

M. V. JOHNS JR.

APPLIED MATHEMATICS AND STATISTICS LABORATORIES

**STANFORD UNIVERSITY
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**A STOCHASTIC PROCESS ARISING IN THE STUDY OF
MUSCULAR CONTRACTION**

By

SAMUEL W. GREENHOUSE

TECHNICAL REPORT NO. 66

December 5, 1960

PREPARED UNDER CONTRACT Nonr-225(52)

(NR-342-022)

FOR

OFFICE OF NAVAL RESEARCH



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This work was sponsored by the Army, Navy, and Air Force through the Joint Services Advisory Group for Research Groups in Applied Mathematics and Statistics by Contract No. Nonr-225(52)(NR 342-022).

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A STOCHASTIC PROCESS ARISING IN THE STUDY OF MUSCULAR CONTRACTION

Samuel W. Greenhouse

National Institute of Mental Health
and Stanford University

1. Introduction.

Assume two parallel line segments of indefinite length, one of which is fixed and the other of which is movable, moving in a linear direction, parallel to the fixed line. Along the fixed line there are special points equally spaced which we shall denote as positions. Similarly, on the moving line, there exist equally spaced points which we denote as sites. A site may be in either of two states which we refer to as vacant or filled. After a site's initial state, which is determined, it can change states only after interactions with the positions along the fixed line in the following manner. A site which is vacant can become filled at certain positions. Call these "load" positions. Similarly, a site which is filled can become vacant at the remaining positions. We denote these as "release" positions. We assume an arbitrary fixed starting position on the fixed line with the positions numbered consecutively beyond the starting position and, further, the release and load positions alternate so that the odd numbered positions are release positions and the even numbered ones are load positions. Then, under certain assumptions stated in the next section, the question posed is the probability a site will be filled (or vacant) after a transit of n positions. The model will then be extended to the case where a site can be in any one of $(m + 1)$ states and the analogous question posed is the probability the site will be empty, filled or

in any arbitrary state j after a transit of n positions.

The model given above is related to the following theory concerning the mechanism of muscular contraction as discussed by Podolsky [1]. A muscle fibril, as seen under the electron microscope, consists of alternating thick and thin filaments. It is assumed that sites exist along the two kinds of filaments at which certain chemical interactions occur at the molecular level. The sites on the thin filaments are capable of binding certain molecules and when a site containing the molecule approaches a site on the thick filament an interaction (splitting off of the molecule) may or may not take place.

Observations on the living muscle suggest that during shortening there is relative motion of the two filaments. In our model, we have introduced an idealization by assuming that only the thin filament moves (the moving line) and that the thick filament is rigid (the fixed line). Further, Podolsky assumes that the positions on the thick filament are only release positions and that the site on the thin filament picks up (becomes filled) a molecule from the medium between the two filaments at any point between two positions. For simplicity, we have placed this binding action at a fixed point between two positions and also call this point a position.

2. Assumptions and Notation.

Letting "event" refer to either the occurrence or non-occurrence of an interaction, we make the following assumptions with regard to the process:

- (a) an event between a site and a position is independent of any previous events involving that site and position,
- (b) only one event can occur between a specific site and a specific position,
- (c) the moving line moves with uniform velocity past the fixed line,
- (d) a filled site becomes vacant at a release position with a constant probability which is the same for all release positions; similarly, a vacant site becomes filled at a load position with a constant probability which is the same for all load positions.

Assumptions (c) and (d) deviate from the real situation in the muscular contraction problem in that during shortening a site on the thin filament moves with a varying velocity. The probability of an interaction between a site and a position will clearly be greatly affected by the speed with which a site moves past a position: the slower the speed the greater the probability of an interaction. Hence, a solution based on assumption (d) can only be a first approximation to the question posed in the muscle problem. A more realistic assumption would postulate the probability of an interaction between site and position as a function of speed or time.

We let S represent the state of a site, S_0 being the state of the site when it is vacant and S_1 when it is filled. If

$$S_i \rightarrow S_j/n \quad i, j = 0, 1; \quad n = 1, 2, \dots, (2r-1), 2r, \dots$$

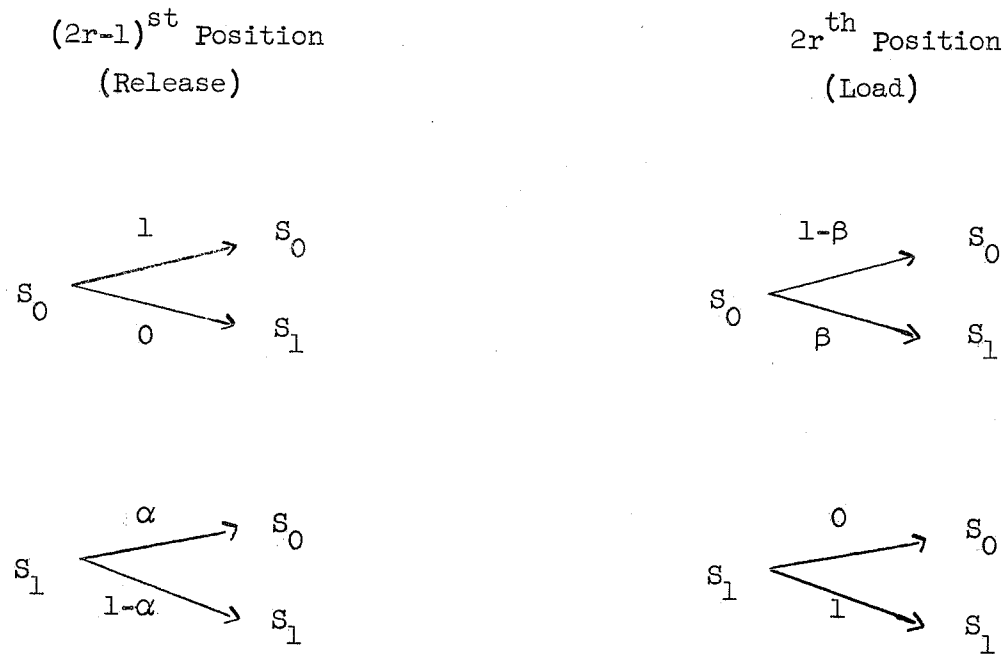
represents the transition of a site from state i to j at the n^{th} position and recalling that an odd position is a release position and an even position is a load position we let

$$\begin{aligned} \alpha &= \Pr(S_1 \rightarrow S_0 / (2r - 1)) \\ 1 - \alpha &= \Pr(S_1 \rightarrow S_1 / (2r - 1)) \\ 0 &= \Pr(S_0 \rightarrow S_1 / (2r - 1)) \\ 1 &= \Pr(S_0 \rightarrow S_0 / (2r - 1)) \\ \beta &= \Pr(S_0 \rightarrow S_1 / 2r) \\ 1 - \beta &= \Pr(S_0 \rightarrow S_0 / 2r) \\ 0 &= \Pr(S_1 \rightarrow S_0 / 2r) \\ 1 &= \Pr(S_1 \rightarrow S_1 / 2r) \\ P_n &= \Pr(S = S_1 / n) \\ 1 - P_n &= \Pr(S = S_0 / n) . \end{aligned}$$

We seek a solution for P_n , the probability the site will be filled at the end of the n^{th} position.

3. Solution Through Difference Equations

The branching process can be illustrated as follows:



We write at once the two joint difference equations

$$(1) \quad P_{2r} = P_{2r-1} + \beta(1 - P_{2r-1}) = \beta + (1 - \beta) P_{2r-1}$$

$$(2) \quad P_{2r-1} = (1 - \alpha) P_{2r-2}$$

from which we obtain the following second order difference equations

$$(3) \quad P_{2r} = \beta + (1 - \alpha)(1 - \beta) P_{2r-2}$$

$$(4) \quad P_{2r-1} = \beta(1 - \alpha) + (1 - \alpha)(1 - \beta) P_{2r-3}$$

The standard solution of (3) and (4) gives respectively

$$(5) \quad P_{2r} = [(1 - \alpha)(1 - \beta)]^r P_0 + \beta \frac{1 - [(1 - \alpha)(1 - \beta)]^r}{1 - (1 - \alpha)(1 - \beta)},$$

$r = 1, 2, \dots$

and

$$(6) \quad P_{2r-1} = [(1 - \alpha)(1 - \beta)]^{r-1} P_1 + \beta(1 - \alpha) \frac{1 - [(1 - \alpha)(1 - \beta)]^{r-1}}{1 - (1 - \alpha)(1 - \beta)}$$
$$= (1 - \alpha) [(1 - \alpha)(1 - \beta)]^{r-1} P_0 + \beta(1 - \alpha) \frac{1 - [(1 - \alpha)(1 - \beta)]^{r-1}}{1 - (1 - \alpha)(1 - \beta)}$$

$r = 1, 2, \dots$

Thus, if the site starts in state S_1 , the boundary condition is $P_0 = 1$

and

$$(7) \quad P_n = [(1 - \alpha)(1 - \beta)]^{n/2} + \beta \frac{1 - [(1 - \alpha)(1 - \beta)]^{n/2}}{1 - (1 - \alpha)(1 - \beta)}$$

$n = 0, 2, 4, \dots$

or

$$(8) \quad P_n = (1 - \alpha) [(1 - \alpha)(1 - \beta)]^{(n-1)/2} + \beta(1 - \alpha) \frac{1 - [(1 - \alpha)(1 - \beta)]^{(n-1)/2}}{1 - (1 - \alpha)(1 - \beta)}$$

$n = 1, 3, 5, \dots$

If the site starts in state S_0 , so that $P_0 = 0$, we have

$$(9) \quad P_n = \beta \frac{1 - [(1 - \alpha)(1 - \beta)]^{n/2}}{1 - (1 - \alpha)(1 - \beta)} \quad n = 0, 2, 4, \dots$$

or

$$(10) \quad P_n = \beta(1 - \alpha) \frac{1 - [(1 - \alpha)(1 - \beta)]^{(n-1)/2}}{1 - (1 - \alpha)(1 - \beta)} \quad n = 1, 3, 5, \dots$$

4. Solution Through Transition Matrices

It is of interest to obtain the solution to this problem involving only dichotomous states of a site using transition matrices. This method can be employed to solve the more general problem.

From the branching process given previously, we obtain the matrix of transition probabilities for the state of a site as it passes an odd position to be

State before (2r-1) st position	State after S ₀	(2r - 1) st position S ₁
S ₀	1	0
S ₁	α	1-α

and the transition matrix as the site passes an even position to be

State before 2r th position	State after S ₀	2r th position S ₁
S ₀	1-β	β
S ₁	0	1

Denote the transpose of the above matrices by \underline{A} and \underline{B} respectively,
i.e.,

$$\underline{A} = \begin{pmatrix} 1 & \alpha \\ 0 & 1-\alpha \end{pmatrix}$$

and

$$\underline{B} = \begin{pmatrix} 1-\beta & 0 \\ \beta & 1 \end{pmatrix}$$

Let $p_{j,n} = \Pr(S = S_j/n)$, $j = 0, 1$ and $\underline{P}(n) = (p_{0,n}, p_{1,n})$, a row vector of probabilities of the two possible states of a site at the end of the n^{th} position. Then

$$\begin{aligned}\underline{P}(2r) &= \underline{B} \underline{P}(2r-1) \\ \underline{P}(2r-1) &= \underline{A} \underline{P}(2r-2) \quad r = 1, 2, \dots\end{aligned}$$

Hence for n even,

$$\begin{aligned}(11) \quad \underline{P}(n) &= \underline{B} \underline{A} \underline{P}(n-2) \\ &= (\underline{B} \underline{A})^{n/2} \underline{P}(0)\end{aligned}$$

Since

$$\underline{B} \underline{A} = \begin{pmatrix} 1-\beta & \alpha(1-\beta) \\ \beta & 1 - \alpha(1-\beta) \end{pmatrix},$$

we have

$$\begin{pmatrix} p_{0,n} \\ p_{1,n} \end{pmatrix} = \begin{pmatrix} 1-\beta & \alpha(1-\beta) \\ \beta & 1 - \alpha(1-\beta) \end{pmatrix}^{n/2} \begin{pmatrix} p_{0,0} \\ p_{1,0} \end{pmatrix}$$

$n = 0, 2, 4, \dots,$

where $p_{0,0}$ and $p_{0,1}$ are the initial conditions of the process. If the site starts filled, $p_{0,0} = 0$ and $p_{1,0} = 1$; if it starts empty $p_{0,0} = 1$ and $p_{1,0} = 0$.

For n odd, we get

$$(12) \quad \begin{aligned} \underline{P}(n) &= \underline{AB} \underline{P}(n-2) \\ &= (\underline{AB})^{(n-1)/2} \underline{P}(1) \end{aligned}$$

which yields

$$\begin{pmatrix} p_{0,n} \\ p_{1,n} \end{pmatrix} = \begin{pmatrix} 1 - \beta(1-\alpha) & \alpha \\ \beta(1-\alpha) & 1-\alpha \end{pmatrix}^{(n-1)/2} \begin{pmatrix} p_{0,1} \\ p_{1,1} \end{pmatrix}$$

$$n = 1, 3, 5, \dots,$$

where $p_{0,1} = \alpha$ and $p_{1,1} = 1 - \alpha$ if the site starts filled, and $p_{0,1} = 1, p_{1,1} = 0$ if the site starts empty.

5. Generalization

We extend the problem to the case where each site can be in any one of $m + 1$ states S_0, S_1, \dots, S_m . When a site in state S_i ($i = 0, 1, \dots, m$) on the moving line encounters an odd (release) position on the fixed line segment, any number $(i-j)$ ($j = 0, 1, \dots, i$)

of interactions can occur resulting in the site changing from state S_i to S_j . Similarly, when a site in state S_i ($i = 0, 1, \dots, m$) encounters an even (load) position on the fixed line segment, any number $(j-i)$ ($j = i, i+1, \dots, m$) of interactions can occur resulting in the site changing from state S_i to S_j . It is assumed that the number of interactions occurring at the juxtaposition of a site and a position has a binomial distribution with parameter α at a release position and parameter β at a load position.

We now let

$$p_{i,n} = \Pr(S = S_i/n) \quad i = 0, 1, \dots, m$$

and

$$\underline{P}_{m,n} = (p_{0,n}, p_{1,n}, \dots, p_{m,n})'$$

be an $(m + 1) \times 1$ column vector. In general, we desire to determine any component of $\underline{P}_{m,n}$ although there may be some particular interest associated with $p_{0,n}$ or $p_{m,n}$, the probabilities the site is empty or filled, respectively, as the site has moved past n positions.

Since we assume the number of interactions is a binomial variate, we may then write for the transition probability at an odd position

$$\begin{aligned} \Pr(S_i \rightarrow S_j/2r - 1) &= \binom{i}{i-j} \alpha^{i-j} (1 - \alpha)^j \\ &= b_{i, i-j}(\alpha) && \text{for } j \leq i, \\ \Pr(S_i \rightarrow S_j/2r - 1) &= 0, && \text{for } j > i, \\ &&& (i = 0, 1, \dots, m; j = 0, 1, \dots, i) \end{aligned}$$

and for the transition probability at an even position,

$$\begin{aligned} \Pr(S_i \rightarrow S_j/2r) &= \binom{m-i}{j-i} \beta^{j-i} (1 - \beta)^{m-j} \\ &= b_{m-i, j-i}(\beta) && \text{for } j \geq i, \\ \Pr(S_i \rightarrow S_j/2r) &= 0 && \text{for } j < i, \\ &&& (i = 0, 1, \dots, m; j = i, i+1, \dots, m). \end{aligned}$$

Then the transition matrix at an odd position is

	S_0	\dots	S_j	\dots	S_i	\dots	S_m
S_0	1	\dots	0	\dots	0	\dots	0
\vdots	\vdots		\vdots		\vdots		\vdots
S_i	$b_{i,i}(\alpha)$	\dots	$b_{i,i-j}(\alpha)$	\dots	$b_{i,0}(\alpha)$	\dots	0
\vdots	\vdots		\vdots		\vdots		\vdots
S_m	$b_{m,m}(\alpha)$	\dots	$b_{m,m-j}(\alpha)$	\dots	$b_{m,m-i}(\alpha)$	\dots	$b_{m,0}(\alpha)$

where $\sum_{j=0}^i b_{i,i-j}(\alpha) = 1$. Denote this matrix by A' , the prime representing the transpose.

The transition matrix at an even position is

	S_0	...	S_i	...	S_j	...	S_m
S_0	$b_{m,0}(\beta)$...	$b_{m,i}(\beta)$...	$b_{m,j}(\beta)$...	$b_{m,m}(\beta)$
\vdots	\vdots		\vdots		\vdots		\vdots
S_i	0	...	$b_{m-i,0}(\beta)$...	$b_{m-i,j-i}(\beta)$...	$b_{m-i,m-i}(\beta)$
\vdots	\vdots		\vdots		\vdots		\vdots
S_m	0	...	0	...	0	...	1

where $\sum_{j=i}^m b_{m-i,j-i}(\beta) = 1$. Denote this matrix by B' .

We then have

$$P_{\mathbb{M}}(2r) = B P_{\mathbb{M}}(2r - 1)$$

and

$$P_{\mathbb{M}}(2r - 1) = A P_{\mathbb{M}}(2r - 2)$$

so that

$$\begin{aligned} \underline{P}_{\underline{m}}(2r) &= \underline{BA} \underline{P}_{\underline{m}}(2r-2) = (\underline{BA})^2 \underline{P}_{\underline{m}}(2r-4) \\ &= (\underline{BA})^{(2r)/2} \underline{P}_{\underline{m}}(0) . \end{aligned}$$

Similarly,

$$\begin{aligned} \underline{P}_{\underline{m}}(2r-1) &= \underline{AB} \underline{P}_{\underline{m}}(2r-3) = (\underline{AB})^2 \underline{P}_{\underline{m}}(2r-5) \\ &= (\underline{AB})^{(2r-1)/2} \underline{P}_{\underline{m}}(1) \\ &= (\underline{AB})^{(2r-1)} \underline{A} \underline{P}_{\underline{m}}(0) . \end{aligned}$$

Therefore,

$$(13) \quad \underline{P}_{\underline{m}}(n) = (\underline{BA})^{n/2} \underline{P}_{\underline{m}}(0) , \quad n = 0, 2, 4, \dots ,$$

and

$$(14) \quad \underline{P}_{\underline{m}}(n) = (\underline{AB})^{(n-1)/2} \underline{A} \underline{P}_{\underline{m}}(0) , \quad n = 1, 3, 5, \dots .$$

$\underline{P}_{\underline{m}}(0)$ is the vector whose components $\{p_{i,0}\}$ ($i = 0, 1, \dots, m$) represent the initial conditions. Of interest, are the cases where $p_{m,0} = 1, p_{i,0} = 0, i \neq m$, or where $p_{0,0} = 1, p_{i,0} = 0, i \neq 0$. The former case holds when the site starts in state S_m , i.e. it is filled, the latter case represents the situation where the site starts in state S_0 , i.e. it is empty.

6. Estimation of Parameters in the Simple Case.

If α and β are known then clearly the probability that a site will be either empty or filled at any position n is immediately determined by equations (7)-(10) (or (11)-(12)) in the special case. Likewise the probability that a site is in any state S_0 to S_m is determined by (13)-(14) in the general case. If a fixed number of sites in known starting states are observed at the end of a transit past n positions, then the set of proportions, $\{p_{i,n}\}$, $i = 0, 1, \dots, m$, of sites observed to be in state i are random variables having a joint multinomial distribution or a binomial distribution when $m = 1$. The statistical problems might then be in testing the binomial model.

Of greater interest is the case where α and β are unknown. We consider the problem of estimating α and β only in the special case where the possible states of the site are dichotomous so that we have solutions in closed form as given by equations (7)-(10). We illustrate the procedure by employing equation (7), similar techniques being applicable to the other forms.

In (7), let $\theta = (1 - \alpha)(1 - \beta)$ to obtain

$$(15) \quad P_n = \theta^{n/2} + \beta \frac{1 - \theta^{n/2}}{1 - \theta}, \quad n = 0, 2, 4, \dots; \quad 0 < \theta < 1.$$

Now $\lim_{n \rightarrow \infty} P_n = \beta/(1 - \theta)$. Let N be large enough so that we may write to a given degree of accuracy

$$(16) \quad P_N = \beta/(1 - \theta).$$

Then

$$(17) \quad P_n = \theta^{n/2} + P_N(1 - \theta^{n/2})$$

yielding

$$(18) \quad \theta^{n/2} = \frac{P_n - P_N}{1 - P_N}$$

and hence

$$(19) \quad \theta = \left[\frac{P_n - P_N}{1 - P_N} \right]^{2/n}$$

Let u and v be two independent estimates of P_n and P_N respectively.

Then an estimate of θ is

$$(20) \quad \hat{\theta} = \left[\frac{u - v}{1 - v} \right]^{2/n}$$

From (16), and the definition of θ , we get

$$(21) \quad \hat{\beta} = (1 - \hat{\theta}) v$$

and

$$(22) \quad \hat{\alpha} = 1 - \frac{\hat{\theta}}{1 - \hat{\beta}}$$

If $n = 2$, that is, u is observed at the second position on the fixed line, these estimates become

$$(23) \quad \hat{\theta} = \frac{u - v}{1 - v}$$

$$(24) \quad \hat{\beta} = \frac{1 - u}{1 - v} v$$

$$(25) \quad \hat{\alpha} = \frac{(1-u)(1-v)}{1 - 2v + uv}$$

The observables u and v can be obtained in the following manner. Consider starting with m sites all in state S_1 (since we are using (7) which is obtained with this initial condition). Then if the states of each site are noted at a selected n^{th} position, u is the proportion of sites observed to be in state S_1 . Repeat this with another set of sites and now if the state of each these sites are noted at a large distance along the fixed line from the starting position so that N is large enough for the approximation (16) to take hold, v will be the proportion of sites in S_1 at the N^{th} position. Thus u and v are independent, binomial variables with expectations P_n and P_N and variances $P_n(1 - P_n)/m(n)$ and $P_N(1 - P_N)/m(N)$ respectively.

If the number of sites involved in the experiments, $m(n)$ and $m(N)$, are large, then we may obtain an estimate of the variance of $\hat{\theta}$ by the usual Taylor series approximation. This gives

$$\hat{V}(\hat{\theta}) = \frac{4}{n^2 \hat{\theta}^{(n-2)} (1 - v)^2} \left(\hat{\sigma}_u^2 + \frac{(1 - u)^2}{(1 - v)^2} \hat{\sigma}_v^2 \right)$$

The estimates of variance of $\hat{\alpha}$ and $\hat{\beta}$ are more difficult to obtain for general values of n because of the covariance between v and $\hat{\theta}$ and between $\hat{\beta}$ and $\hat{\theta}$. However, for $n = 2$, the estimates $\hat{\alpha}$ and $\hat{\beta}$ are functions only of u and v , and estimates of their variances are

$$\hat{\sigma}_{\hat{\beta}}^2 = \frac{1}{(1-v)^2} \left(v^2 \hat{\sigma}_u^2 + \frac{(1-u)^2}{(1-v)^2} \hat{\sigma}_v^2 \right)$$

and

$$\hat{\sigma}_{\hat{\alpha}}^2 = \frac{1}{(1-2v+uv)^4} \left((1-v)^4 \hat{\sigma}_u^2 + (1-u)^4 \hat{\sigma}_v^2 \right).$$

7. Concluding Remarks

The previous discussion was based on two major assumptions: (1) the probabilities of the two kind of interactions, α and β , were constant over all positions, and (2) the transition probabilities were binomial. We could relax both conditions and with little change in the development obtain a solution of P_{mn} .

Let

$$\Pr(S_i \rightarrow S_j / (2r-1)) = p_{ij}(\alpha(2r-1))$$

$i \geq j$, $i = 0, 1, \dots, m$, $j = 0, 1, \dots, i$, where α , the probability of a release interaction, is now a function of the position number along the fixed line, and p is some discrete probability function whose parameter is $\alpha(2r-1)$. Also denote the transition matrix whose elements are the transition probabilities just defined by $A_{(2r-1)}$. Similarly, we let

$$\Pr(S_i \rightarrow S_j/2r) = q_{ij}(\beta(2r))$$

$i \leq j$, $i = 0, 1, \dots, m$, $j = i, i + 1, \dots, m$, where β , the probability of a load interaction, also depends upon the position number, and q is a discrete probability function with parameter $\beta(2r)$, not necessarily of the same type as p . Denote the transition matrix at an even site by $B_{m/2r}$. Then we have, for example, for n even, the very general solution

$$P_{m/2r}(n) = B_{m/2r}(n) A_{m/2r}(n-1) B_{m/2r}(n-2) A_{m/2r}(n-3) \cdots B_{m/2r}(2) A_{m/2r}(1) P_{m/2r}(0)$$

Now with α and β functions of n , we may approximate the muscle problem more closely since in effect α and β can be taken as velocity functions.

REFERENCE

- [1] R. J. Podolsky, "The Chemical Thermodynamics and Molecular Mechanism of Muscular Contraction" Annals of the New York Academy of Sciences, Vol. 72 (1959), pp. 522-537.

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