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## V.N.KOTOV, A.N.KOROL

## KINETICS OF THE EARLY GROWTH OF ACTINOMYCETE STREPTOMYCES COELICOLOR

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Various growth characteristics of Streptomyces coelicolor are considered and numerous relations among them are discussed. An attempt is made to tie the events at the hyphal level to an understanding of phenomena at the organism level. The results are presented as corollaries of a theoretical model based on a special stochastic branching process involving apices of three types. Theoretical conclusions are compared to the experimental data on growth and branching of colonies of S.coelicolor from paper 111.

The results of this communication may be easily carried over to any mycelial organism.

Figs 4. Refs 12./17 p./

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The authors of paper [1] showed that growth kinetics of the filamentous actinomycete Streptomyces coelicolor were similar to those of filamentous fungi. This fact allows to describe the early growth of this actinomycete by means of branching processes [4,5] in the manner as it was done when modelling the growth of fungal mycelium [6-9].

The present communication is a concise mathematical commentary on a prominent experimental work by E.Allan and J.Prosser [1] devoted to the study of growth and branching of S.coelicolor A3(2).

Before proceeding to discussion of quantitative regularities of growth of S. coelicolor, we shall retell some facts from [1].

Similarly to the filamentous fungi, the filamentous streptomycete S. coelicolor A3(2) grown on solid medium eventually forms a circular colony. The development of S. coelicolor usually involves the outgrowth of more than one germ tube (at most four germ tubes were observed). The formation of a circular colony with hyphae radiating outwards from the spore is associated with the establishment of a ceaseless hyphal interaction in the growth zone is. The hyphae of S. coelicolor only occasionally crossed over each other. On the occasions when a branch tip almost touched another branch the growth of that tip would stop. Cessation of growth also resulted from growth into crowded areas. The partions of branches which stopped growing in a large colony were 47 %, 60 % and 44 % for primary, secondary and tertiary branches respectively.

Fig. 1 represents the plots describing the development of one mycelial tree within the large colony mentioned above, which produced three germ tubes. About 8 hours after spore germination the total mycelial length and the total number of apices started increasing exponentially at the specific rates of  $0.26 \pm 0.002$  and  $0.25 \pm 0.001$  h<sup>-1</sup> respectively. The mean hyphal growth unit for 12 mycelial trees was  $32.63 \pm 1.60$  µm.

Fig. 2 represents frequency distribution of 200 internode lengths with the mean of  $9.91 \pm 0.52 \mu m$ . The mean length for 150 apical segments (that is, the segments of parent hyphae from apex to the nearest branch) was  $35.2 \pm 1.12 \mu m$ . The mean extension rate of hyphae varied from  $10.8 \pm 0.6$  to  $17.8 \pm$ 



Fig. 1. Total mycelial length  $\lambda(t)$  (•), number of tips  $\xi(t)$  (•) and their ratio HGU(t) (•) in a developing mycelium of S. coelicolor on minimal medium (redrawn from [1]).

1.4 um h<sup>-1</sup>.

All measurements are given as a mean value + standard error.

Now we proceed to the mathematical analysis of the above growth characteristics of S. coelicolor.

Denote by d(1) and  $D(1) = \int_0^1 d(u) du$  the distribution density and the distribution function for lengths of internodes on a single hypha. Assign to each internode of length  $\lambda$  its formation time  $\tau = \lambda/v_{-}$ , where v is a model parameter to be specified below. The distribution function and the distribution density of the random variable  $\tau$  are of the form

$$F(t) = D(v_{z}t), \quad f(t) = v_{z}d(v_{z}t).$$
 (1)



internode length, µm

## Fig. 2. Frequency distribution of internode lengths in colonies of S. coelicolor (redrawn from [1]) and approximating density $d'(l) = 0.04l \exp(-0.2l).$

Apices of a growing colony are classified under three types. Apices of the extending parent hyphae refer to type  $T_{1}$  and those of the young extending hyphae without laterals, to type  $T_{4}$  (see Fig. 4). The authors of paper [1] indicate that some hyphae stop growing under unfavourable conditions. The apices of nonextending hyphae refer to type  $T_{4}$ . As defined above, an apical segment is the segment of a hypha from its tip to the nearest node. The type of an apical segment is the same as the type of its apex.

Denote by  $\boldsymbol{\xi}_{\star}(t)$  the number of spices of type T. , i= 1, 2, 3, in a colony at moment t. For any fixed value of t  $\boldsymbol{\xi}_{\star}(t)$  is a random variable, while with increasing t it becomes a stochastic process. Introduce  $\boldsymbol{\xi}(t) = \boldsymbol{\xi}_{\star}(t) + \boldsymbol{\xi}_{\star}(t) + \boldsymbol{\xi}_{\star}(t)$ to denote the total number of tips in the colony.  $\boldsymbol{\xi}(t)$  is a stochastic branching process with the following apex production [4, 5] : each apex of type T<sub>1</sub> or T<sub>2</sub> exists a random time  $\boldsymbol{\tau}$  distributed with density  $\boldsymbol{f}(t)$  of form (1) and upon the lapse of that time produces with probability  $\boldsymbol{\rho}$  one apex of type T<sub>1</sub> and one apex of type T<sub>2</sub> (i.e., there



Fig. 3. Frequency distribution of lengths of the type T apical segments in colonies of S. coelicolor (redrawn from [1]) and theoretical distribution  $g_{\text{err.T.}}^{*}(1) = 0.037(1+21.5)erp(-0.21)+0.01(1-12.22)erp(-0.071)$ .

appear a lateral branch of type  $T_1$  and an internode of length  $\lambda = v_2 \tau$  while the parent hypha continues elongating) and with complementary probability  $q = 1 - \rho$ , one apex of type  $T_3$  (i.e., the hypha stops growing). The apices of type  $T_3$ produce no offspring and do not vanish. The process  $\xi(t)$  is initiated at time  $t_0 = 0$  with one apex of type  $T_1$  (the germ tube apex). Apex production in the branching process  $\xi(t)$ is schematically presented in Fig. 4. The letters over arrows denote probabilities of the corresponding forms of apex production.

Denote by  $A_i(t)$ , i = 1, 2, 3, the mean number of the type  $T_i$  epices in a colony at moment t, that is,  $A_i(t) = E \xi_i(t)$ , where E is the symbol of mathematical expectation, and put  $A(t) = E \xi(t) = A_i(t) + A_i(t) + A_i(t)$ . Functions  $A_i(t)$  satisfy the following renewal equations [4,5]:

$$A_1(t) = 1 - (1+p)F(t) + p \int_0^t F(t-u) f(u) du +$$

$$+2p\int_{a_{1}}^{t}A_{1}(t-u)f(u)du;$$

$$A_{2}(t) = pF(t) - p\int_{a}^{t}F(t-u)f(u)du +$$

$$+2p\int_{0}^{t}A_{2}(t-u)f(u)du;$$

$$A_{3}(t) = qF(t) + 2p\int_{a}^{t}A_{3}(t-u)du.$$
(2)

It follows from these equations that the mean numbers of apices of types  $T_1$ ,  $T_2$  and  $T_3$  as well as the mean number of all apices in a colony increase asymptotically exponentially at the same specific growth rate  $\propto$  [4,5]. More precisely, for  $t - \infty$ 

 $A_i(t) \sim A_i e^{\alpha t}$ ,  $\iota=1,2,3$  and  $A(t) \sim A e^{\alpha t}$ , (3)

where & is the maximum real root of the equation

$$\widetilde{f}(s) = \int_{0}^{\infty} f(u) e^{-su} du = \frac{1}{2\mu}$$
(4)

and

$$\frac{2n-1}{11^2} = \frac{2n-1}{8\alpha p^2 \tilde{f}(\alpha)}, \quad \frac{1}{13} = \frac{1-p}{4\alpha p^2 \tilde{f}'(\alpha)}, \quad \frac{1}{4\alpha p \tilde{f}'(\alpha)}$$
 (5)

(here and further on a prime means differentiation). In the context of this communication mathematical idealization 'for  $t \rightarrow \infty$ ' should be understood as 'for sufficiently large number of apices'. Fig. 1 presents a plot of increase of the total number of apices in the colony of S. coelicolor A3(2). As is seen in this figure, for S. coelicolor relations (3) hold true with a satisfactory accuracy from the moment there appear about 7 to 10 apices, that is, 8 to 10 hours after spore germination.

In order to proceed from the number of spices in a colony to the total length of hyphae, we must introduce the rates  $V_1$ and  $V_2$  of movement of the type  $T_2$  and type  $T_2$  spices. The

mean rate of movement of a single apex in a colony is random and equal to

$$v(t) = \frac{v_{4}\xi_{4}(t) + v_{2}\xi_{2}(t)}{\xi(t)}$$
(6)

As  $t \rightarrow \infty$  the mean rate v(t) attains a constant value [4,5] equal to

$$\mathbf{v} = \frac{A_1 \mathbf{v}_1 + A_2 \mathbf{v}_2}{A} = \frac{(2p-1)(\mathbf{v}_1 + \mathbf{v}_2)}{2p} . \tag{7}$$

The mean rate V defined by relation (7) is equal to the actual mean extension rate of a s in g l e hypha and coincides with that computed by Trinci's formula (1) from [10].

The total length of hyphae in a colony at moment  $\overline{t}$  is described by the stochastic process

$$\lambda(t) = v_1 \int_0^t \xi_1(u) du + v_2 \int_0^t \xi_2(u) du .$$

For the mean value of this process at moment t the following relations may be derived:

$$L(t) = M\lambda(t) = v_1 \int_0^t A_i(u) du + v_2 \int_0^t A_2(u) du \sim \frac{VA}{c} e^{\alpha t}, (B)$$

where  $\alpha$ , A and V are given by formulas (4), (5) and (7). Comparing (3) to (8) shows that on the average the total number of apices in a colony and the total length of hyphae increase at the same specific growth rate. This fact was established earlier experimentally and caused introduction of the hyphal growth unit into mycological investigations [11].

Proceed now to the study of the hyphal growth unit by means of the theory of stochastic processes. To that end introduce into consideration stochastic process  $HGU(t) = \lambda(t)/\xi(t)$  equal to the ratio of the (random) total length of hyphae to the (random) total number of apices in a colony at moment t. It follows from paper [12] and relations (5) and (8) that the process HGU(t) which has a random nature for small numbers of apices becomes stable in the course of time and equal to the constant



Fig. 4. Schematic illustration of apex production in the branching process  $\xi(t)$ :  $\tau_4$  - formation time of the first internode on the germ tube,  $\tau$  - formation time of the last internode on the hypha under consideration.

$$HGU = \lim_{t \to \infty} \frac{L(t)}{A(t)} = \frac{v}{\infty} .$$
(9)

Thus, stabilization of the stochastic process HGU(t) at the level of HGU and relation (9) for HGU are fundamental properties of mycelial organisms [10]. The stochastic process HGU(t)attains a constant value shortly after spore germination. According to Fig. 1 in case of S. coelicolor HGU(t) becomes time-invariant from the moment there are about 8 to 10 apices in the colony.

At the beginning of this communication we defined the distribution density for the internode lengths on a s ingle h y p h a. Let us turn now to the distribution of internode lengths with in a colony. The density of this distribution will be denoted by d(U). For this reason consider function S'(t, u) equal to the mean number of internodes in a colony at moment t whose formation time is less than u. This function satisfies the following renewal equation:

 $S(t, u) = pF(t) \chi\{t \le u\} + pF(u) \chi\{t > u\} +$ 

$$+2p\int_{0}^{t}S(t-w,u)f(w)dw, \qquad (10)$$

where  $X{X}$  is the indicator of the set X. It follows from equation (10) that for  $t \rightarrow \infty$ 

$$\delta^{*}(t,u) \sim - \frac{e^{\alpha t} \int_{0}^{t} \tilde{f}(w) e^{-\alpha W}}{2\alpha \tilde{f}'(\alpha)}$$
 (11)

According to the results of paper  $\begin{bmatrix} 12 \end{bmatrix}$  the probability to encounter an internode in a colony whose formation time is less than  $\mu$  is equal to

$$F(u) = \lim_{t \to \infty} \frac{S(t, u)}{A(t)} = 2p \int_{0}^{u} f(w) e^{-\alpha w} dw \qquad (12)$$

as  $t \rightarrow \infty$  . Clearly, this probability does not coincide with the probability F(u) to encounter an internode on a sin - gle hypha whose formation time is less than u.

Therefore, the probability  $D^{*}(1)$  to encounter an internode in a colony of length less than 1 differs from the probability to encounter such an internode on a single hypha. To be more specific.

$$D^{*}(1) = F^{*}(1/v_{2})$$
 (13)

Formulas (1), (12) and (13) yield the following expressions for the corresponding densities:

$$f_{(u)}^{*} = \frac{dF_{(u)}^{*}}{\frac{du}{du}} = 2pf(u)e^{-\alpha u}, \quad (14)$$

$$d^{*}(t) = \frac{dD^{*}(t)}{dt} = \frac{dF^{*}(t/v_{2})}{e^{-\alpha t/v_{2}}} = \frac{2r}{v_{2}}f(t/v_{2})e^{-\alpha t/v_{2}} = 2pd(t)e^{-\alpha t/v_{2}}. \quad (15)$$

The next formula which is used below deserves a special attention:

$$f(u) = \frac{V_e}{2p} \stackrel{!}{=} \stackrel{!}{(v_2}u) e^{u} .$$
 (16)

Fig. 2 represents frequency distribution of internode lengths in colonies of S. coelicolor redrawn from paper [1]. This experimental distribution is well approximated by the density of gamma-distribution of the form

$$d^{*}(l) = \frac{a^{\kappa} l^{\kappa-1}}{\Gamma(\kappa)} e^{-\alpha l}$$
(17)

with  $\kappa = 2$  and  $\alpha = 0.2$ . The curve of this density for the specified values of  $\kappa$  and  $\alpha$  is plotted in Fig. 2. In case of distribution (17) the mean internode length in a colony is equal to

$$l_{intnd}^* = \frac{\kappa}{n}$$
(18a)

and standard deviation is

$$6^* = \frac{\sqrt{\kappa}}{a} . \qquad (18b)$$

The above-mentioned estimates of the shape parameter,  $\kappa_{\bullet}$  and the scale parameter,  $\alpha$ , are in full agreement with the

mean internode length  $l_{introd} = 9.91 \,\mu\text{m}$  and standard error  $6^{+}/\sqrt{n} = 0.52 \,\mu\text{m}$  (n = 200) specified in paper [1]. Really, in case of gamma-distribution (17)

$$\kappa = \left(\frac{l_{introd}^{*}}{6^{*}}\right)^{2} = 1.82 , \quad l_{introd}^{*} = \frac{\kappa}{\alpha} = 10 \, \mu m$$

and, finally,  $6^{*}/\sqrt{n} = \sqrt{\kappa}/(a\sqrt{n}) = 0.5 \ \mu m$ .

It follows from (4), (16) and (17) that the formation times of internodes on a single hypha are distributed with the density

$$f(t) = \frac{1}{\Gamma(\kappa)} \left\{ \alpha v_2(2p)^{-\frac{4}{\kappa}} \right\}^{\frac{1}{\kappa}} t^{\kappa-1} e^{-\alpha v_2(2p)^{\kappa}} t , \quad (19)$$

while the specific growth rate is equal to

$$\alpha = \alpha v_2 \left\{ 1 - (2p)^{-\frac{1}{\kappa}} \right\} . \tag{20}$$

Then according to (1)

$$d(l) = \frac{1}{\Gamma(\kappa)} \left\{ \alpha(2p)^{-\frac{1}{\kappa}} \right\}^{\kappa} l^{\kappa-1} = \alpha(2p)^{-\frac{1}{\kappa}} l^{\kappa}$$
(21)

whence the mean internode length on a single hypha is equal to

$$l_{introd} = (2p)^{\overline{k}} l_{introd}^{\dagger} .$$
 (22)

Now we turn to the distribution of length of the type  $T_1$  apical segments in colonies. Denote by W(t,u) the mean number of the apical segments of type  $T_1$  or  $T_2$  in a colony at moment t, which have appeared after the moment t-u. This function satisfies the renewal equation

$$W(t, u) = \left[1 - F(t)\right] \chi \left\{t \le u\right\} +$$
(23)  
+ 2 $\rho \int_{0}^{t} W(t-w, u) f(w) dw$ .

As 
$$t \rightarrow \infty$$
  
 $W(t,u) \sim - \frac{e^{\alpha t} \int_{0}^{u} [1 - F(w)] e^{-\alpha w} dw}{2\rho f(\alpha)}$  (24)

According to the results of paper  $\begin{bmatrix} 12 \end{bmatrix}$  the probability to encounter an extending apical segment in a colony, which has appeared after the moment t-u, is equal to

$$B(u) = \lim_{t \to \infty} \frac{W(t, u)}{A_{1}(t) + A_{2}(t)} = \frac{2 \alpha p}{2 \alpha p - 1} \int_{0}^{u} \left[1 - F(w)\right] e^{-\alpha w} dw$$
(25)

as  $t \to \infty$ . Therefore, the length of the type  $T_1$  apical segments is distributed in colonies with the density

$$g_{apc}^{+} T_{1}^{(1)} = \frac{d B(1/v_{1})}{d1} = \frac{2 \alpha p |1 - F(1/v_{1})| e}{v_{1}(2p-1)}$$
(26)

and the mean

$$i_{apc T_{i}}^{*} = \int_{0}^{\infty} u g_{apc T_{1}}^{*}(u) du =$$

$$= \frac{v_{1}}{\alpha} - \frac{v_{1}}{v_{2}(2p-1)} \qquad (27)$$

Proceed now to the length of the type  $T_z$  apical segments. When  $t\to\infty$  , it is distributed so as the random variable

$$\frac{v_2}{v_a}\eta^* + \frac{v_1 - v_2}{v_a}\lambda^*,$$

where  $\eta$  has the density  $g_{acc}^{*}$ , (l) and  $\lambda^{*}$ , the density  $d^{*}(l)^{*}$ , that is, with the density

$$g_{apc}^{*}T_{2}(l) = \frac{v_{1}}{v_{1}-v_{2}} \int_{0}^{l} d^{*}\left(\frac{v_{2}x}{v_{1}-v_{2}}\right) g_{apc}^{*}T_{1}\left[\frac{v_{1}}{v_{2}}(l-x)\right] dx \qquad (28)$$

and the mean

$$l_{apc}^{*} T_{2} = \frac{V_{2}}{\alpha} - \frac{(2p-1)V_{1} - 2pV_{2}}{V_{2}(2p-1)} l_{introd}^{*}$$
(29)

The mean length of the type  $T_3$  spical segments in a colony, that is, of the spical segments which stopped extending, is

$$l_{apc}^{*} T_{3} = \frac{V_{1}}{V_{2}} l_{intnd}^{*}$$
(30)

According to relations (3) and (5) the probabilities to encounter spical segments of types  $T_1$ ,  $T_2$  or  $T_3$  in a colony are

$$(2p-1)/(2p)$$
,  $(2p-1)/(2p)$  and  $q/p$ 

respectively. Hence the mean length of all the apical segments in a colony, that is, of the apical segments of all three types, is equal to

$$l_{apc}^{*} = \frac{2\rho - 1}{2\rho} \left( l_{apc}^{*} T_{1} + l_{apc}^{*} T_{2} \right) + \frac{q}{\rho} l_{apc}^{*} T_{3} = \frac{V}{ck} - l_{intnd}^{*}$$
(31)

Taking into account relation (28) we receive from (31) the following fascinating equality

$$HGU = 1_{apc}^{*} + 1_{inind}^{*}$$
 (32)

This equality asserts that the hyphal growth unit is equal to the sum of the mean length of apical segments and that of internodes in an entire colony (not only on a single hypha ).

Thus, the growth kinetics of colonies of S. coelicolor are described by formulas (3), (5), (7) - (9), (18), (19), (21), (23), (27) - (32). All these formulas are asymptotic and oriented towards the colonies in steady exponential growth, when the growth characteristics such as V, HGU,  $l_{introd}^{2}$ ,  $l_{acc}^{2}$ ,

 $l_{apc}^{*}$ ,  $l_{apc}^{*}$ , and  $l_{apc}^{*}$  are stable and do not change with time. After the exponential stage the hyphal growth unit, HGU, and the mean marginal internode length,  $l_{atad}^{*}$ start increasing [2], [3], [8]. From that moment on the model presented in this communication becomes unfit and the other models similar to that which was used in [8] for modelling the second stage of growth of the fungal colonies are needed. It follows from what was said above that the proposed model may be applied only at the time interval, when the mean extension rate and the mean internode length are time-invariant.

Any five independent growth parameters may serve as the input data of the model, for instance a,  $\kappa$ ,  $\rho$ ,  $\alpha$ , and  $l_{acc} T_2$ . The parameters of gamma-distribution (17) were discussed above. They are  $\kappa = 2$  and a = 0.2. The value of  $\rho$  can be estimated from the percentage of the apical segments which stopped extending [1] and the theoretical probability to encounter a type  $T_3$  apex in a colony equal to  $q/\rho$ . This yields  $\rho \approx 0.7$ . Relation (20) allows to calculate  $v_{\alpha} = 8.4 \ \mu m \ h^{-1}$ . From equation (29)  $v = 31.83 \ \mu m \ h^{-1}$ . By formula (7)  $v = 11.5 \ \mu m \ h^{-1}$ .

To determine the mean rate of hyphal extension, v, entering into relation (9), Trinci [10] used the following formula

$$E = \frac{2[\lambda(t+1) - \lambda(t)]}{\xi(t+1) + \xi(t)}, \quad (33)$$

which is of prime practical significance. The right-hand side of (33) becomes equal within short time to the constant very close to the mean rate, v, defined through formula (7). In case of colonies of S. coelicolor for which  $\alpha = 0.26 \text{ h}^{-1}$  the above-mentioned constant equals 0.99 v. The mean extension rate,  $v = 11.5 \mu \text{m} \text{ h}^{-1}$ , calculated by formula (7) is close to that which is obtained by formula (33) from the plots presented in Fig. 1.

Formula (9) yields  $HGU = 44.2 \ \mu m$  versus 32.63  $\mu m$  specified in paper 111. To our mind, this minor discord occurred due to the different procedures of calculating the hyphal growth unit. Allen and Prosser [1] averaged the values of HGU over 12 mycelial trees, while we were reasoning in such a way as if the total mycelial length in all the 12 trees were first computed and then divided by the total number of apices in them. The latter procedure egrees with that used by Allan and Prosser in 11 to calculate the mean internode length and the mean length of the type  $T_{a}$ , apical segments.

The length distribution density of the type  $T_{a}$  apical segments in colonies of S. coelicolor calculated from equations (16), (17), (26), and (28) is of the form

 $g_{apc}^{*} T_{2}^{(l)} = 0.057(l + 21.5) \exp(-0.2l) + + 0.01(l - 12.22) \exp(-0.07l).$ 

The curve of this density is presented in Fig. 3.

Thus, due to the introduction of a special branching process it has become possible to view various kinetic regularities of the early growth of colonies of S. coelicolor from the unified theoretical standpoint and to achieve a fairly high accuracy of agreement of theory with factual data. To conclude with, we would like to stress that the introduction of stochastic branching processes into the research of the mycelial growth offers ample scope for new ideas and experiments. The main difficulty which arises on this way is that such synthesis of experimental experience with probabilistic reasoning demands equal skilfulness in biology and probability theory, which becomes characteristic of modern science and which can be brought about nowadays only through tight contacts of specialists in relevant spheres of knowledge.

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