conclusion that ampullary transport must be purely random based on the apparent quadratic dependence between transport time and transport distance. However, according to Einstein's equation, the typical figures of diffusion coefficient assumed by Portnow et al. (1977a) ($D = 0.12$ cm^2/s) would imply frequencies or lengths of the egg motions approximately two orders of magnitude larger than those previously found in the rabbit ampulla by Verdugo et al. (1976) and Halbert et al. (1976). Our data does indeed allow to directly estimate the diffusion coefficient of the ovum in the ampulla and indicate that ampullary egg transport in the rabbit cannot be described on the basis of a purely random mechanism (Verdugo et al., 1976).

Nevertheless, the choice of inappropriate supporting evidence should not detract from the heuristic value of the concept put forward by Portnow and his colleagues, i.e., if the appropriate boundary conditions exist, random egg motion produced by tubal muscle contractions can lead to net transport of the ovum. This concept is most relevant since it might serve to describe isthmic transport.

Based on their demonstration of random myoelectric activity, Talo and Hodgson (1978) have proposed that ovum transport in the isthumus must be random. Surprisingly, however, they did not explain the regulation of isthmic ovum transport on the basis of its intrinsic stochastic nature. Instead they considered the rate of ovum transport to be dependent upon the progression toward the uterus of an "active-inactive border" which is postulated to exist in the isthmus. They proposed that once the egg enters the isthmus the AIJ becomes a reflecting barrier. The smooth muscle of the isthmus, inactive during the initial period of egg transport, becomes progressively activated and slowly moves the "active-inactive border" toward the uterus. According to this hypothesis the inactive area would behave as an absorbing barrier and its rate of progression, which is under physiologic control, would regulate the rate of isthmic egg transport (Portnow et al., 1977b).

Although there is some experimental basis for the existence of a progressing active-inactive border in the isthmus in vitro (Talo and Hodgson, 1978), it is not conclusive and it has not been demonstrated in vivo. More importantly, if isthmic egg transport is indeed random, as Talo and Hodgson's (1978) evidence seems to indicate, the dea of an active-inactive border is obviously an unnecessary constraint for explaining the regulation of isthmic transport rate. Admittedly, there might be a double, redundant control for egg transport. However, it is certainly more consistent to explain the mechanism of control of a random phenomenon on the basis of the specific properties of a stochastic process. If isthmic transport is random, the rate of progression of the egg in the isthmus must strictly depend on the diffusion coefficient D and its determinants: the magnitude (ℓ) and the frequency (n) of the pendular egg motions.

Ciliary activity of the ampulla can indeed function as a reflecting barrier for the egg at AIJ, assuming that the uterus would behave as an absorbing barrier, the relationship of ℓ, n, and isthmic transport time can be predicted according to Einstein's relationship as:

$$t = \frac{L^2}{n\langle \ell^2 \rangle}; \quad L = (x_0 - x). \tag{19}$$

The thick wall of the isthmus has inhibited the direct view of egg motion preventing the statistical analysis of isthmic transport. Nevertheless, we can preliminarily verify Einstein's equation to describe isthmic transport by comparing the predicted length of egg pendular motions with the distance of spread of mioelectric activity in the isthmus (Talo and Hodgson, 1978) which has been shown to be correlated with intraluminal movements of ovum surrogates (Hodgson et al., 1977). The graphic illustration of Eq. 19 shown in Fig. 2, was obtained using the following data for the rabbit oviduct: the length of the isthmus is 45 mm; the isthmic transport time is 45–60 h (Harper et al., 1960; Greenwald, 1961; Polidoro et al., 1973; Pauerstein et al., 1974; Hodgson and Pauerstein, 1976); and the frequency of isthmic contractions, which determines the egg motions, is 1–15 contractions/min (Aref and Hafez, 1973). A rather striking feature that can be observed in Fig. 2 is that within the range of frequency of contractions observed in the rabbit isthmus, the predicted magnitude of the random motions of the egg, corresponding to normal isthmic transport time (shaded area), is 0.1–0.8 mm. This is similar to the average values measured in the ampulla of the rabbit by Verdugo et al. (1976) and to the distance of spread of myoelectric activity in the rabbit isthmus observed by Talo and Hodgson (1978). Therefore, predictions based on Einstein's equation (19) strongly suggest that a purely stochastic mechanism can indeed be responsible for isthmic egg transport and that the diffusion coefficient may be approximately similar
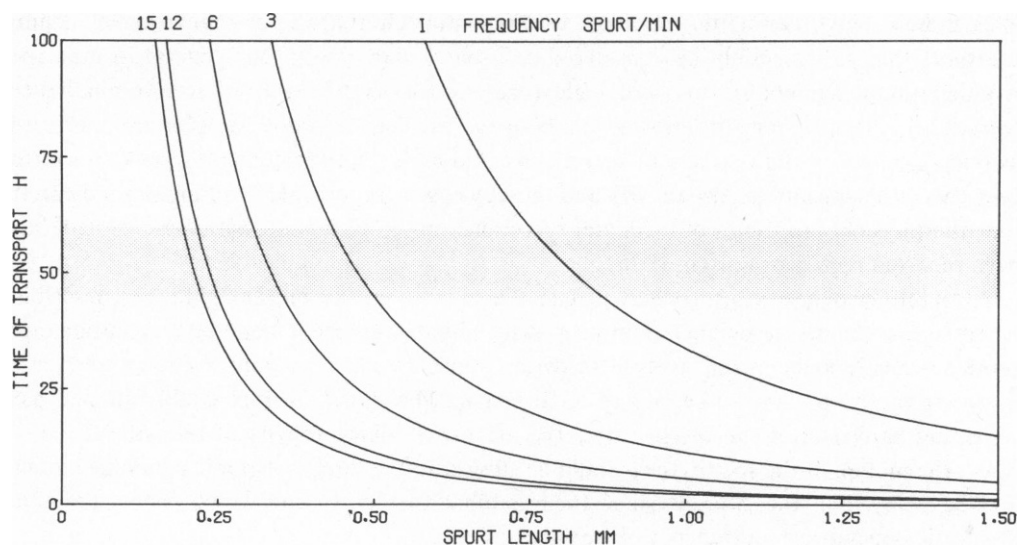

FIGURE 2   Relationship between the size of random pendular motions of the egg in the oviduct (spurts), the frequency of spurts, and isthmic transport time in the rabbit, as predicted by Einstein's equation. Shadowed area corresponds to normal transport time.

throughout the rabbit oviduct. The main difference of transport of the egg in the ampulla and the isthmus would be the bias introduced by ciliary force in the ampulla.

Einstein's equation also identifies the two parameters of random muscle contractions that could control the isthmic transport rate, namely the frequency of contractions and the distance a contraction is propagated along the oviductal wall which, according to Hodgson et al. (1977), determines the magnitude of random egg motions. It can be appreciated from Fig. 2 that small changes in the frequency and/or the magnitude of random egg motions can produce large delays or acceleration of isthmic egg transport, making this a very efficient mechanism for regulating ovum transport rate. Therefore, neurohormonal or pharmacologic influences on egg transport could exert their effect by changing the frequency and/or degree of spatial coupling of oviductal smooth muscle contractions. A predicted mechanism that is in remarkably good agreement with the data of Talo and Hodgson (1978) which indicate that by the time of isthmic egg transport, i.e., 45–68 h after human chorionic gonadotropin (HCG), higher frequency of activity and larger distances of propagation of myoelectric activity can be observed in the rabbit oviduct as compared to controls obtained at 18–24 h after HCG. Also, estrogen treatment at 24 h after HCG produces a slight decrease in the frequency of activity. However, the distance of propagation of myoelectric activity is found increased in the isthmus, which could explain the acceleration of ovum transport observed in these rabbits. Long distances of myoelectric propagation after estrogen treatment in castrated rabbits has also been reported by Brundin and Talo (1972). Finally Hodgson and Talo (1978) have observed that the acceleration of ovum transport induced by progesterone is accompanied by a marked increase in the frequency of myoelectric activity of the oviduct, which is also consistent with the predicted mechanism suggested by the present model.

Although the slow isthmic transport does not seem to be consistent with a mechanism dependent upon long range propogated peristalsis, the idea of a pseudorandom directionally-biased short range peristaltic transport is a potential alternative for regulation of isthmic transport that can certainly be considered as a particular case in our general formulation. Another factor susceptible to physiologic regulation is the viscosity of intraluminal tubal secretions. Although very little is known about the rheological properties of secretions of the oviduct, changes in the viscosity of secretions could affect both frictional forces (f) exerted directly on the egg and ciliary activity and thereby egg transport rate. Preliminary indications that the physical properties of oviductal secretions might be under physiologic control have been reported recently (Jansen, 1978).

Available evidence is insufficient to test the validity of the present model in describing sperm transport in the oviduct. However, with slightly different boundary conditions, the same stochastic mechanism involved in ovum transport could account for the transport of sperm from the uterus to the site of fertilization. The uterine cervix could function as a reflecting barrier after the sperm enters the uterus. If ciliary activity of the isthmus do not affect the motion of the sperm, they would be subject to the random isthmic pendular motions and be delayed in the isthmus since their isthmic transport time would follow the same quadratic dependence on transport distance as the ova.

Overstreet and Cooper (1978) and Overstreet et al. (1978) have recently reported that, as in the ovum, the isthmic transport of the fertilizing sperm is also very slow and sperms tend to accumulate in the middle isthmus. This evidence is, at least qualitatively, in agreement with the prediction of the present model.

Owing to the difficulties involved in conducting detailed measurements of oviductal egg transport along the whole Fallopian tube, the verification of the proposed stochastic model has been restricted to the rabbit ampulla which represents a particular but complex instance in which both ciliary forces and random tubal contractions are involved in ovum transport.

Quantitative evidence is still insufficient to validate fully the stochastic formulation for isthmic egg transport. However, the predictions of our model are consistent with the qualitative evidence available and suggest possible and testable mechanisms of regulation or random isthmic transport as well as the potential mode of action of hormonal and pharmacologic interventions.

Although there has been no attempt to include in this paper all available data or to apply the present stochastic formulation to describe egg transport in species other than the rabbit, it is important to emphasize that, with appropriate constraints, the generic equations of this model still remain valid for all the potential modes of interaction between ciliary force, frictional force, and random or nonrandom muscle contractions in the oviduct. Also, to account for accelerations and delays in egg transport in the different segments of the oviduct, this model predicts several alternatives, only some of which have been discussed in detail here. Others remain to be verified in the future. The proposed model is consistent with previous observations, it can serve as a predictive tool to guide further experimentation and, we hope, it will contribute to a new and more formalized insight into the egg transport process.

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