Prediction of Schistosome Cercarial Shedding with a Physiological-Time Model*

K-L LEE[1] and E R LEWIS[2]

Lee, K-L (Department of Electrical Engineering and Computer Sciences and the Electronics Research Laboratory, University of California, Berkeley, California 94720, USA) and Lewis, E R. Prediction of schistosome cercarial shedding with a physiological-time model. *International Journal of Epidemiology* 1977 **6**: 161–167.
While making longitudinal observations on schistosome cercarial shedding, Pitchford and Visser found that there is an annual fluctuation in the minimum time for cercarial development, which is apparently related to temperature (1). Schistosome control strategy could be designed to take advantage of this fluctuation if it were predictable. Inspired by the successes of physiological time models ('heat-unit models') in predicting life-stage durations of various agricultural pests (2,3), we have developed a model of this type for the schistosomes. This model fits the data of Pitchford and Visser quite well. Coupled with recent temperature history and short term temperature forecast, it could be a useful tool for predicting the onset of cercarial shedding.

I. BASIC PHYSIOLOGICAL-TIME MODEL

Entomologists have for some time recognized the effects of ambient temperature on rates of development of insects in various life stages: several mathematical models to describe the relationship between temperature and development rate have been proposed (3). Perhaps the simplest of these models is based on the assumption that below a certain (threshold) temperature, development does not proceed at all and at higher temperatures the rate of development is directly proportional to the difference between actual ambient temperature and threshold temperature. Integrating this difference over time, therefore, we would obtain the model's prediction of the total progress of development. There are two ways to envisage this integral: (1) as an accumulation of heat, over time, or (2) as an accumulation of development time, with each time increment weighted appropriately with respect to temperature. The first interpretation led to the older label 'heat unit model' and the second to the more recent label 'physiological time model'.

Regardless of its label, the model has been quite successful in predicting development of various insect stages both under controlled laboratory conditions (2) and more recently in the field (4). In the light of this success, we decided to attempt to apply this concept to the development of schistosome cercariae.

Consider a cohort of miracidia that have invaded snails: before the members of this cohort ultimately emerge as cercariae, they must undergo a development process. If all parameters of the larval schistosomes' environment were constant, then one might also expect the maturation time to be relatively constant. Because of the homeostatic mechanisms of the snail host, most of the parameters of the internal milieu are buffered from the external environment and vary little, but the major exception is temperature as the snail is poikilothermic. We make the following assumptions:

1 that the observed variations in maturation time of schistosome larvae in snail hosts are the direct result of variations in ambient temperature patterns;

2 that maturation proceeds only when the ambient temperature exceeds a certain threshold, and when the temperature falls below this threshold the maturation process stops but does not reverse;

3 that when the temperature exceeds threshold, the maturation rate is directly proportional to the difference between the actual ambient temperature and the threshold;

5

4 that maturation must reach a threshold level for cercarial shedding to begin.

Thus we assume that the progress made towards initiation of shedding is directly proportional to a 'physiological time' variable measured in units of degree days. We denote the temperature threshold as β_1, the maturation threshold as β_0, the time of miracidia invasion of snail hosts as time 0. Let

$$T(t) = \text{the temperature at time } t, \qquad (1)$$

$$X(t) = \begin{cases} 1 & \text{if } T(t) \geqslant \beta_1, \\ 0 & \text{otherwise} \end{cases} \qquad (2)$$

$z(t) =$ total maturation accumulated from time 0 to time t, $\qquad (3)$

$x(t) =$ amount of time between 0 and t during which $T \geqslant \beta_1$, $\qquad (4)$

$t_s =$ time of initiation of cercarial shedding. $\qquad (5)$

Then we have

$$x(t) = \int_0^t X(\tau)d\tau, \qquad (6)$$

and

$$\begin{aligned} z(t) &= \int_0^t X(\tau)\,[T(\tau) - \beta_1]d\tau \\ &= \int_0^t X(\tau)T(\tau)d\tau - \beta_1 \int_0^t X(\tau)d\tau \\ &= \int_0^t X(\tau)T(\tau)d\tau - \beta_1 x(t). \end{aligned} \qquad (7)$$

According to our assumptions, when $z(t)$ reaches β_0, the shedding starts. Therefore,

$$\begin{aligned} \beta_0 &= z(t_s) \\ &= \int_0^{t_s} X(\tau)T(\tau)d\tau - \beta_1 x(t_s). \end{aligned} \qquad (8)$$

Let

$$y(t) = \int_0^t X(\tau)T(\tau)d\tau, \qquad (9)$$

then

$$\beta_0 = y(t_s) - \beta_1 x(t_s), \qquad (10)$$

or

$$y(t_s) = \beta_0 + \beta_1 x(t_s). \qquad (11)$$

This, then, is our physiological-time model for schistosome larval stages in snail hosts. It has two parameters, β_0 and β_1. The first step in testing the potential use of this model is to determine how well it can be made to fit existing data by proper choice of the values of these two parameters. If, from available experimental data such as that of Pitchford and Visser, we have the time from snail penetration to initiation of shedding, the temperature history over that time, and an educated guess of the value of β_1, we can obtain $y(t_s)$ and $x(t_s)$. Then we can treat equation (11) as a linear regression model and obtain a least-square estimator, $\hat{\beta}_0$, for β_0. However, in this process a least-square estimator, $\hat{\beta}_1$, for β_1 accompanies $\hat{\beta}_0$ and this $\hat{\beta}_1$ may not be the same as our initial guess of β_1. Then an iterative method can be used to obtain estimates of these threshold values for our model. Let

$\beta_1(0)$ be the initial guess of β_1,
$\hat{\beta}_0(i)$ and $\hat{\beta}_1(i)$ be the least square estimators for β_0 and β_1, respectively in the ith iteration, $i=1,2...,$
n be the number of observations,
x_j be the value of x of the jth observation, $j = 1,2...,n,$
y_j be the value of y of the jth observation, $j = 1,2,...,n,$
x be the vector $[x_1 \, x_2 \, ... \, x_n]^T$,
and y be the vector $[y_1 \, y_2 \, ... \, y_n]^T$.

Note that x and y have to be calculated with a β_1 value given. Also let

$x_j(i)$ be the value of x_j used in the ith iteration, $j = 1,2,...,n,$
$i = 1,2,...,$
$y_j(i)$ be the value of y_j used in the ith iteration, $j = 1,2,...,n,$
$i = 1,2,...,$
$x(i)$ be $[x_1(i) \quad x_2(i) \, ... \, x_n(i)]^T, \quad i = 1,2,...,$
$y(i)$ be $[y_1(i) \quad y_2(i) \, ... \, y_n(i)]^T, \quad i = 1,2,...$

Therefore, we start with an initial guess of $\beta_1(0)$ and obtain $x(1)$, $y(1)$ to be used in the first iteration for obtaining $\hat{\beta}_0(1)$ and $\hat{\beta}_1(1)$. $\hat{\beta}_1(1)$ is then used to obtain $x(2)$, $y(2)$ which are later to be used in the second iteration to get $\hat{\beta}_0(2)$ and $\hat{\beta}_1(2)$, and so on. If this process converges for the data we use, it is stopped when certain preset conditions are met. Different rules can be applied. In the following two examples we stop the iteration when

$$\left. \begin{aligned} \hat{\beta}_0(i) - \hat{\beta}_0(i-1) &\leqslant (1/100)\,\hat{\beta}_0(i-1), \\ \hat{\beta}_1(i) - \hat{\beta}_1(i-1) &\leqslant (1/100)\,\hat{\beta}_1(i-1) \end{aligned} \right\} i > 1 \qquad (12)$$

Notice that if the initial guess of β_1 (i.e., $\beta_1(0)$) and

the first least square estimator of β_1 (i.e., $\hat{\beta}_1(1)$) both are no greater than the minimum observed temperature, then no further iteration is needed.

II. APPLICATION OF THE MODEL TO SCHISTOSOMA MANSONI

In this section, our model is applied to a set of data on the minimum cercarial incubation period of *Schistosoma mansoni* in snails of the species *Biomphalaria pfeifferi* (1). Batches of 30 new snails were exposed every two weeks to *S. mansoni* miracidia and the first cercarial sheddings recorded. We adopt the data for 24 snail cohorts for which corresponding weekly water temperature records are available. The temperature data reproduced in Figure 1 are taken from Figure 2 of reference (1).

We have $n = 24$. Assume that β_1 is any value below $14 \cdot 00°C$, which is the lowest temperature during the entire observation period. Then for each cohort, the $X(t) = 1$ throughout the period from time 0 to time t_s. The calculated x (1) and y(1) are listed in Table I. Based on x(1) and y(1), the least square estimators $\hat{\beta}_0(1)$ and $\hat{\beta}_1(1)$ in equation (11) are

$$\hat{\beta}_0(1) = 460 \cdot 27, \qquad (13)$$

$$\hat{\beta}_1(1) = 14 \cdot 09. \qquad (14)$$

Since

$$\hat{\beta}_1(1) - \hat{\beta}_1(0) = 14 \cdot 09 - 14 \cdot 00$$
$$= \cdot 09$$
$$< (1/100) \, \hat{\beta}_1(0), \qquad (15)$$

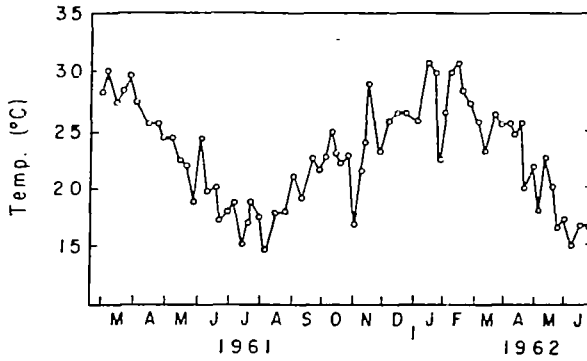we do not need to do any further iteration.

FIG. 1

Weekly water temperature at 10 am in the area where shedding data were taken (reproduced from Fig. 2 of reference 1)
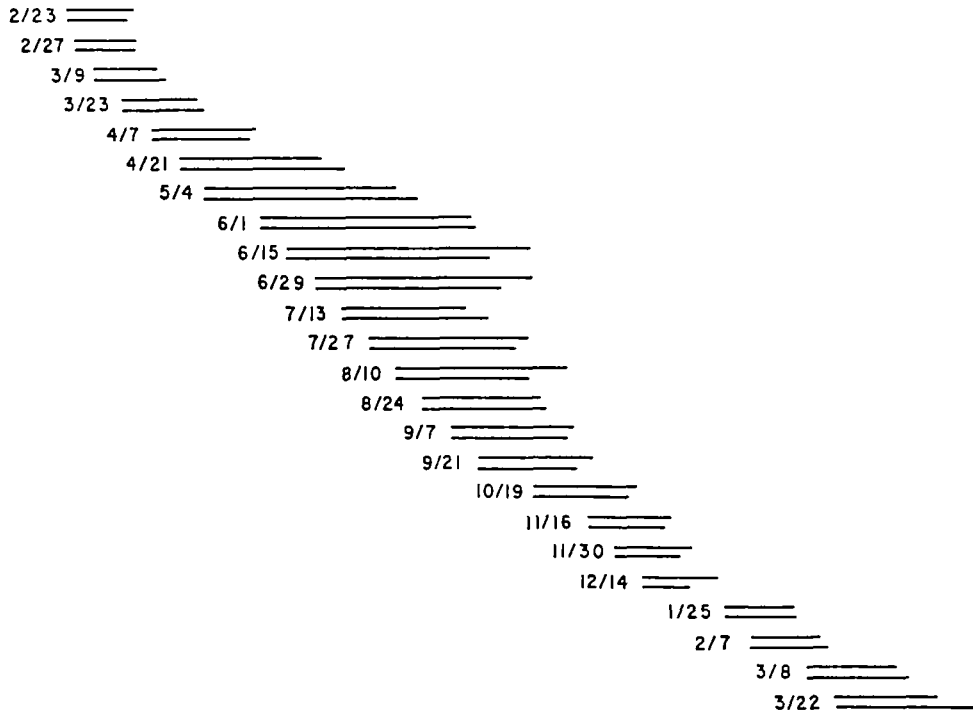

FIG. 2

Observed (upper lines) and predicted (lower lines) minimum incubation periods for *S. mansoni*. Numbers on left give dates of infection for each pair of lines

TABLE I

The values of x(1), y(1) for calibrating our model in the case of S. mansoni

j	x_j(1)	y_j(1)
1	35	991·25
2	31	879·25
3	32	847·00
4	38	965·75
5	58	1440·25
6	73	1442·50
7	98	1802·25
8	109	1960·25
9	124	2242·50
10	113	2063·25
11	75	1402·75
12	82	1655·50
13	89	1763·75
14	61	1307·50
15	63	1360·00
16	60	1319·25
17	54	1279·00
18	43	1127·75
19	39	1063·25
20	39	1215·25
21	35	939·75
22	36	916·25
23	45	889·25
24	53	1091·50

TABLE II

Observed and Predicted Minimum Cercarial Incubation Periods for S. mansoni in B. pfeifferi

Date of Miracidia Entry		Date of Initiation of Shedding observed	predicted
1961:	2/23	3/30	3/27
	2/27	3/30	3/31
	3/9	4/10	4/13
	3/23	5/1	5/4
	4/7	6/5	6/2
	4/21	7/3	7/15
	5/4	8/10	8/21
	6/1	9/18	9/20
	6/15	10/17	9/27
	6/29	10/20	10/2
	7/13	9/26	10/6
	7/27	10/17	10/11
	8/10	11/7	10/16
	8/24	10/24	10/25
	9/7	11/9	11/6
	9/21	11/20	11/11
	10/19	12/12	12/7
	11/16	12/29	12/25
	11/30	1/8/62	1/2/62
	12/14	1/22/62	1/7/62
1962:	1/25	3/1	3/2
	2/7	3/15	3/19
	3/8	4/22	4/29
	3/22	5/14	6/3

We conclude that we can calculate $X(t)$ using $\beta_1 = 14·09$. If $T(t)$ is given, the beginning of cercarial shedding t_s can be calculated by solving

$$460·27 = \int_0^{t_s} X(\tau)T(\tau)d\tau - 14·07x(t_s). \tag{16}$$

The observed minimum incubation periods and the predicted ones based on β_0, β_1 as given in equations (13) and (14) are shown in Table II and Figure 2. The average observed minimum incubation period is 62 days and the root mean square error of prediction is 10 days.

III. APPLICATION OF THE MODEL TO SCHISTOSOMA HAEMATOBIUM

The application of our model to the minimum cercarial incubation period data of *Schistosoma haematobium* (1) is illustrated in this section.

The water temperature data are the same as shown in Figure 1. In the period for which we have temperature data, 22 cohorts of 30 new snails *B. physopsis* were exposed every two weeks to *S. haematobium* miracidia and their minimum cercarial incubation periods have been recorded (1). Now $n = 22$. As in the preceding section, we try a first guess

$$\beta_1(0) = 14·00, \tag{17}$$

and start our iteration. The values for $x(i)$, $y(i)$, = 1,2,3,4,5, are listed in Table III. The obtained $\beta_0(i)$, $\beta_1(i)$, $i = 1,2,3,4,5$, are

$$\beta_0(1) = 420·30, \tag{18}$$
$$\beta_1(1) = 15·73, \tag{19}$$
$$\beta_0(2) = 463·78, \tag{20}$$
$$\beta_1(2) = 14·89, \tag{21}$$
$$\beta_0(3) = 436·00, \tag{22}$$
$$\beta_1(3) = 15·42, \tag{23}$$
$$\beta_0(4) = 448·34, \tag{24}$$
$$\beta_1(4) = 15·19, \tag{25}$$
$$\beta_0(5) = 442·57, \tag{26}$$
$$\beta_1(5) = 15·30. \tag{27}$$

Note that for this set of data, the iteration method does converge to give us

$$\beta_1(4) - \beta_1(3) = ·23$$
$$> (1/100)\beta_1(3), \tag{28}$$

and

$$\beta_1(5) - \beta_1(4) = ·11$$
$$< (1/100)\beta_1(4). \tag{29}$$

TABLE III

The values of x(i), y(i), i = 1,2,3,4,5, for calibrating our model in the case of S. haematobium

j	$x_j(1)$	$y_j(1)$	$x_j(2)$	$y_j(2)$	$x_j(3)$	$y_j(3)$	$x_j(4)$	$y_j(4)$	$x_j(5)$	$y_j(5)$
1	174	3416·00	162	3151·00	169	3308·00	166	3235·00	167·50	3268·50
2	158	3046·50	146	2781·75	153	2938·50	150	2871·50	151·50	2905·00
3	145	2727·00	133	2462·00	140	2619·00	137	2552·00	138·50	2585·50
4	126	2175·25	114	1910·25	121	2067·25	118	2000·25	119·50	2033·75
5	118	2153·75	106	1888·75	113	2045·75	110	1978·75	115·50	2012·25
6	141	2513·50	129	2248·50	136	2405·50	133	2338·50	134·50	2372·00
7	140	2533·00	128	2268·00	135	2425·00	132	2358·00	133·50	2391·50
8	81	1623·75	81	1623·75	81	1623·75	81	1623·75	81·00	1623·75
9	70	1503·00	70	1503·00	70	1503·00	70	1503·00	70·00	1503·00
10	68	1510·25	68	1510·25	68	1510·25	68	1510·25	68·00	1510·25
11	61	1425·25	61	1425·25	61	1425·25	61	1425·25	61·00	1425·25
12	61	1457·50	61	1457·50	61	1457·50	61	1457·50	61·00	1457·50
13	57	1469·00	57	1469·00	57	1469·00	57	1469·00	57·00	1469·00
14	49	1277·25	49	1277·25	49	1277·25	49	1277·25	49·00	1277·25
15	46	1224·75	46	1224·75	46	1224·75	46	1224·75	46·00	1224·75
16	42	1270·75	42	1270·75	42	1270·75	42	1270·75	42·00	1270·75
17	49	1280·75	49	1280·75	49	1280·75	49	1280·75	49·00	1280·75
18	47	1169·00	47	1169·00	47	1169·00	47	1169·00	47·00	1169·00
19	48	1169·00	48	1169·00	48	1169·00	48	1169·00	48·00	1169·00
20	49	969·00	49	969·00	49	969·00	49	969·00	49·00	969·00
21	60	1208·25	60	1208·25	60	1208·25	60	1208·25	60·00	1208·25
22	63	1266·75	63	1266·75	63	1266·75	63	1266·75	63·00	1266·75

According to our stopping rule, we take

$$\beta_1 = \beta_1(5)$$
$$= 15·30, \tag{30}$$

and

$$\beta_0 = \beta_0(5)$$
$$= 442·57. \tag{31}$$

Thus, if $T(t)$ is given, t_s for *S. haematobium* can be calculated by solving

$$442·57 = \int_0^{t_s} X(\tau)T(\tau)d\tau - 15·30\ x(t_s). \tag{32}$$

The observed minimum incubation periods and the predicted ones with β_0, β_1 as given in equations (31) and (30) are shown in Table IV and Figure 3. The average observed minimum incubation period is 90 days and the root mean square error of prediction is 24 days. Eighty-one per cent of the total square error is that of the first cohort.

Comparing equations (32) and (16), we notice that for *S. haematobium* the temperature threshold is slightly higher and the maturation threshold slightly lower than for *S. mansoni*.

IV. DISCUSSION

At first glance, Figures 2 and 3 indicate a reasonably good overall fit of our adaptation of the physio-logical-time model to cercarial development. The standard objective measure, root mean square

TABLE IV

Observed and Predicted Minimum Cercarial Incubation Periods for S. haematobium *in* B. physopsis

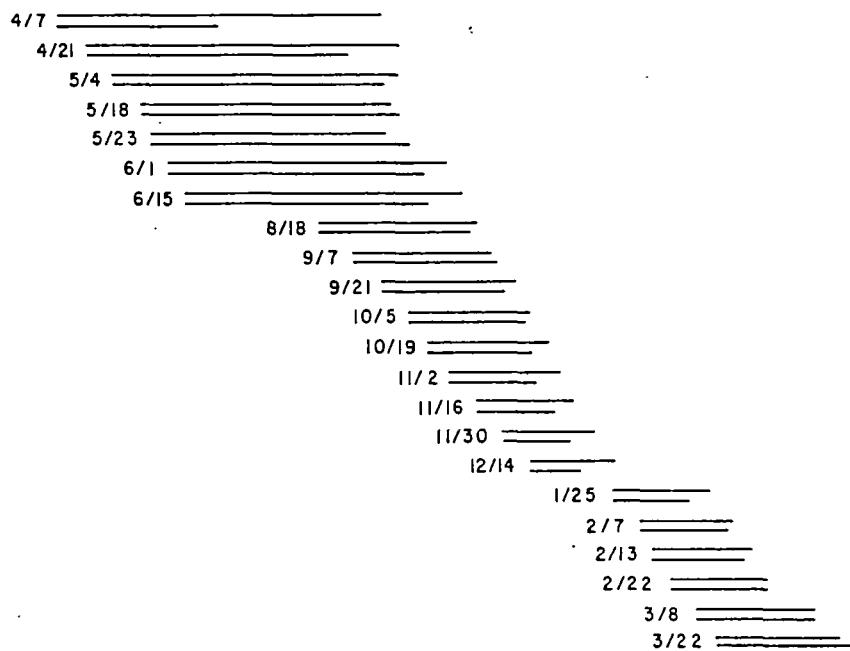| Date of Miracidia Entry		Date of Initiation of Shedding observed	predicted
1961:	4/7	9/28	6/20
	4/21	9/26	8/30
	5/4	9/26	9/17
	5/18	9/21	9/26
	5/23	9/18	10/1
	6/1	10/20	10/8
	6/15	11/2	10/15
	8/18	11/7	11/4
	9/7	11/16	11/19
	9/21	11/28	11/21
	10/5	12/5	12/3
	10/19	12/19	12/11
	11/2	12/29	12/17
	11/16	1/4/62	12/27
	11/30	1/15/62	1/3/62
	12/14	1/25/62	1/7/62
1962:	1/25	3/15	3/4
	2/7	3/26	3/23
	2/13	4/2	3/31
	2/22	4/12	4/13
	3/8	5/7	5/7
	3/22	5/24	

FIG. 3

Observed (upper lines) and predicted (lower lines) minimum incubation periods for *S. haematobium*. Numbers on left give dates of infection for each pair of lines

(rms) error, confirms this subjective conclusion. In the case of *S. mansoni*, the rms error is 16 per cent of the mean observed value, while in the case of *S. haematobium* the rms error is 27 per cent of the mean observed value. By its very nature, rms error places disproportionate emphasis on large errors. For example, if the single entry corresponding to 4/7 in Figure 3 is removed, the rms error for *S. haematobium* is reduced from 27 per cent of the mean to 10 per cent of the mean. Examining the large error entries for both *S. haematobium* and *S. mansoni*, one finds that with the exception of that one 4/7 entry, the errors follow an interesting pattern: the model tends to overestimate minimum incubation time when incubation begins in a period of warm ambient temperatures, followed by a period of cold ambient temperatures; and it tends to underestimate minimum incubation time when incubation begins in a period of cold ambient temperatures, followed by a period of warm ambient temperatures. This may indicate that temperature is more important during early phases of development than during later phases. However, if we tried to include such effects in our model, the already large error in the 4/7 entry of Figure 3 would be further increased. It is interesting that the data for the 4/7 entry were taken by Pitchford and Visser for a single shedding snail, whereas the data for most entries were taken for at least ten

shedding snails. Therefore, it is possible that the 4/7 entry data is anomalous.

V. CONCLUSION

Bearing the objective of control in mind, instead of modelling the entire transmission dynamics of schistosomiasis (see [5] to [10]) which would require a large-scale effort in field work to determine the parameters, we chose to model a single phase of the life cycle, where good data were already available. The simple model presented here is not intended to interpret the mechanisms underlying sporocyst development, but merely to predict the beginning of cercarial shedding by snails exposed to schistosome miracidia. Coupled with knowledge of the approximate size of a snail population, such predictions could be useful in the timing of control measures (for example one might wish to apply molluscicides just prior to a predicted large emergence of cercariae).

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