Introduction to modeling biological populations

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0. Introduction

Modelling population growth is an extremely fertile area of mathematical applications. This wide area cannot be covered satisfactorily within our limits on scope. Our purpose was rather to provide a glimpse of various approaches and diverse complexity induced by our nature. This work focuses on papers and books imparting readily applicable knowledge, avoiding to deepen into long theoretical problems with no palpable applications. One of the most basic and profound papers published on this topic exploited orthogonal polynomial theory to connect it with the recurrence formulae for transition probabilities of linear growth processes [Karlin, 1958, Karlin, 1982, Renshaw, 1972, Karlin, 1957]

The structure of this paper is as follows. The first five chapters – based on the book of Renshaw [Renshaw, 1991] – introduce the most essential population dynamics models, enriched with computer simulations [Excel, MapleV], and all emerging proofs are completed and/or established by the author of this paper.

The last chapter was inspired by numerous articles on predictive food microbiology, with focus on stochastic modelling. This chapter – apart from the historical review – represents purely novel ideas by the author as an effort to try to put the theoretical tools of stochastic processes into practise in the hope that these initiatives can be improved to be profitable in applications.

1. The pure birth process

Population of organisms exhibit a special kind of development usually over a relatively short period of their lifetime. Suppose that

(i) they live in crowd–free environment

(ii) supplied unlimited food resource

Assume furthermore that

(iii) organisms do not die

(iv) develop without interaction

(v) they have a common birth rate (λ),

which does not depend on their age, and independent of the progress of time.

1.1 Deterministic Model

Let *N(t)* denote the population size at time *t*. As the consequence of our assumptions the increase of population size over a small time interval (*h*) is due to λh growth of each *N(t)* organisms.

This yields

$$N(t+h) = N(t) + \lambda h N(t) + o(h). \qquad (1.1)$$

Thus letting h tend to zero we obtain the following differential equation

$$N'(t) = \lambda N(t) \qquad (1.2)$$

with the well–known solution

$$N(t) = N(0)\, e^{\lambda t} \qquad (1.3)$$

Or in more usual form

$$\log N(t) = \log N(0) + \lambda t \qquad (1.4)$$

which gives full play to direct applications of linear regression. As we have seen these plain initial assumptions led us to exponential or – on the logarithmic scale – to linear growth curve.

1.2 Stochastic Model

To bring these strict assumptions into harmony with reality, relax some of the restrictions (i)–(v). Firstly, we can not say that every cell will certainly divide in a specific time interval, rather we should say that it will happen only with a certain probability. Another objection to emerge readily is that *N(t)* can only take integral values, which indicates discrepancies between actual and predicted figures at low population size.

Suppose therefore that in a short time interval (*t, t+h*) the probability of a single cell to divide is $\lambda h + o(h)$. By choosing h sufficiently small, the appearance of more than one birth can be – by hypothesis – regarded as negligible. More precisely $(N(t), t \geq 0)$ is a pure birth process if

$$N(t) \in \mathbf{N} \tag{1.5}$$

$$N(t) \text{ is a Markoff–process} \tag{1.6}$$

$$\Pr(N(t+h) = n+1 \mid N(t) = n) = \lambda N(t)h + o(h) \tag{1.7}$$

$$\sum_{m=2}^{\infty} \Pr(N(t+h) = n+m \mid N(t) = n) = o(h) \tag{1.8}$$

This is a special case of the general birth process, where the function $\lambda_N(t)$ stands for $N(t)h$ in (1.7). [Michaletzky, 2001] On denoting

$$p_N(t) = \Pr(\text{population is of size N at time t}) \tag{1.9}$$

we can formulate the governing difference equation

$$p_N(t+h) = p_N(t)(1-\lambda Nh) + p_{N-1}(t)\lambda(N-1)h + o(h) \tag{1.10}$$

which yields (performing the operations $-p_N(t)$, $/h$, $h \to 0$ on both sides)

$$p_N'(t) = -\lambda N p_N(t) + \lambda(N-1) p_{N-1}(t), \qquad N = N(0), N(0)+1, \ldots \tag{1.11}$$

Theorem The solution of this differential equation system is as follows

$$p_N(t) = \binom{N-1}{n_0-1} e^{-\lambda n_0 t} \left(1-e^{-\lambda t}\right)^{N-n_0} \text{ , for } N = n_0, n_0+1, \ldots \tag{1.12}$$

where – for convenience – denote *N(0)* by n_0.

Proof

The above formula can easily be proven, by mathematical induction.

Suppose that we know the solution for $n = n_0, \ldots, N$ and would like to produce that the formula holds for *N+1* as well. It is widely known that for a differential equation of the form $x'(t) = a(t)x(t) + b(t)$ the solution is

$$\exp\left(\int_0^t a(s)ds\right) \int_0^t b(s) \exp\left(\int_0^s -a(u)du\right) ds + x_0 \exp\left(\int_0^t a(s)ds\right) \tag{1.13a}$$

which is in this case easily integrable

$$p_{N+1}(t) = e^{-\lambda(N+1)t} \left(\lambda N \binom{N-1}{n_0-1} \int e^{\lambda t} \left(e^{\lambda t}-1\right)^{N-n_0} dt\right) = \tag{1.13b}$$

$$e^{-\lambda(N+1)t} \left(\lambda N \binom{N-1}{n_0-1} \frac{\left(e^{\lambda t}-1\right)^{N-n_0+1}}{\lambda(N-n_0+1)}\right) = \tag{1.14}$$

$$\binom{N}{n_0-1} e^{-\lambda n_0 t} \left(1-e^{-\lambda t}\right)^{N+1-n_0} = \tag{1.15}$$

This is exactly what we wanted to prove. ♦

Informed this way, for fixed time *t* the population will follow negative binomial distribution (i.e. $p_N(t) \sim \mathrm{NB}(n_0, \exp(-\lambda t))$), the parameters of which depend only on the initial number of cells and the (λt) factor. Thus its mean and variance are obtained readily from the properties of the negative binomial distribution

$$m(t) = n_0 e^{\lambda t} \tag{1.16}$$

$$V(t) = n_0 e^{\lambda t} \left(1- e^{\lambda t}\right) \tag{1.17}$$

We are interested in the maximum of the probability $p_N(t)$ attained at population size N_m. It is to be obtained by finding the index for which the ratio

$$p_N(t) / p_{N-1}(t) = (1-e^{-\lambda t})(N-1)/(N-n_0) \tag{1.18}$$

equals one.

Hence

$$N_m = (n_0 - 1)\, e^{\lambda t} + 1 \tag{1.19}$$

Let us define the coefficient of variation – CV(t) – as

$$\sqrt{V(t)} \;/\; m(t) = \sqrt{(1- e^{-\lambda t})/ n_0} \rightarrow 1/\sqrt{n_0} \tag{1.20}$$

which points out that the relative variation decreases as we boost the initial population size n_0.

The advantage of this approach is that although the particular realisation of the process is unknown, useful statistical properties may be drawn. Mention must be made of the importance of the independence assumption, which guarantees that the deterministic solution agrees with the mean of the stochastic process.

1.3 Simulated Model

For simulational convenience we shall examine the following $G_n(s)$ function denoting the probability of no event occurring in the time interval $(t,t+s)$, with n cells being alive at time t. More concisely

$$G_n(s) = \Pr\left(N(t+s) = n \mid N(t) = n\right) \tag{1.21}$$

To compute this we need the following equation

$$P(N(t+s+h) = n \mid N(t) = n) = P(N(t+s+h) = n, N(t+s) = n \mid N(t) = n) = \tag{1.22}$$

$$\frac{P(N(t+s+h) = n, N(t+s) = n, N(t) = n)}{P(N(t) = n)} \tag{1.23}$$

and by the definition of the conditional probability we obtain

$$G_n(s+h) = P(N(t+s+h) = n \mid N(t+s) = n, N(t) = n)\,\frac{P(N(t+s) = n, N(t) = n)}{P(N(t) = n)} \tag{1.24}$$

now using the Markoff property

$$G_n(s+h) = P(N(t+s+h) = n \mid N(t+s) = n)\;\; P(N(t+s) = n \mid N(t) = n) = G_n(s)\, G_n(h) \tag{1.25}$$

To complete the proof, let make a use of it for $G_n(s)= [G_n(s/j)]^j$, combined with the fact that $G_n(h) = (1–\lambda Nh) + o(h)$, from the recurrence relation.

Hence $G_n(s) = \lim_{j\to\infty} (1 – \lambda Ns/j)^{\,j} = \exp(–\lambda Ns)$.

The equivalent form of this result is as follows. Let a random variable, S, be the interevent time twixt two successive birth event.

$$\Pr(S \geq s) = 1 – \exp(–\lambda Ns) \tag{1.26}$$

in a different manner, $S \sim \exp(\lambda N)$, i.e. S is exponentially distributed, with parameter λN.

Now we are in the position to perform a simulation. One such result is shown in fig. 1.1, using Microsoft Excel simulation. From the theoretical results we see that the stochastic growth curve tends to the deterministic one as we increase the initial number of cells.

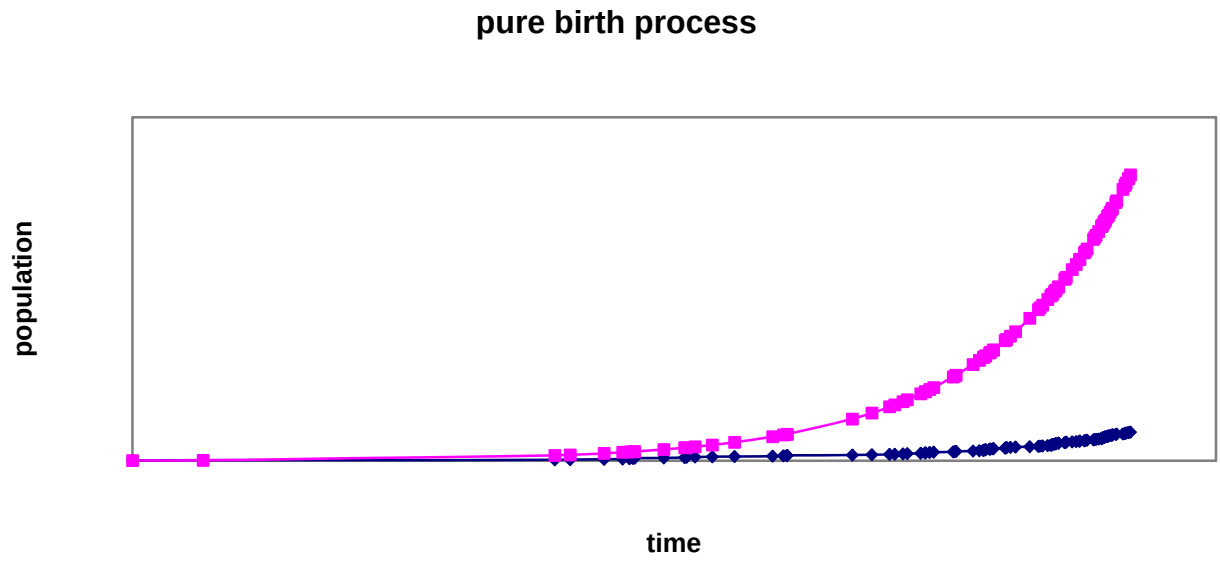

Fig 1.1 A simulated pure birth process (with parameter value $\lambda = 0.3$), where the population size was plotted against time.

1.4 Time to given state

To become more acquainted with the properties of the pure birth process we shall therefore examine the stopping time, T_a, defined by

$$T_a = \inf \{t \mid N(t) \geq a\} \tag{1.27}$$

i.e. the time at which population size level *a* is first reached. This variable plays a crucial rule in microbial infections and food safety analysis, which topic will be discussed comprehensively at a later stage. In a nutshell the phenomenon is the following. A host infected with n_0 number of bacteria, but exhibits symptoms of illness only when their number reaches a critical threshold level, say *a*.

Explicit formulae can be drawn from the foregoing results. For the sake of simplicity we shall n_0 assume to be 1.

$$P(T_a \leq t) = \sum_{N=a}^{\infty} e^{-\lambda t}(1 - e^{-\lambda t})^{N-1} = (1 - e^{-\lambda t})^{a-1} \tag{1.28}$$

This lead us to the probability density function for T_a , by a simple differentiation

$$f(t) = \lambda\,(a-1)\, e^{-\lambda t}(1 - e^{-\lambda t})^{a-2} \tag{1.29}$$

As we have seen in 1.3, there is another approach to the birth process. According to which the interevent time between two successive birth of a cell, when the population size is of N, follows exponential distribution with parameter λN. Thus

$$T_a = \sum_{j=n_0}^{a-1} Z_j \tag{1.30}$$

where $Z_j \sim \exp(\lambda j)$, consequently

$$E[T_a] = \sum_{j=n_0}^{a-1} \frac{1}{\lambda j} = \frac{1}{\lambda}\left[\sum_{j=1}^{a-1} \frac{1}{j} - \sum_{j=1}^{n_0-1} \frac{1}{j}\right] \tag{1.31}$$

By the means of approximation formula

$$\sum_{j=1}^{n} \frac{1}{j} = \gamma + \log(n) + O(1/n) \tag{1.32}$$

where γ is the Euler's constant, we have

$$E[T_a] \approx (1/\lambda)\,[(\gamma + \log(a-1)) - (\gamma + \log(n_0 - 1))] \approx (1/\lambda)\log(a/n_0) \tag{1.33}$$

The agreement between stochastic and deterministic model can be verified by the T_a value gained from the deterministic equation, namely $a = N(T_a) = n_0 \exp(\lambda T_a)$, which gives $(1/\lambda)\log(a/n_0)$ for T_a.

The variance of Var (T_a) is computable along the same lines, using the well known limit

$$\sum_{j=1}^{\infty} \frac{1}{j^2} = \pi^2 / 6. \tag{1.34}$$

Using this gives an upper bound for the variation

$$\mathrm{Var}(T_a) \approx \pi^2 / (6\lambda^2) - \sum_{j=1}^{n_0 - 1} (1/\lambda j)^2 \tag{1.35}$$

of T_a , namely $\pi^2 / (6\lambda^2)$. A fairly better estimate can be drawn from following straightforward path. By term–by–term inequality the above chain of inequalities holds

$$\frac{1}{n} - \frac{1}{m+1} = \sum_{j=n}^{m} \frac{1}{j(j+1)} \le \sum_{j=n}^{m} \frac{1}{j^2} \le \sum_{j=n}^{m} \frac{1}{j(j-1)} = \frac{1}{n-1} - \frac{1}{m} \tag{1.36}$$

which yields not only a by far better and explicit upper bound for the variance,

$$\frac{1}{\lambda^2}\left(\frac{1}{n_0 - 1} - \frac{1}{a - 1}\right) \tag{1.37}$$

but boosts with accuracy of $O(1/(\lambda n_0)^2)$, obtained by performing the difference between the left and right hand side. Our result is confirmed by simulation results, shown in *Fig 1.2*.

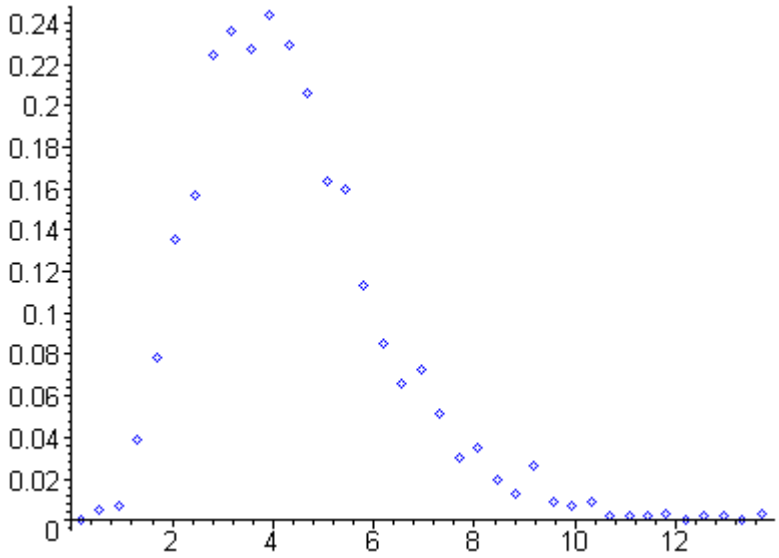

Fig 1.2 An approximate frequency distribution drawn from 1500 simulations of detection time. Initial number of cells 2, detection level 8, λ = 0.4, sample mean 4.371954321 and sample variance 1.864154411 (our enhanced estimate gave a rough upper bound 5.357142857, but still demonstratively outplaying the formerly proposed 10.28083792.)

2. Pure Death Process

In this section we are considering the opposite to birth, namely death process. From mathematical point of view it does not carry any interest, as it does not bring into play any new formulae. In spite of this fact, it is widely applicable in modelling nature. For instance, it can happen that due to a pollution an isolated population becomes incapable of reproduction. Our assumptions are as follows

(i) cells do not give birth

(ii) they develop independently from each other

(iii) death rate, μ, is uniform, and independent of time

2.1 Deterministic Model

This process has no mathematical novelty value, as the only change to be done is to substitute λ by $-\mu$ in the original pure birth process. Hence the result is

$$\log (N(t)) = \log (N(0)) - \mu t \tag{2.1}$$

2.2 Stochastic Model

As it can be expected upon simple consideration, the stochastic death process is by far more simple than the birth one. Let q(t) (p(t)) denote the probability that a particular organism is alive (dead) at time *t*. Subsequently

$$q(t+h) = q(t)\,(1-\mu h) + o(h) \tag{2.2}$$

hence (on letting *h* tend to zero)

$$q'(t) = -\mu\, q(t) \tag{2.3}$$

i.e.

$$q(t) = \exp(-\mu t) \text{ and } p(t) = 1 - \exp(-\mu t) \tag{2.4}$$

Using the same notation as in *Section 1.2*,

$$p_N(t) = \binom{n_0}{N} q^N(t)\, p^{n_0 - N}(t) = \binom{n_0}{N} e^{-N\mu t} [1 - e^{-\mu t}]^{n_0 - N} \tag{2.5}$$

This says that N(t) follows binomial distribution, and directly gives

$$m(t) = n_0 e^{-\mu t} \tag{2.6}$$

$$V(t) = n_0 e^{-\mu t} (1 - n_0 e^{-\mu t}) \tag{2.7}$$

The most straightforward estimate for μ results from $N(t_1) = N(t_0) \exp(-\overline{\mu}(t_1 - t_0))$, on rearranging we obtain

$$\overline{\mu} = -\frac{\log(N(t_1)/N(t_0))}{(t_1 - t_0)} \tag{2.8}$$

2.3 Time to Extinction

Once all the N(0) organisms have died, the population is extinct, the distribution of which in time is acquirable from (2.5), by substituting zero to N. Hence the p.d.f. flows from differentiation.

$$\Pr(T_0 \le t) = p_0(t) = [1 - e^{-\mu t}]^{n_0} \; I_{(t \ge 0)} \tag{2.9}$$

$$f_{ext}(t) = n_0 \mu \; e^{-\mu t} [1 - e^{-\mu t}]^{n_0 - 1} \tag{2.10}$$

Following the same chain of ideas as in *Section 1.4*, denote Z_N to be the total length of time when the population size is *N*. From ageless property of the exponential distribution (i.e. if $X \sim exp(\alpha)$ then $\Pr(X \ge t + s \mid X \ge t) = \Pr(X \ge s)$) and that the life expectancy distribution of an individual cell is exponentially distributed we gain

$$\Pr(Z_N \ge t) = \Pr\left(\text{N cells are alive at time } \left(t + \sum_{j=N+1}^{n_0} Z_j\right) \mid \text{N cell was living at time } \sum_{j=N+1}^{n_0} Z_j\right) = \tag{2.11}$$

$$\left[\Pr\left(\text{an individual cell is alive at time } \left(t + \sum_{j=N+1}^{n_0} Z_j\right) \mid \text{cell is alive at } \sum_{j=N+1}^{n_0} Z_j\right)\right]^N = \tag{2.12}$$

$$= [e^{-\mu t}]^N$$

Hence $Z_N \sim \text{Exp}(\mu N)$, therefore the mean and the variance for T_0 is given by the formulae

$$E(T_0) = \sum_{j=1}^{n_0} \frac{1}{\mu j} \tag{2.13}$$

$$\text{Var}(T_0) = \sum_{j=1}^{n_0} \frac{1}{(\mu j)^2} \tag{2.14}$$

For large n_0 values we can use the asymptotic formulae for $\sum_{j=1}^{n_0} (1/j)$ and $\sum_{j=1}^{n_0} (1/j^2)$ as used in 1.4, which yield

$$E(T_0) \approx [\gamma + \log(n_0)] / \mu \qquad (2.15)$$

$$Var(T_0) \approx \pi^2 / 6\mu^2 \qquad (2.16)$$

2.4 Simulation

Simulation of the pure death process sets no new programming challenge for us after the birth process simulation. The importance of simulations lies in the fact that important properties can be deduced from repetition of successive simulations without computing distribution formula. Simulation results are plotted in *fig 2.1*.

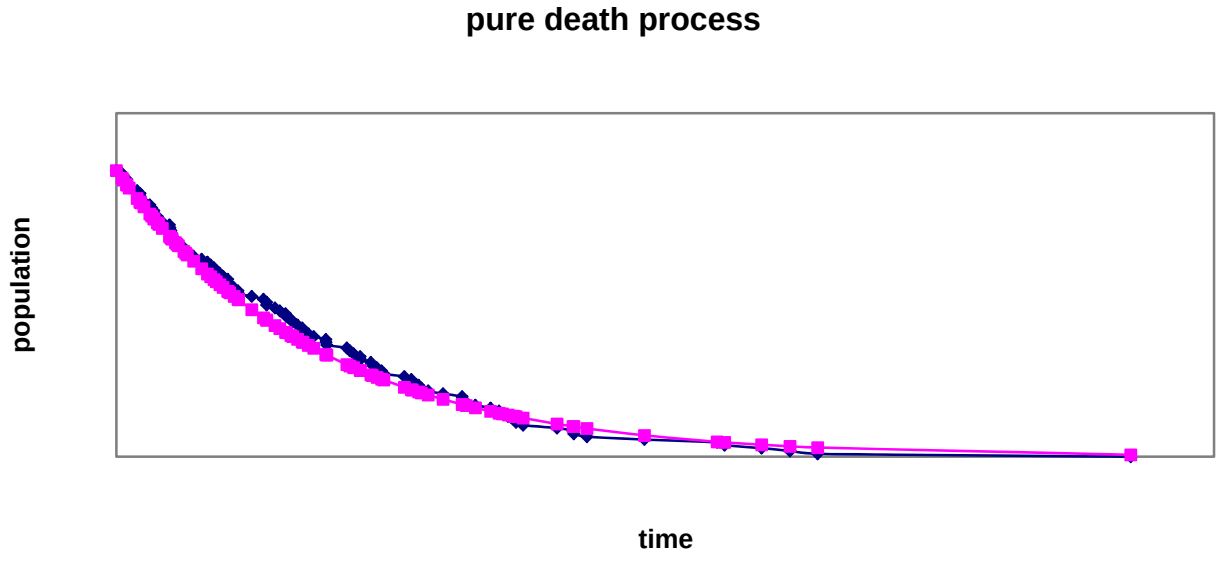

Fig 2.1 Illustrates a stochastic realisation in comparison with the deterministic curve, at $\lambda = 0.3$.

3. Simple Combined Process

3.1 The Simple Linear Birth and Death Process

Combining the pure birth and death processes we obtain a model which clearly describes the dynamics of a population with greater accuracy. However it leads to a more complex model this way, its mathematical complexity remains more or less the same. Nevertheless we should not overestimate the degree of agreement with reality. Naturally more realistic models produce even higher mathematical complexity.

3.1.1 Deterministic Model

As expected, mathematically it carries nothing new. The equation is

$$N'(t) = (\lambda - \mu)\, N(t) \tag{3.1}$$

leading to the solution,

$$N(t) = N(0)\exp[(\lambda - \mu)t] \tag{3.2}$$

3.1.2 Stochastic Model

Here we consider three possible case what can happen to a cell during a short time interval (t, t+h). With probability λh it will divide, with probability μh it will die or, the third case: nothing happens to it. This conduce to the equation

$$p_N(t+h) = p_N(t)\,[1 - N(\lambda+\mu)h] + p_{N-1}(t)\,[\lambda(N-1)h] + p_{N+1}(t)\,[(N+1)\mu h] + o(h) \tag{3.3}$$

Following the same lines as earlier in same situation

$$\begin{gathered} p_N'(t) = p_N(t)[N(\lambda+\mu)] + p_{N-1}(t)\,[\lambda(N-1)] + p_{N+1}(t)\,[(N+1)\mu] \quad , \text{for } N \geq 1 \\ \text{and} \\ p_0'(t) = \mu\, p_1(t) \end{gathered} \tag{3.4}$$

To understand the behaviour of population with n_0 initial cells, it is sufficient to examine the one with 1 cell at time zero. As the process is the same as n_0 separate population each of initial size one.

Suppose that the solution is of the form

$$p_N(t) = [1 - a(t)]\,[1 - b(t)]\,[b(t)]^{N-1} \qquad \text{for } N = 1, 2,\ldots \tag{3.5}$$

If there is a solution for functions a(t), b(t), we obtained a solution of the differential equation system. Check what kind of equation should hold for these auxiliary functions to fulfil the restrictions induced by (3.4). As

$$\begin{aligned} p_N\,'(t) = &- a\,'(t)\,[1-b(t)]\,[b(t)]^{N-1} - b\,'(t)\,[1- a(t)]\,[b(t)]^{N-1} + \\ &+ [1-a(t)]\,[1-b(t)]\,(N-1)\,b\,'(t)\,[b(t)]^{N-2} \end{aligned} \tag{3.6}$$

Therefore

$$\begin{aligned} &-a\,'(t)\,[1-b(t)]\,[b(t)]^{N-1} - b\,'(t)\,[1- a(t)]\,[b(t)]^{N-1} + \\ &+ [1-a(t)]\,[1-b(t)]\,(N-1)\,b\,'(t)\,[b(t)]^{N-2} = \end{aligned}$$

$$\begin{aligned} &= \lambda\,(N-1)\,[1 - a(t)]\,[1 - b(t)]\,[b(t)]^{N-2} - \\ &- (\lambda+\mu)\,N\,[1 - a(t)]\,[1 - b(t)]\,[b(t)]^{N-1} \mu\,(N+1)\,[1 - a(t)]\,[1 - b(t)]\,[b(t)]^{N} \end{aligned} \tag{3.7}$$

Both sides are linear in N, thus it imposes two equations, one for the constant (in N) term, and one for the coefficient of N. (After dividing by $[b(t)]^{N-2}$, it yields)

$$[1 - a(t)]\,[1 - b(t)]\,b'(t) = [1 - a(t)]\,[1 - b(t)]\,[\lambda - (\lambda+\mu)\,b(t) + \mu\,b^2(t)] \tag{3.8}$$

and

$$\begin{aligned} &-a\,'(t)\,[1 - b(t)]\,b(t) - b(t)\,[1 - a(t)]\,b(t) - [1 - a(t)]\,[1 - b(t)]\,b\,'(t) = \\ &= [1 - a(t)]\,[1 - b(t)][-\lambda + \mu\,b^2(t)] \end{aligned} \tag{3.9}$$

From the first one we have

$$b'(t) = [1 - b(t)]\,[\lambda - \mu\,b(t)] \tag{3.10}$$

which – when $\lambda \neq \mu$ – is equivalent to

$$\begin{aligned} &\frac{1}{\lambda - \mu}\,b\,'(t)\left(\frac{1}{1 - b(t)} - \frac{1}{\lambda - \mu\,b(t)}\right) = 1 \;\Leftrightarrow \\ &[\log(\lambda - \mu\,b(t))]\,' - [\log(1 - b(t))]\,' = (\lambda - \mu) \end{aligned} \tag{3.11}$$

which integrates

$$b(t) = \left(\frac{Ce^{(\lambda - \mu)t} - \lambda}{Ce^{(\lambda - \mu)t} - \mu} \right) \tag{3.12}$$

where C is a positive constant. Plus we know that $p_N(0) = I_{(N=1)}$, b(0) = 0, hence C=λ. Otherwise (when $\lambda = \mu$) $b'(t) = \lambda [1 - b(t)]^2$, whence (bearing in mind that b(0) =0)

$$\left(\frac{1}{1 - b(t)} \right)' = \lambda \Leftrightarrow b(t) = 1 - \left(\frac{1}{\lambda t + D} \right) \Leftrightarrow b(t) = \left(\frac{\lambda t}{\lambda t + 1} \right) \tag{3.13}$$

The other equality in a simplified form

$$- a'(t) [1 - b(t)] b(t) - b'(t) [1 - a(t)] = [1 - a(t)] [1 - b(t)] [- \lambda + \mu b^2(t)] \tag{3.14}$$

substituting the expression for b'(t) from (3.10), dividing by (1 – a(t)) (1 – b(t)) , then adding λ to both sides, finally dividing by b(t), we obtain

$$\mu - a'(t) / [1 - a(t)] = \mu b(t) \Leftrightarrow - a'(t) / [1 - a(t)] = - \mu [1 - b(t)] \tag{3.15}$$

exploiting the above formula for b'(t) again, but now arranged for *[1 – b(t)],*

$$[\log (1 - a(t))]' = [\log (\lambda - \mu b(t)]' \tag{3.16}$$

Integrating the equation then expressing a(t) with the help of b(t) – when $\lambda \neq \mu$ –

$$a(t) = 1 - D\{\lambda - \mu b(t)\} = \left(\frac{\lambda [1 - D(\lambda - \mu)] e^{(\lambda - \mu)t} - \mu}{\lambda e^{(\lambda - \mu)t} - \mu} \right) \tag{3.17}$$

Moreover we know that a(0) = 0, as $p_N(0) = I_{(N=1)}$, which guarantees
$\lambda [1 - D(\lambda - \mu)] e^{(\lambda - \mu)t} - \mu$ to be zero.
Therefore the unique solution is

$$a(t) = \left(\frac{\mu e^{(\lambda - \mu)t} - \mu}{\lambda e^{(\lambda - \mu)t} - \mu} \right)$$

and

$$b(t) = \left(\frac{\lambda e^{(\lambda - \mu)t} - \lambda}{\lambda e^{(\lambda - \mu)t} - \mu} \right) \tag{3.18}$$

In case $\lambda = \mu$, – using a(0) = 0 –

$$a(t) = b(t) = \left(\frac{\lambda t}{\lambda t + 1} \right) \tag{3.19}$$

Finally the formula for $p_0(t)$ flows from $\sum_{j=0}^{\infty} p_j(t) = 1$, which gives $p_0(t) = a(t)$.

Now we are in the position to say that $p_N(t)$ follows geometric distribution, consequently

$$m(t) = n_0 \frac{1 - a(t)}{1 - b(t)} = n_0 e^{(\lambda - \mu)t} \tag{3.20}$$

$$V(t) = n_0 \frac{[1 - a(t)][a(t) + b(t)]}{[1 - b(t)]^2} = n_0 [(\lambda + \mu) / (\lambda - \mu)] \; e^{(\lambda - \mu)t} [e^{(\lambda - \mu)t} - 1] \tag{3.21}$$

For $\lambda = \mu$ it gives $m(t) = n_0$, $V(t) = 2 n_0 \lambda t$. Hence the asymptotic behaviour of the coefficient variation ($CV(t) = \sqrt{V(t)}$) / m(t))varies widely according to the relative values of λ and μ.

If $\lambda > \mu$, then CV(t) remains constant

$$CV(t) \rightarrow \sqrt{(\lambda + \mu)/[n_0(\lambda - \mu)]} \tag{3.22}$$

when $\lambda = \mu$, then CV(t) increases as $\sqrt{t}$

$$CV(t) \rightarrow \sqrt{2\lambda t/n_0} \tag{3.23}$$

and the most unstable case, $\lambda < \mu$, then CV(t) increases exponentially

$$CV(t) \rightarrow \sqrt{(\lambda + \mu)/[n_0(\lambda - \mu)]} \exp (1/2 (\mu - \lambda)t) \tag{3.24}$$

The obvious objection to exponential growth models that they do not mirror reality in long term (as t increases). It is fairly evident that population growth has many upper bound restrictions imposed by the laws of nature. This drawback of the model can be eliminated by arguing that we use this model to describe just the initial state of growth. This reason is fully supported by the goals of this study. Namely in most cases (for instance in epidemology, food microbiology, food safety) the only phase of growth in limelight is the growth curve preceding the exponential burst of multiplication. Even with this aim in mind the feasibility of predicting future may turn to be unreliable.

3.1.3 Simulations

Simulations can show three different characteristics of the stochastic process depending on the relation of λ and μ. (0.4, 0.2, 0.2, 0.2, 0.2, 0.4 respectively)

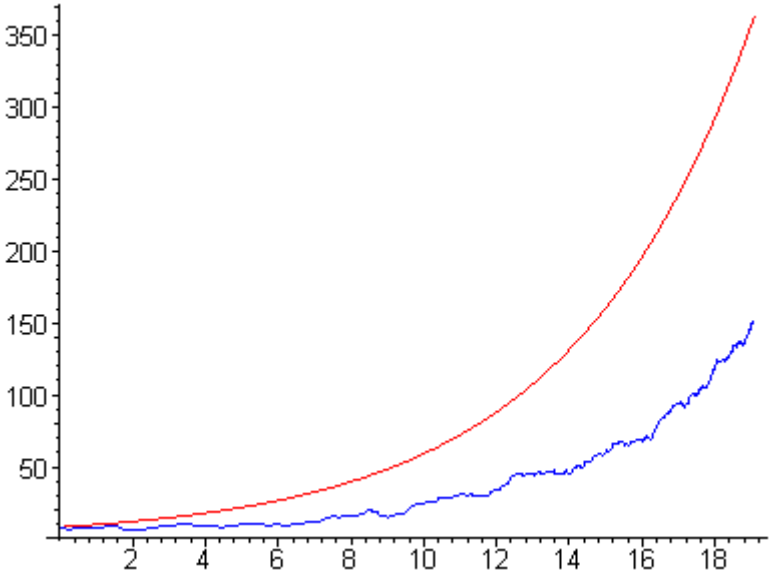

Fig 3.1 Blue dots represent a stochastic realisation, while red ones show its expectation

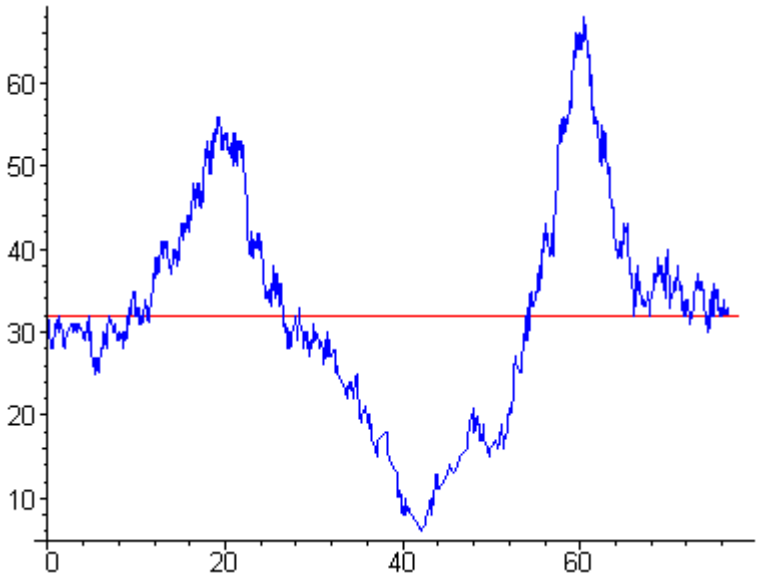

Fig 3.2 Stochastic process shows random fluctuations around its expectation

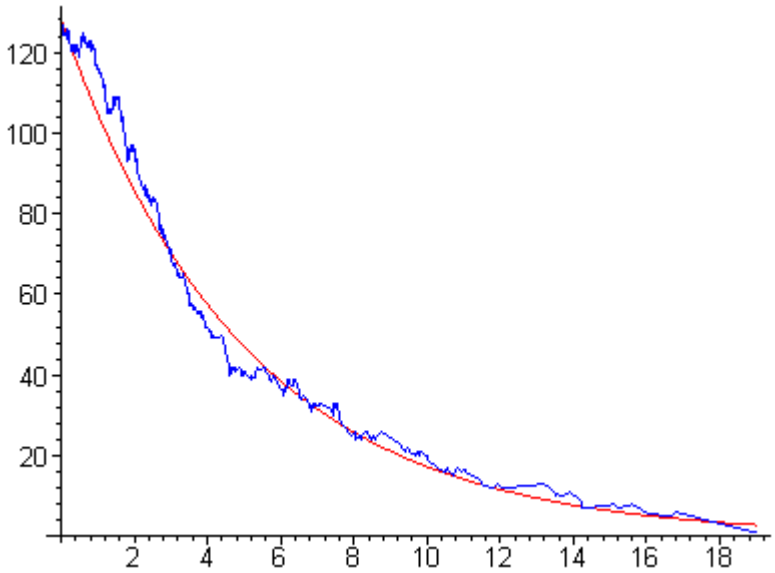

Fig 3.3 To be able to examine the process in long term N(0) was set to be higher

3.1.4 Probability of Extinction

From the results of the previous section, it is easy to express the probability of extinction at time *t*.

$$p_0(t) = [a(t)]^{n_0} = \left(\frac{\mu\, e^{(\lambda-\mu)t} - \mu}{\lambda e^{(\lambda-\mu)t} - \mu}\right)^{n_0} \qquad \text{when } \lambda \neq \mu \tag{3.25}$$

or

$$p_0(t) = [\lambda t / (1 + \lambda t)]^{n_0} \qquad \text{when } \lambda = \mu \tag{3.26}$$

Hence the probability of ultimate extinction can be obtained by letting $t \to \infty$. Therefore it is essential to separate the outcome according to the relative relation of λ and μ.

$$\lambda \leq \mu : \qquad p_0(\infty) = 1 \tag{3.27}$$

$$\lambda > \mu : p_0(\infty) = (\mu / \lambda)^{n_0} \tag{3.28}$$

It's worth noting that even when the $\lambda > \mu$, the extinction is still probable, however it tends to zero as the initial population zooms to infinity. Furthermore the ultimate extinction is certain even if the birth and death rates are the same. Next we are to examine the mean time to extinction, T_m, where *m* stands for the initial population number. Start off to determine T_1. Let us denote the stopping time when (with n_0=1) the population dies out with S. In general S_m stands for the stopping time, when the initial population consists of *m* cells. First consider that

$$P(S \leq t) = p_0(t) = \left(\frac{\mu\, e^{(\lambda-\mu)t} - \mu}{\lambda e^{(\lambda-\mu)t} - \mu}\right) = F(t) \tag{3.29}$$

For a positive random variable we can use the following formula for its expectation

$$E[S] = \int_0^\infty [1 - F_S(t)]dt \tag{3.30}$$

Which can be computed as follows

$$T_1 = E[S] = \int_0^\infty [1 - F_S(t)]dt = \int_0^\infty \frac{(\lambda - \mu)\, e^{(\lambda - \mu)t}}{-\mu + \lambda\, e^{(\lambda - \mu)t}}\, dt =$$

$$= \left[\frac{1}{\lambda} \log\left(\mu + \lambda\, e^{(\lambda - \mu)t}\right)\right]_0^\infty = -\frac{1}{\lambda} \log\left(1 - \frac{\lambda}{\mu}\right) \tag{3.31}$$

Let now Z_m denote the length of time during which the population size is of m. Juggling along the same line as in Section 2.3 it is deducted that $Z_m \sim \text{Exp}((\lambda + \mu)m)$. Now it is clear that

$$S_m = Z_m + \frac{\mu}{\lambda+\mu} S_{m-1} + \frac{\lambda}{\lambda+\mu} S_{m+1} \tag{3.32}$$

As after Z_m time a birth or a death will happen, with the appropriate probability and then we can use recursively the result for the "adjacent" population sizes. It is high time to take expectations

$$T_m = E[Z_m] + \frac{\mu}{\lambda+\mu} T_{m-1} + \frac{\lambda}{\lambda+\mu} T_{m+1} = \frac{1}{(\lambda+\mu)m} + \frac{\mu}{\lambda+\mu} T_{m-1} + \frac{\lambda}{\lambda+\mu} T_{m+1} \tag{3.33}$$

For notational convenience introduce $q_m = T_m - T_{m-1}$, and rearrange the equation

$$\frac{\mu}{\lambda} q_m - \frac{1}{\lambda m} = q_{m+1} \tag{3.34}$$

Theorem

$$q_m = \frac{1}{\mu}\left(\frac{\mu}{\lambda}\right)^m \left\{ -\log\left(1 - \frac{\lambda}{\mu}\right) - \sum_{k=1}^{m-1} \frac{1}{k}\left(\frac{\lambda}{\mu}\right)^k \right\} \tag{3.35}$$

Proof

It is open and shut that mathematical induction would lead us immediately to the result. Suppose that we know the result for m and – using the recurrence relation (3.34) – deduce the formula for (m+1).

$$q_{m+1} = \frac{1}{\mu}\left(\frac{\mu}{\lambda}\right)^{m+1}\left\{ -\log\left(1-\frac{\lambda}{\mu}\right) - \sum_{k=1}^{m-1}\frac{1}{k}\left(\frac{\lambda}{\mu}\right)^{k}\right\} - \tag{3.36}$$

$$-\frac{1}{\mu}\left(\frac{\mu}{\lambda}\right)^{m+1}\left[\mu\left(\frac{\lambda}{\mu}\right)^{m+1}\frac{1}{m\lambda}\right] =$$

$$= \frac{1}{\mu}\left(\frac{\mu}{\lambda}\right)^{m+1}\left\{ -\log\left(1-\frac{\lambda}{\mu}\right) - \sum_{k=1}^{m}\frac{1}{k}\left(\frac{\lambda}{\mu}\right)^{k}\right\} \tag{3.37}$$

which is the formula for (m+1). (It is straight to verify that the formula holds for m =1.) We can rewrite it by using the power series expansion of the log function

$$\log(1-z) = \sum_{j=1}^{\infty}\frac{z^n}{n} \tag{3.38}$$

and combined with

$$T_m = \sum_{j=1}^{m} q_j \tag{3.39}$$

Therefore firstly

$$q_m = \frac{1}{\mu}\left(\frac{\mu}{\lambda}\right)^{m}\left\{\sum_{k=m}^{\infty}\frac{1}{k}\left(\frac{\lambda}{\mu}\right)^{k}\right\} = \frac{1}{\mu}\left(\frac{\mu}{\lambda}\right)^{m}\left\{\sum_{k=0}^{\infty}\frac{1}{k+m}\left(\frac{\lambda}{\mu}\right)^{k+m}\right\} = \tag{3.40}$$

$$= \frac{1}{\mu}\left\{\sum_{k=0}^{\infty}\frac{1}{k+m}\left(\frac{\lambda}{\mu}\right)^{k}\right\} \tag{3.41}$$

Hence

$$T_m = \sum_{j=1}^{m} q_j = \sum_{j=1}^{m} \frac{1}{\mu} \left\{ \sum_{k=0}^{\infty} \frac{1}{k+j} \left(\frac{\lambda}{\mu}\right)^k \right\} = \frac{1}{\mu} \sum_{k=0}^{\infty} \left(\frac{\lambda}{\mu}\right)^k \left\{ \sum_{j=1}^{m} \frac{1}{k+j} \right\} \qquad (3.42)$$

We can use either computer simulations to have a picture about the distribution of time to distinction random variable. The results are as follows

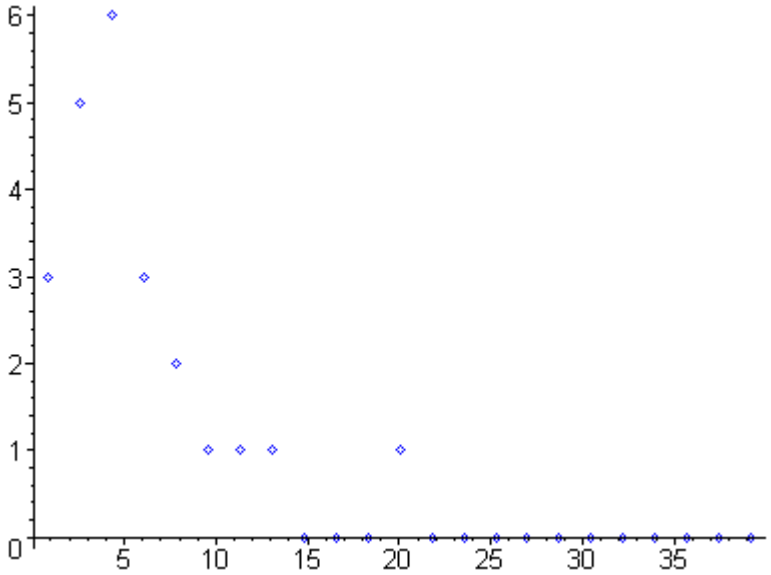

Fig 3.3 Dots represent the frequency distribution of T_8, giving 6.303062844 on average.

3.2 The Simple Immigration–Birth–Death Process

In the models mentioned so far two extremities were out of control. When it is the case $\lambda \leq \mu$, the ultimate extinction was certain to happen, which ignores real biological mechanisms. The other end of the spectrum when $\lambda > \mu$, when with probability $1 - \left(\frac{\mu}{\lambda}\right)^{n_0}$ the population size zooms off to infinity. Therefore let us see how introducing immigration could eliminate these drawbacks.

3.2.1 Deterministic Model

Assume that immigration is independent of population size and occurs randomly at rate αh in a time interval of length h. Consequently the governing equation

$$N(t + h) - N(t) = (\lambda - \mu)hN(t) + \alpha h + o(h) \Leftrightarrow \quad N'(t) = (\lambda - \mu)\, N(t) + \alpha \tag{3.43}$$

which integrates

$$N(t) = n_0 \exp((\lambda - \mu)t + [\alpha / (\lambda - \mu)] [\exp\{(\lambda - \mu)\, t\} - 1] \tag{3.44}$$

This excluded the case of extinction, but infinite growth is still probable.

3.2.2 Equilibrium Probabilities

Upgraded with the immigration factor the probability equations turn into

$$p_0'(t) = -\alpha p_0(t) + \mu p_1(t) \tag{3.45}$$

$$p_N'(t) = [\alpha + \lambda(N-1)]\, p_{N-1}(t) - [\alpha + (\lambda + \mu)N]\, p_N(t) + \mu(N+1)\, p_{N+1}(t) \tag{3.46}$$

The solution of this differential equation system is – due to its numerical complexity – not much of use. It is more captivating what happens to the system in long term. Suppose that it reaches an equilibrium state, with constant equilibrium probability values π_N. From its nature $\pi_N'(t) = 0$, which fact transforms the equations into

$$0 = \alpha\pi_0 - \mu\pi_1 \tag{3.47}$$

$$[\alpha + \lambda(N-1)]\, \pi_{N-1} - \mu N\, \pi_N = [\alpha + \lambda N]\, \pi_N - \mu(N+1)\, \pi_{N+1} \tag{3.48}$$

It gives that

$$0 = \alpha\pi_0 - \mu\pi_1 \qquad \text{and} \qquad [\alpha + \lambda(N-1)]\,\pi_{N-1} = \mu N\,\pi_N \tag{3.49}$$

which yields (by simple successive iteration)

$$\pi_N = \pi_0\,[\alpha + (N-1)\lambda]\,[\alpha + (N-2)\lambda]\,\ldots[\alpha]\,/\,(\mu^N\,N!) = \tag{3.50}$$

$$= \pi_0(\lambda/\mu)^N\,[\alpha/\lambda + (N-1)]\,[\alpha/\lambda + (N-2)]\,\ldots[\alpha/\lambda]\,/\,(N!) =$$
$$= \pi_0(\lambda/\mu)^N \binom{N - 1 + (\alpha/\lambda)}{N} \tag{3.51}$$

In terms of distributions, π follows binomial distribution. The standard form of which is

$$\binom{N - 1 + r}{N}\,p^r q^N \tag{3.52}$$

This determines π_0 (= $(1 - \lambda/\mu)^{\alpha/\lambda}$) and yields the equilibrium mean ($rq/p = \alpha/(\mu - \lambda)$) and variance ($rq/p^2 = \alpha\mu/(\mu - \lambda)^2$). It is nothing new to say about the case $\lambda > \mu$, as it carries infinite growth. There is a special case worth examining, namely when $\lambda = 0$ (i.e. the immigration–death process). Keeping in mind that $\sum_{N=0}^{\infty}\pi_N = 1$

$$\pi_N = \pi_0\alpha^N\,/\,(\mu^N\,N!) = \pi_0\,(\alpha/\mu)^N\,/N! \quad \text{and} \quad \pi_0 = \exp\,(-\alpha/\mu) \tag{3.53}$$

With concise notation, $\pi \sim \text{Poi}(\alpha/\mu)$.

4. General Birth-Death process

So far we dealt with dynamics where the increase or drop in population number remained constant in time and independent of population size. In real biological situations it is not that fact as the prolific cells are limited by the shortage of resources. The level where the carrying capacity appears to impose its effect, is called as the *saturation level*. Consider now four reasons to effect a change in the population: birth, immigration, death and emigration. The first two and the latter two combine to form the general birth–, and death rates, B(N) and D(N) respectively.

4.1 General population growth

Our deterministic approach leads to the formula below

$$N(t+h) = N(t) + [B(N) - D(N)]h + o(h) \quad \Rightarrow \quad N'(t) = (B - D)(N) \qquad (4.1)$$

In case no straightforward integration available, it can be solved numerically by successive use of the original formula for small *h*. The integration can be cumbersome, to illustrate this let us just sketch the solution in case where
(B – D) is a second order polynomial. Looseness in notation (writing N in lieu of N(t)) will emerge, but it causes no ambiguousness.
First, suppose that $r \neq s$.

$$N'(t) = P(N) = a\,(N - r)(N - s) \quad \Leftrightarrow \quad \frac{N'(t)}{N - r} - \frac{N'(t)}{N - s} = \frac{a}{r - s} =: b \quad \Leftrightarrow$$

$$\Leftrightarrow \frac{N - r}{N - s} = C \exp(bt) \qquad (4.2)$$

Combined with the fact that $N(0) = n_0$, we have the solution for N(t)

$$N(t) = \frac{(r - n_0)\, s \exp(bt) - r(s - n_0)}{(r - n_0) \exp(bt) - (s - n_0)} \qquad (4.3)$$

When r =s (the case of multiple roots) – along the same lines – it integrates to give

$$N(t) = r + \frac{n_0 - r}{1 - (n_0 - r)t} \qquad (4.4)$$

4.1.1 Stochastic Approach

Using the usual notation [B(–1) = 0] the difference equation turns into

$$p_N(t+h) = p_{N+1}(t)\, D(N+1)h + p_N(t)\,[1 - \{B(N) + D(N)\}h] + p_{N-1}(t)\, B(N-1)h \qquad (4.5)$$

or

$$p_N'(t) = p_{N+1}(t)\, D(N+1) - p_N(t)\,\{B(N) + D(N)\} + p_{N-1}(t)\, B(N-1) \qquad (4.6)$$

Its general solution is practically impossible to compute, even the easier particular cases causes many difficulties. Although with the help of advanced tools of orthogonal polynomials theory (see [Karlin]) many special cases can be solved, these powerful tools were not shown extensively in practise.

As a consolation way to deal with the problem, it is recommended to examine the equilibrium probabilities. Repeating the same train of thought it yields

$$D(N+1)\,\pi_{N+1} - \{B(N) + D(N)\}\,\pi_N + B(N-1)\,\pi_{N-1} = 0 \qquad (4.7)$$

introducing the same trick

$$D(N+1)\,\pi_{N+1} - B(N)\pi_N = D(N)\,\pi_N - B(N-1)\,\pi_{N-1} \qquad (4.8)$$

thus,

$$D(N)\,\pi_N = B(N-1)\,\pi_{N-1} \quad \text{for all } N = 1, 2\ldots \qquad (4.9)$$

Therefore – combining with the information that the π_N probabilities sum up to 1 – we have the complete solution for π_N

$$\pi_N = \frac{B(0)\,B(1)\,\ldots\,B(N-1)}{D(1)\,D(2)\,\ldots\,D(N)}\,\pi_0 \qquad (4.10)$$

where

$$\pi_0 = \left(1 + \prod_{i=2}^{\infty} \frac{B(0)\,B(1)\,\ldots\,B(i-1)}{D(1)\,D(2)\,\ldots\,D(i)}\right)^{-1} \qquad (4.11)$$

As an illustration let us define $B(N) = \lambda N$ and $D(N) = \mu N(N-1)$. It is perfectly simple to calculate that the equilibrium probabilities will follow censored Poisson distribution (i.e. weighted Poisson distribution for the positive and the zero values).

The shape of theoretical values suggest us that normal approximation could be used. The estimate for its parameters can be the following. $\mu = \sum N\pi_N$ and $\sigma^2 = \sum N^2\pi_N - \mu^2$. From this approach confidence intervals can easily be drawn.

It is widespread to use binomial, negative binomial, Poisson or normal distribution approximation for π_N according to the relation between the obtained μ and σ^2 . The first three distributions constitute the (a,b)-distribution family, which represent distributions, where probabilities are defined recursively. The normal approximation comes from the central limit theorem. Namely, where the mean turns out to be larger it is suggested to use rather binomial–, otherwise negative binomial approximation.

4.2 Logistic population growth

4.2.1 Verhulst–Pearl Equation

Consider the following general equation

$$N'(t) = N\, f(N) \tag{4.12}$$

In case f(N) = r – sN, we call it Verhulst–Pearl logistic equation. In a more reasonable form f(N) can be defined as

$$f(N) = r\,[1 - N/K] \tag{4.13}$$

where r is interpreted as the growth rate in case of unlimited resources, and K is the maximum attainable population size. Exploiting the results of section 2.1, the solution for N (t) goes

$$N(t) = \frac{K}{1 + \{(K - n_0) / n_0\} \exp(-rt)} = \frac{K}{1 + \exp[-r\,(t - t_0)]} \tag{4.14}$$

where

$$t_0 = \frac{1}{r} \log\left(\frac{K}{n_0} - 1\right) \tag{4.15}$$

This function was first in use to describe human population growth in 1838, but remained ignored until 1920, when it was reinvented. It tend to K as t zooms to infinity, and to zero as t goes to minus infinity. Furthermore it has an inflexion (first derivative changes sign) at time point t_0. The estimate for parameters r and K calculated by least square method fitted on the sample observation values.

Let $Y(t) = \log[(K - N) / N] = \log[(K - n_0) / n_0] - rt$, for which simple linear regression would do. This method tested on growth of yeast population exhibits excellent fitting properties. In spite of these promising results, care must be taken as good summary statistics do not always mean that the model reflects the underlying processes well. Moreover considering long–term predictions, unexpected population

fluctuations can ruin any conclusions derived from this model. Contemplating these uncertainties the logistic model may ceased to be valid once the number of cells reached the maximum value.

4.2.2 Simulation of General Population Process

As expected, juggling along the same line as in the simple birth–death process will provide the solution. At population size N the probability of the next event being birth is B(N) / R(N) and for death: D(N) / R(N), where R(N) = D(N) + B(N). Still nothing new about determining the interevent distribution: S ~ Exp(R(N))

Usual general models are of the form

$$B(N) = N(a_1 - b_1N) \qquad D(N) = N(a_2 + b_2N) \qquad (4.16)$$

Simulations agree with the mentioned principle that for large population values the stochastic process shows no agreement with the deterministic model.

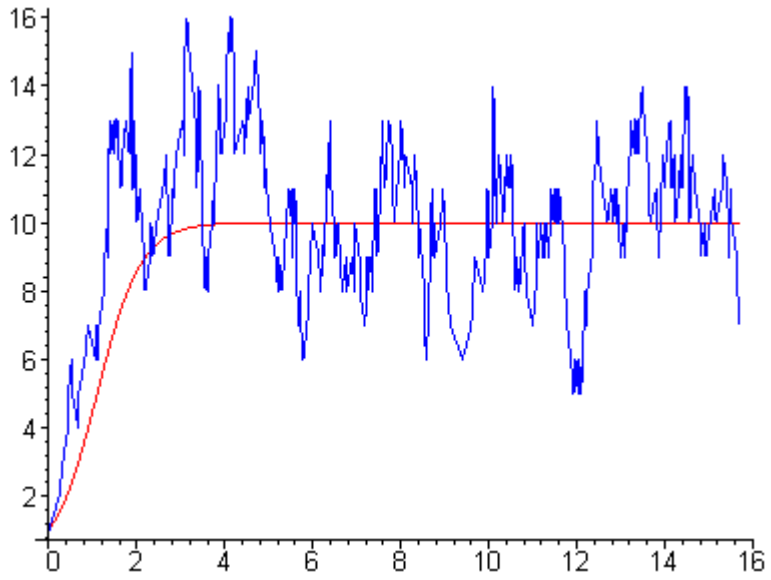

Fig 4.1 Simulation of the stochastic process, with parameters N(0)=1, a_1=2.2, a_2=0.2, b_1=b_2= 0.1

4.2.3 Probability of Ultimate Extinction

Neglecting immigration, let E_i denote $p_0(\infty)$ when the initial size was of i. Thus

$$E_i = [E_{i+1} B(i) + E_{i-1} D(i)] / [B(i) + D(i)] \quad \text{and} \quad E_0 = 1 \tag{4.17}$$

With successive iteration it gives

$$E_n = E_1 + (E_1 - 1)(S_1 + S_2 + \ldots + S_{n-1}), \qquad \text{where } S_i = \frac{D(1)D(2)\ldots D(i)}{B(1)\,B(2)\ldots B(i)} \tag{4.18}$$

Although it is not complete, still suggests that if $\sum_{i=1}^{\infty} S_i = \infty$ then – as $0 \le E_n \le 1 - E_1 =$ 1, thus $E_n = 1$. Even if the sum is finite – in case of infinitely growing populations – $E_\infty = 0$, therefore

$$E_1 = \sum_{i=1}^{\infty} S_i \left[1 + \sum_{i=1}^{\infty} S_i \right]^{-1} \tag{4.19}$$

whence

$$E_n = \sum_{i=n}^{\infty} S_i \left[1 + \sum_{i=1}^{\infty} S_i \right]^{-1} \tag{4.20}$$

For instance, when $B(N) = \lambda N$, $D(N) = \mu N$, we get $(\mu/\lambda)^n$ for E_n. The other extreme, when N reaches a steady state level, say K, $D(N) \ge B(N)$, thus $E_n = 1$, so the ultimate extinction is certain.

4.2.4 Mean Time to Extinction

To grasp a qualitative indicator of a populations stability it is straightforward to use $T_E(n)$, the mean time to extinction with initial population size n. For historical reasons, the stability index is defined as $log(T_E(n))$ and denote it with ξ. To obtain this value, we use the reformulated model, where the time to the first event is exponentially distributed with parameter $B(n) + D(n)$, then the probability of the first event being birth is $B(n)$ and being death is $D(n)$. Hence the recursive formula is readily obtained

$$T_E(n) = \{1 + B(n)T_E(n+1) + D(n)T_E(n-1)\}/\{B(n) + D(n)\} \quad (4.21)$$

To solve this equation we have to redefine everything in terms $\Delta_n = T(n) - T(n-1)$. With this notation the recurrence formula will turn into

$$D(n)\,\Delta_n - 1 = B(n)\,\Delta_{n+1} \quad (4.22)$$

Introduce the following quantities

$$S_i = \frac{D(1)D(2)\ldots D(i)}{B(1)\,B(2)\ldots B(i)} \quad \text{and} \quad q_i = \frac{B(1)\ldots B(i-1)}{D(1)\,D(2)\ldots D(i)} \quad (4.23)$$

We will show by mathematical induction that

$$\Delta_1 = \sum_{i=1}^{N} q_i + \left(\prod_{i=1}^{N} \frac{B(i)}{D(i)}\right)\Delta_{N+1} \quad (4.24)$$

Granted this letting N tend to infinity the second term will vanish and we have

$$\Delta_1 = \sum_{i=1}^{\infty} q_i$$

Proof

To prove(4.24) from (4.22) we have the formula for N=1. Assuming that the formula holds for N, it will be shown to be true for N+1. Substitute () for n = N+1 into () to gain

$$\Delta_1 = \sum_{i=1}^{N} q_i + \left(\prod_{i=1}^{N} \frac{B(i)}{D(i)}\right)\left(\frac{B(n+1)}{D(n+1)}\Delta_{N+2} + \frac{1}{D(n+1)}\right) =$$

$$= \sum_{i=1}^{N} q_i + \left(\prod_{i=1}^{N+1} \frac{B(i)}{D(i)} \right) \Delta_{N+1} + q_{N+1} \qquad (4.25)$$

which is the formula for N+1.

♦

Now Δ_1 is known, namely $\Delta_1 = \sum_{i=1}^{\infty} q_i$. Now let us verify the following formula

$$\Delta_n = S_{n-1} \sum_{i=n}^{\infty} q_i \qquad (4.26)$$

Naturally it is to be proven by induction using the recurrence formula (4.22). Checking the equality for N=1 [$S_0 = 1$], plus

$$\Delta_{n+1} = \frac{D(n)}{B(n)} \Delta_n - \frac{1}{B(n)} = \frac{D(n)}{B(n)} S_{n-1} \left(\sum_{i=n}^{\infty} q_i - \frac{1}{S_n B(n)} \right) = S_n \left(\sum_{i=n}^{\infty} q_i - q_n \right) = S_n \sum_{i=n+1}^{\infty} q_i \qquad (4.27)$$

completes the proof. ♦

As $T_E(n) = \sum_{i=1}^{n} \Delta_i$, we have

$$T_E(n) = \sum_{i=1}^{n} S_{i-1} \sum_{j=i}^{\infty} q_j \qquad (4.28)$$

As an example, consider a simplified logistic growth curve, viz. B(n)=r n and D(n) = r n^2 / K . Here

$q_i = K^i$ / [r i i!] and S_i = i! / (K^i) From this we see that for i > K the mean time to extinction is infinite. On the other end

$$T_E(1) = (1/r) \sum_{i=1}^{\infty} K^i / [i\ i!] \approx \frac{1}{rK} \exp(K) \qquad (4.29)$$

holds for large K values [see Murray, 1974].

5. Time–lag models of population growth

This chapter provides a short introduction to time-lag models, with emphasis on simulations. It is rather a preparatory chapter for Chapter 6, where deep analysis will be carried out to shed some light on the nature of time-lag occurring in microbiology. It is fairly obvious that extreme care must be taken when using deterministic models to predict population growth. Results suggest pros and contras in the debate of relying on deterministic concept of population dynamics. It is immensely important that these well-funded models are able to characterise several growth properties, where reasonable biological consideration was imparted into the governing equations.

5.1 Introduction

In the deterministic models examined so far the model ignored the fact that in reality there is a the time–lag between the inception of an action and the resulting change.

The first type of this approach was introduced by Hutchinson (1948) to describe biocoenosis of lakes, and was used in modelling economy as well. This is called reaction time-lag. The governing equation is as follows

$$N'(t) = r\,N(t)\,[1 - N(t - t_d)/K] \qquad (5.1)$$

The model can be interpreted to be the number of herbivores grazing upon a plant which recovers in time t_d.

An other type of time-lag models is where the birth rates are delayed, i.e.

$$N'(t) = B[N(t - t_d)] - D[N(t)] \qquad (5.2)$$

Or, in a wholly general form

$$N'(t) = H[N(t), N(t - t_d)] \qquad (5.3)$$

There are time-lags of various nature, connected to multitudes of biological processes. Therefore (5.1) is advised to be revisited and extended in the following way

$$N'(t) = r\, N(t - t_G)\, [\, 1 - N(t - t_d)/K] \qquad (5.4)$$

Where t_G is responsible for the gestation time, while the effect of dense proliferation is delayed by different time period. Paving our the way to more sophisticated models in biosciences, the next step was to treat population lag as a random variable, described by its density function z(s). This consideration turns (5.2) into

$$N'(t) = r \int_0^{\infty} z(s) B[N(t-s)]\, ds - D[N(t)] \qquad (5.5)$$

In Chapter 6 deeper investigation will be carried out on this topic.

5.2 Deterministic Analysis

Solving these kind of complex equations mentioned earlier, linearizing is a commonly used technique. As the system (5.1) has a steady state population size K, putting N(t) in the form

$$N(t) = K[1 + n(t)] \tag{5.6}$$

And ignoring the terms of second order it yields

$$n\,'(t) = - r\, n(t - t_d) \tag{5.7}$$

To examine the local behaviour of the linearized system let us assume that the solution is of the form

$$n(t) = \exp(-ct)\exp(iwt) \tag{5.8}$$

Solving equation (5.7) for functions of this form, the following equations emerge for the real and the imaginary part.

$$\begin{aligned} c\cos(wt) + w\sin(wt) &= r\exp(c\,t_d)\cos[w(t - t_d)] \\ -w\cos(wt) + c\,\sin(wt) &= r\exp(c\,t_d)\sin[w(t - t_d)] \end{aligned} \tag{5.9}$$

Which simplifies to give

$$c = r\exp(ct_d)\cos(wt_d) \tag{5.10}$$

and

$$w = r\exp(ct_d)\sin(wt_d) \tag{5.11}$$

For the *overdamped stability* (exponential damping with no oscillation) $c > 0$ and $w = 0$ conditions are required. This concludes to

$$\log(c/r) = (c/r)\,(rt_d) \tag{5.12}$$

Finally to have a solution for see we need $rt_d < 1/e$.

Similarly, for underdamped stability ($c > 0$, $w \neq 0$)

$$1/e < rt_d < \pi/2 \tag{5.13}$$

whilst for instability

$$rt_d > \pi/2. \tag{5.14}$$

5.3 Numerical solutions

To check our local results it worth elaborating a numerical method to approximate the system's behaviour. In this case the equation to be solved numerically

$$N\,'(t) = N(t)\,[1 - 0.02N(t-2)] \qquad (5.15)$$

Results are shown in *fig 5.1*, and agree with our theoretical results.

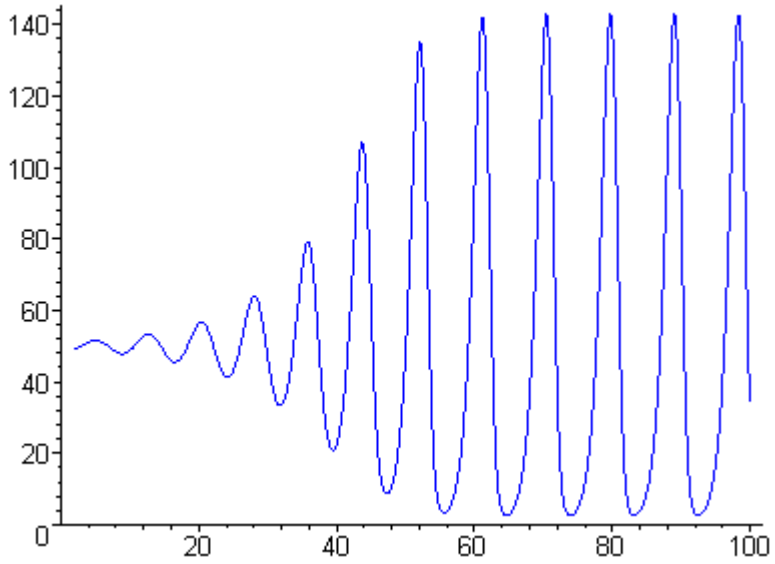

Fig 5.1 Approach to the limit cycle for the deterministic time delayed equation $rt_d = 2$.

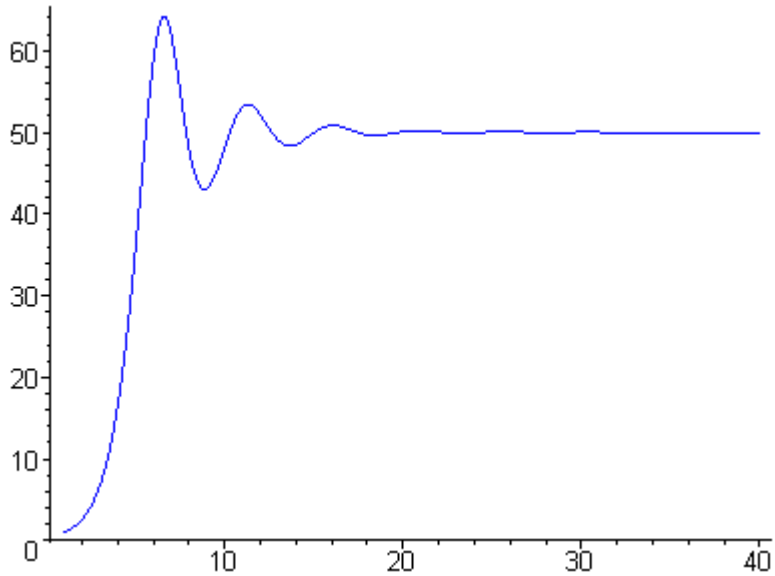

Fig 5.2 Exponential underdamping, $rt_d = 1$.

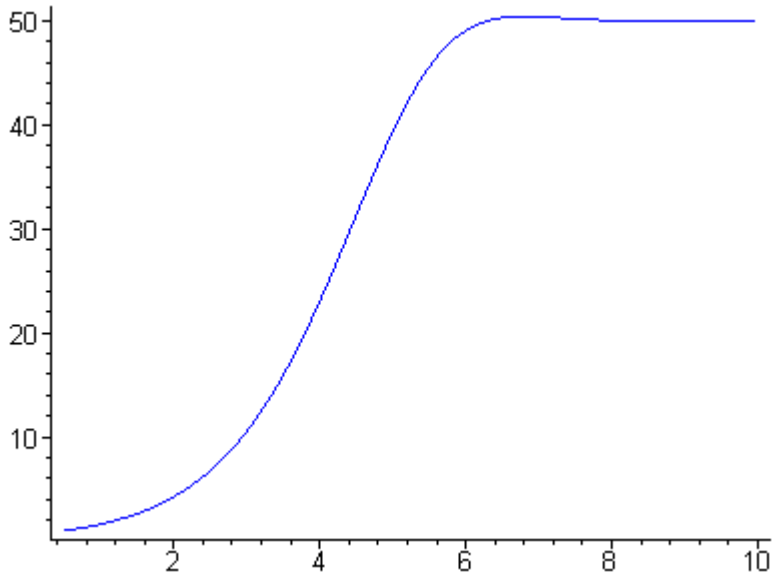

Fig 5.3 Exponential overdamping, rt_d =0.25

5.4 Stochastic Analysis of reaction time-lag

We will proceed along the same lines as in earlier chapters of stochastic approach. The transition probabilities should be determined by the B[N(t)] and D[N(t)] functions, where these functions constituted the deterministic process equation (4.1).

$$\Pr\{N(t+h) = N(t) + 1\} = B[N(t)]h$$
$$\Pr\{N(t+h) = N(t) - 1\} = D[N(t)]h. \qquad (5.16)$$

At this stage B[N(t)] = r N(t) and D[N(t)] = r N(t) N(t – t_d) / K. It can be observed that the more complicated model is proposed, the less tools we have to examine them. To have an skin-deep insight into its complex structure let us apply computer simulations. Fig 5.4 shows a realisation for r=1, K=50, t_d=1, N(0)=50.

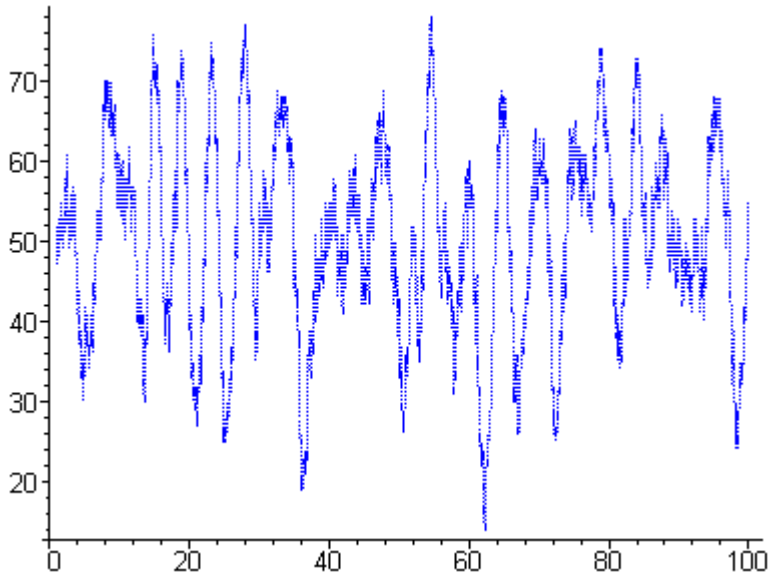

Fig 5.4 The stochastic process shows cycles of varying amplitude and period

5.5 Periodic and chaotic solutions

In population dynamics related to biology some special time series models are used when population growth takes place at discrete intervals of time. Two such difference equations are as follows

$$N(t+1) = N(t)\,[\,(1+r) - (r/K)\,N(t)] \qquad (5.17)$$

and

$$N(t+1) = N(t)\,\exp\{r(1 - N(t)/K)\} \qquad (5.18)$$

The time series induced by these equations exhibits strikingly similar properties, thus we are to deal with the first one. The second one was successfully used by Ricker to describe fish populations.

After normalising $M(t) := N(t)/K$, we have $M(t+1) = M(t)\,[(1+r) - rM(t)]$. Running simulations for r values 1.9, 2.4, 2.55 and 3, all possible behaviour will be perfectly demonstrated, i.e. stable equilibrium, stable 2-point-cycle, stable 8-point-cycle and chaos, respectively.

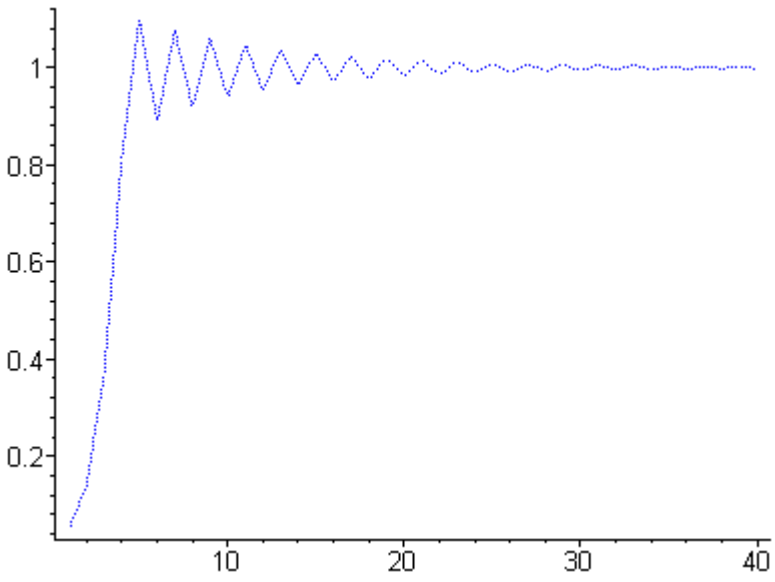

Fig 5.5 Solutions for the difference equation for r=1.9

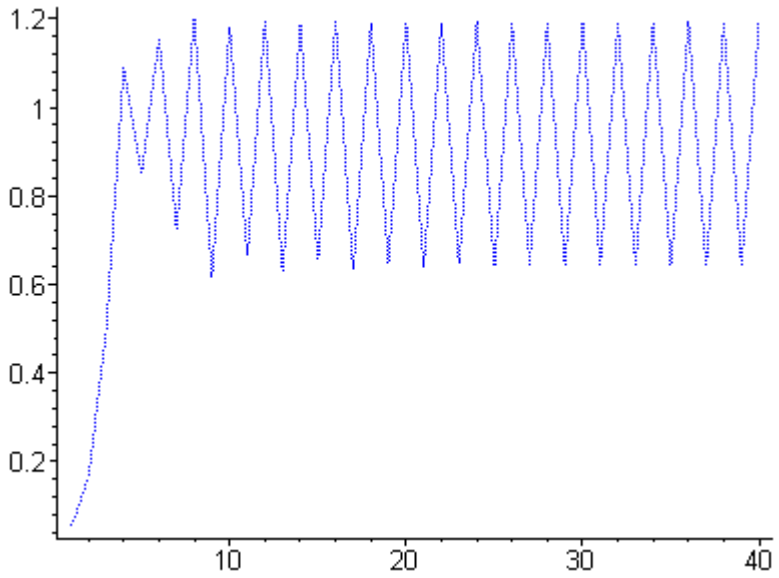

Fig 5.6 Oscillatory curve for r=2.4

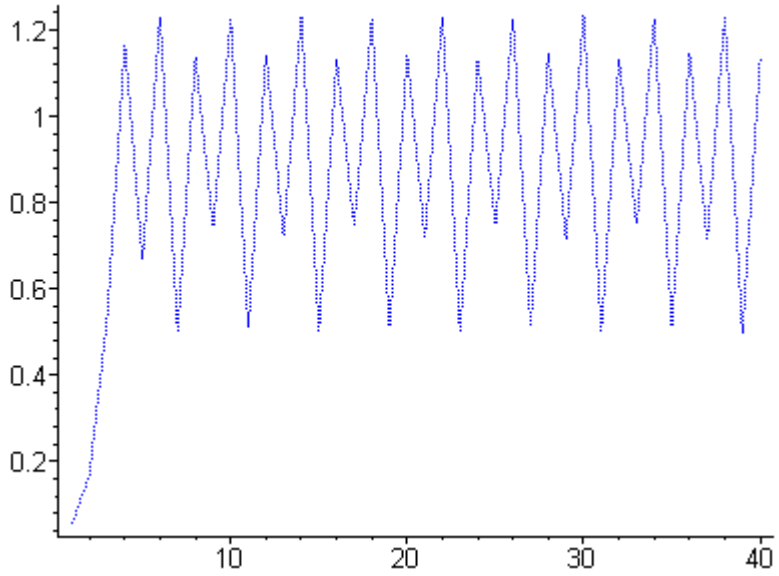

Fig 5.7 8-point-cycle for r=2.55

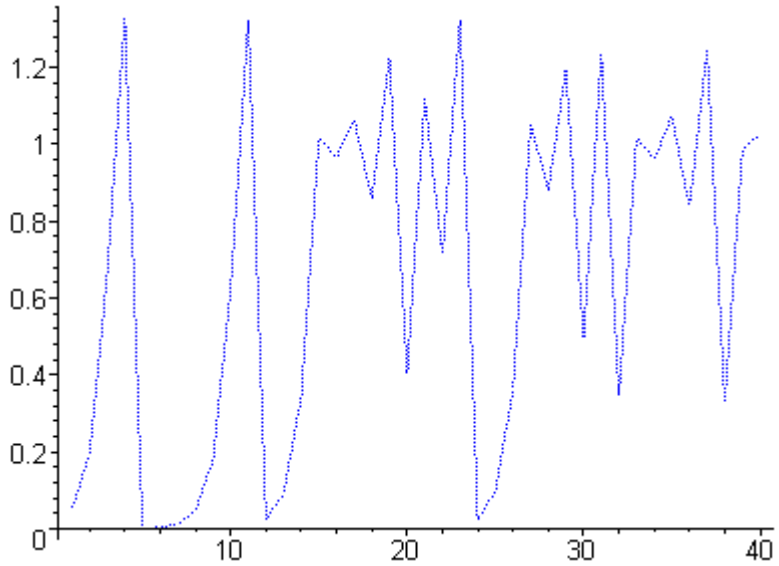

Fig 5.8 Chaos (r=3)

6. Stochastic Modelling of Microbial Growth

In the last century myriad of papers have been published on modelling microbial growth in food environment to predict the time when reaching spoilage level. It is essential in food safety analysis to provide reliable predictions to prevent food poisoning. On one hand the proliferation of bacteria can be monitored under constant conditions to understand its mechanism in full depth. The other basic type of research is when scientists measure phenotypic bacterial response for external stimuli, like change in temperature, pH, water activity, initial cell number. [Masana, 2002, Augustin, 2000, Pin, 2002, Pin, 1998, Hills, 1994, Xiong, 1999, Soboleva, 2001, Bréand, 1997, Salter, 2000, Miles, 1997, Ross, 1996, Robinson, 1998, Valík, 1999]

Up to now bulk of approaches have been applied in modelling population growth, using various areas of mathematical sciences. The earliest and most straightforward concept was to fit special curves to the experimental data set (logistic model, Richards model, Gompertz model, exponential model) [Dalgaard, 2001]. Other branch of models are based on dynamical systems and differential equations with variant level of deep biological justification and sometimes limited scope of use. Besides their practically good computability and considerable usefulness in predicting population growth, these tools can perfectly co-operate with stochastic models to unify their strength and diminish their drawbacks. Moreover, with these tools we are able to model coexistent species living in direct proximity to each other (Lotka-Wolterra). Some models proved to be successful in merging two-species models with the most sophisticated single isolated population models [Vereecken, 2000, Dens, 1999]. Due to the increasing demand for interdisciplinary research biological understanding of cell kinetics helped mathematicians to upgrade their models [Rubinov, 1975]. Finally the 1990s saw a profound breakthrough in this area [Hills, 1994, Baranyi, 1993, Baranyi, 1994, Baranyi, 1995, Silva, 1997, McKellar, 1997, Pin, 2002, Geeraerd, 2000].

There have been many pros and contras mentioned in connection with probabilistic neural networks spiced up with fuzzy logic and bayesian decision strategies in context of modelling population dynamics [Simon, 2001]. Although this

approach is clearly out of our scope, it is has to be stated that those models should be established with extreme care to accumulate the laws of cell kinetics.

Next stage in the history of microbial modelling was probabilistic approach to cell kinetics. Two possible ways were explored. Firstly scientists tried to exploit already existing time series models (ARIMA) or stochastic integrals (Wiener process) [van der Meer, 2000, Soboleva, 2001] , then mathematicians turned to new models, specially brought to life to fit all possible known properties of microbial growth [Baranyi, 1998, Wu, 2000, van Boekel, 2002, Baranyi, 2001, Aparicio, 2001, Baranyi, 2002] .

Deterministic cell kinetic models cease to work properly as environmental factors approach the growth/no growth interface. This boundary can be interpreted in many ways. It is suggested to be defined as the state where the growth rate is zero and the lag is infinite [McMeekin et al., 2002]. Or in stochastic sense it is the state where the probability of growth equals that of no growth [Robinson et al., 2001]. Methods and models has become more and more sophisticated, and the focus bifurcated to prediction and understanding of cell kinetics. Nowadays most up-to-date researches are about to investigate the influence of genetic properties on ability to adaptation and on time-lag distribution [McMeekin et al., 2002]. In harmony with this, emphasis has moved towards risk assessment analysis by probabilistic approach. In this chapter we are to examine the growth process in itself under unchanged environment.

The reason for not dealing with time varying factors is that models pertaining this area (quadratic and square root models) lack in well-funded biological interpretation. General way of model building consisted of two steps. Firstly estimating model parameters for fixed factors [Grijspeerdt, 1999, Xiong, 1999, McKellar, 1997, Baranyi, 1993], then defining the usually quadratic response curve, i.e. finding the connection between environmental factors and parameters [Masana, 2002, Augustin, 2000, Pin, 2002, Pin, 1998, Bréand, 1997, Salter, 2000, Miles, 1997, Ross, 1996, Robinson, 1998, Valík, 1999].

Another interesting point of view is to compare models, and classify them in sense of difference in validity. These models can co-exist, and the most challenging goal is to compare their approach to the same problem. These investigations can shed light on inherent difference and on well hidden connections. This initiative idea is held back by the extensively different use of nomenclature, definitions, ways of laboratory

measurements, discrepancy in tools and methods in use in different research institutions. However some comparative papers have been published so far [Buchanan, 1997, Wu, 2000, Baranyi, 1998, Baranyi, 2001].

These laboratory experiments are reproducible, thus numerous statistical investigations can be adopted and successfully applied. Some scientists suggest that emphasis will be shifted to the extensive elucidation of growth/no growth response surface and eliciting information about ideal environment (e.g. special heat-treatment) for food to extend the expected time to forfeiture. The goal is to produce stable and safe food without contaminating in nutritional or organoleptical sense. In modelling concept it can be interpreted as the lag phase to be infinite.

There are possible physiological explanations for cessation of growth – denaturation of ribosomes, membrane lipid phase changes, energy diversion for self protection. Understanding and analysing these effects on growth may pave our way to a new era of modelling microbial growth.

Many authors analysed the model parameters and investigated whether there is correlation of any nature between them [Pin, 2002, Robinson, 2001, Delignette-Muller, 1998]. It was shown by laboratory experiments that lag and growth rate are inversely related. This statement will be proven in this paper for stochastic models as well. Some scientists suggested to deal with generation time instead of lag time, as the latter one is more erratic when measured. Here we will show that mathematically they are almost identically distributed random variables. A further reason may be for measuring detection times and generation times in lieu of time-lag, that in food safety these variables has much more straightforward biological interpretation.

6.1 Deriving individual lag from deterministic growth curve

Consider the model, where each cell's lag time (τ_i) follows a common distribution (cdf is *F*, pdf *f*). Assume that they are independent random variables. After the lag phase each will grow exponentially (with parameter μ). We will use the same notation as [Baranyi, 2002]. The stochastic individual cell number at time *t* is $Z_i(t) = I(t<\tau_i) + I(t>\tau_i) \exp(\mu(t-\tau_i))$, where $I(\ )$ is the indicator function, i.e. equals one if the condition in brackets met, zero otherwise. Consequently if there are $X(0) = N$ initial cells at time zero, we end up with the following growth process

$$X(t) = \sum_{i=1}^{N} Z_i(t) = \sum_{i=1}^{N} \left(I(t<\tau_i) + I(t>\tau_i) \exp(\mu(t-\tau_i)) \right) \qquad (6.1a)$$

One obtains the deterministic process by taking expectation, in notation, $x(t) = E[X(t)]$. Furthermore, let us denote $\log(x(t))$ by $y(t)$, and $y_0 := y(0)$, $x_0 := x(0)$. Therefore

$$y(t) = y_0 + \mu t + \ln \{ \exp(-\mu t)(1 - F(t)) + \int_0^t \exp(-\mu s) f(s)\, ds \}. \qquad (6.1b)$$

In microbiology time-lag is defined as limit of $(t - y(t) / \mu)$, as t tends to infinity. This comes from the concept that $y(t) \sim \mu(t - \lambda)$, for large t values, as time-lag is the time shift between the pure exponential growth curve and the asymptotic log-count curve. It can be easily deduced that the estimate for the lag time in this model [by letting *t* tend to infinity] is

$$L(\mu) = -(1/\mu) \ln E[\exp(-\mu\tau)] \qquad (6.2)$$

Theorem Function L is monotone decreasing in μ. Namely, the lag time is a decreasing function of the maximum specific growth rate.

Proof

$$L'(\mu) = (1/\mu^2) \ln E[\exp(-\mu\tau)] + (1/\mu) E[\tau \exp(-\mu\tau)] / E[\exp(-\mu\tau)] \le 0 \qquad (6.3)$$

$$E[\exp(-\mu\tau)] \ln E[\exp(-\mu\tau)] \leq -\mu E[\tau \exp(-\mu\tau)] \tag{6.4}$$

$$\alpha := \exp(-\mu\tau) \tag{6.5}$$

$$E[\alpha] \ln E[\alpha] \leq E[\alpha \ln(\alpha)] \tag{6.6}$$

$G(t) := t \ln(t)$ is convex if $t > 0$ ($G''(t) = 1/t$), thus $E[G(Y)] \geq G(E[Y])$

In this particular case: $E[\alpha \ln(\alpha)] \geq E[\alpha] \ln E[\alpha]$. ♦

Theorem

$$F(t) = 1 - \frac{x(t)}{x_0} + \frac{x'(t)}{\mu x_0} \tag{6.7}$$

Namely, the individual time–lag distribution can explicitly drawn from the growth curve.

Proof

$$y(t) = y_0 + \mu t + \ln\{\exp(-\mu t)(1 - F(t)) + \int_0^t \exp(-\mu s) f(s)\, ds\} \tag{6.8}$$

$$y'(t) = \mu - \frac{\mu \exp(-\mu t)(1 - F(t))}{\exp(-\mu t)(1 - F(t)) + \int_0^t \exp(-\mu s) f(s)\, ds} = \mu - \frac{\mu \exp(-\mu t)(1 - F(t))}{\exp(y(t) - y_0 - \mu t)} \tag{6.9}$$

Thus

$$F(t) = 1 + \frac{1}{\mu} \exp(y(t) - y_0)[y'(t) - \mu] \tag{6.10}$$

Let $x(t) = \exp(y(t))$

$$F(t) = 1 - \frac{x(t)}{x_0} + \frac{x'(t)}{\mu x_0} \tag{6.11}$$

♦

In practise, we estimate – by exploiting simple growth models (like Gompertz) – the maximum specific growth rate and the initial population size. Then use the experimental data to estimate x'(t) for t = t_1, t_2, …, t_N For example, let us consider the function at time point t_{i-1}, t_i, t_{i+1}, then the estimate for

$$x'(t_i) = \frac{a}{(a+b)} \frac{x(t_{i+1}) - x(t_i)}{b} + \frac{b}{(a+b)} \frac{x(t_i) - x(t_{i-1})}{a} \quad , \tag{6.12}$$

where *a* stands for $t_i - t_{i-1}$, and *b* for $t_{i+1} - t_i$.

Simulation

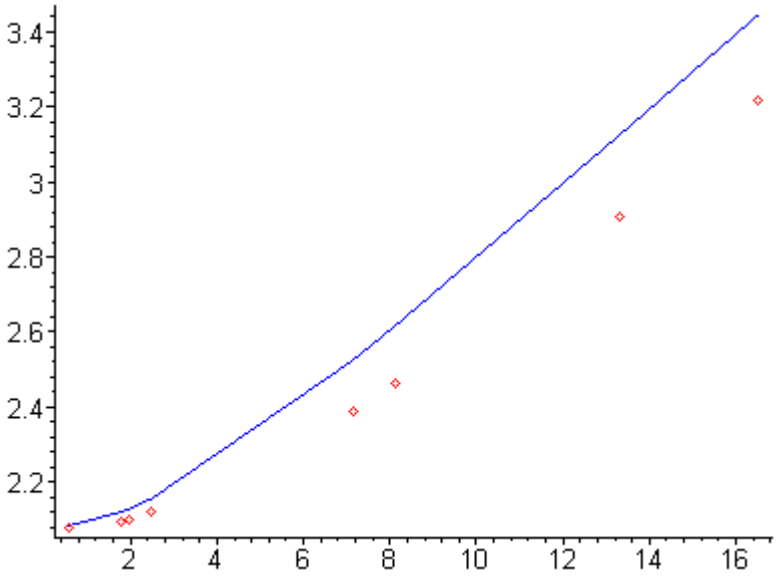

Fig 6.1 Blue line shows the expectation of the stochastic process, while red dots represent a realisation of the stochastic birth process

Remark

Furthermore arranging (6.11) for x'(t) it yields

$$x'(t) = \mu\,[x(t) - x_0(1 - F(t))] \tag{6.13}$$

Namely this model can be derived from a special non–autonomous ordinary differential equation model for the population growth. This can lead us to pose new growth equation for the complete (3-phased) process

$$x'(t) = \mu\,[x(t) - x_0(1 - F(t))]\left(1 - \frac{x(t)}{x_{max}}\right) \qquad (6.13b)$$

Although this differential equation can not be solved explicitly, numerical solution can provide us with valuable information about the nature of growth. Two distributions were used, exponential, and Pareto. Parameters were chosen to produce same expectation for individual time-lag.

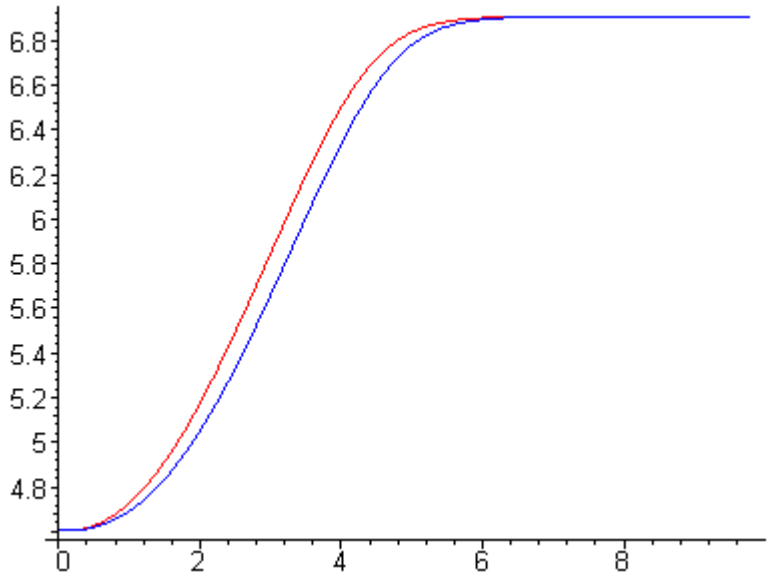

Fig 6.2 Blue graph plots the growth curve for exponentially (ν=0.2) distributed lag, red one on the other hand was computed using Pareto(3,10)

6.2 Predictability

$CV(t) := \sqrt{V(t) / m^2(t)}$, the so–called coefficient variation, where V(t) = Var(X(t)) and m(t) = m(X(t)) = x(t).

Theorem

$$CV(t) \to \sqrt{\frac{1}{x_0}\left(\frac{E[\exp(-2\mu\tau)]}{E[\exp(-\mu\tau)]} - 1\right)} \tag{6.14}$$

as *t* tends to infinity, where τ is the random variable representing the individual lag time and x_0 is the initial number of cells (also referred to as N).

Proof

$Z_i(t) = I(t<\tau_i) + I(t>\tau_i) \exp(\mu(t-\tau_i))$. As τ_i and τ_j are independent, so are $Z_i(t)$ and $Z_j(t)$.

$$\begin{aligned} V(t) &= E\left[\sum_{i=1}^{N} Z_i(t)\right]^2 - (N\,E[Z(t)])^2 = \\ &= E\left[\sum_{i=1}^{N} Z_i^2(t)\right] + \sum_{i\neq j} E[Z_i(t)\,Z_j(t)] - N^2 E^2[Z(t)] = \end{aligned} \tag{6.15}$$

$$= \sum_{i=1}^{N} E[Z_i^2(t)] + N(N-1)\,E^2[Z(t)] - N^2 E^2[Z(t)] \tag{6.16}$$

$$Z_i^2(t) = I(t<\tau_i) + I(t>\tau_i) \exp(2\mu\,(t-\tau_i)) \tag{6.17}$$

$$V(t) =$$

$$N\left\{1 - F(t) + \int_0^t \exp(2\mu(t-s))\, f(s)\, ds - \left[1 - F(t) + \int_0^t \exp(\mu(t-s))\, f(s)\, ds\right]^2\right\} \quad (6.18)$$

$$m^2(t) = N^2\left[1 - F(t) + \int_0^t \exp(\mu(t-s))\, f(s)\, ds\right]^2 \quad (6.19)$$

$$CV^2(t) = \frac{1}{N}\frac{1 - F(t) + \exp(2\mu t)\int_0^t \exp(-2\mu s)\, f(s)\, ds}{\left[1 - F(t) + \exp(\mu t)\int_0^t \exp(-\mu s)\, f(s)\, ds\right]^2} - \frac{1}{N} \rightarrow$$

$$\rightarrow \frac{1}{N}\frac{\int_0^\infty \exp(-2\mu s)\, f(s)\, ds}{\left[\int_0^\infty \exp(-\mu s)\, f(s)\, ds\right]^2} - \frac{1}{N} \quad (6.20)$$

♦

Example

For exponentially distributed lag times (with parameter ν) we have

$$\frac{1}{\sqrt{N}}\frac{\mu}{\sqrt{\nu(2\mu+\nu)}} \quad (6.21)$$

for $CV(\infty)$

Theorem CV(t) is monotone increasing in *t*

Proof

For notational simplifications let us introduce

$$H(\mu) = 1 - F(t) + \exp(\mu t) \int_0^t \exp(-\mu s)\, f(s)\, ds \tag{6.22}$$

It is enough to prove it for $CV^2(t)$, or equivalently its derivative's positivity. Thus

$$(CV^2)'(t) = \frac{1}{N} \frac{\left[2\mu \exp(2\mu t) \int_0^t \exp(-2\mu s)\, f(s)\, ds \right] [H(\mu)]^2}{[H(\mu)]^4} - \frac{2\,[H(\mu)] \left[\mu \exp(\mu t) \int_0^t \exp(-\mu s)\, f(s)\, ds \right] [H(2\mu)]}{[H(\mu)]^4} \tag{6.23}$$

As we are interested only its sign, we can eliminate the denominator all the common positive factors. Which yields to the problem to determine the sign of the expression

$$[H(\mu)] \left[\exp(\mu t) \int_0^t \exp(-2\mu s)\, f(s)\, ds \right] - \left[\int_0^t \exp(-\mu s)\, f(s)\, ds \right] [H(2\mu)] \tag{6.24}$$

Which simplifies to give

$$\int_0^t f(s) \{\exp(\mu(t - 2s)) - \exp(-\mu s)\}\, ds > 0 \tag{6.25}$$

♦

Corollary

Our estimation for the growth, i.e. forecasting, can be a confidence interval like $[x(t)(1 - C), x(t)(1+C)]$, where C depends on the lag distribution and the initial inoculum size. Therefore the length of the confidence interval increases with the time (and the viable count). As a consequence of the model it is not suitable for long term estimations. It is clear from the formula that by increasing the initial number of cells, we can enhance the confidence interval coefficient (C). Combining the last two theorems, we gain that

$$CV(t) < \sqrt{\frac{1}{x_0}\left(\frac{E[\exp(-2\mu\tau)]}{E[\exp(-\mu\tau)]} - 1\right)} \qquad (6.26)$$

for all t, and the accuracy percentage deters with time.

Without any insight into the distribution of X(t), we still can conclude mathematically justified confidence interval, by using Cheisev's inequality. Namely,

$P(|X - E[X]| \geq m) \leq Var(X) / m^2$

Which yields – by substituting X / E[X] for X – $P(|X - E[X]| \geq mE[X]) \leq CV^2(X) / m^2$

Thus if – for safety regulations – the probability of being wrong is to be diminished to α, then the corresponding confidence interval expands to

$$\left[E[X]\left(1 - \sqrt{\frac{1}{\alpha x_0}\left(\frac{E[\exp(-2\mu\tau)]}{E[\exp(-\mu\tau)]} - 1\right)}\right), E[X]\left(1 + \sqrt{\frac{1}{\alpha x_0}\left(\frac{E[\exp(-2\mu\tau)]}{E[\exp(-\mu\tau)]} - 1\right)}\right)\right] \qquad (6.27)$$

For exponentially distributed lag times (with parameter ν) we have

$$E[X]\left(1 \pm \frac{1}{\sqrt{\alpha N}} \frac{\mu}{\sqrt{\nu(2\mu+\nu)}}\right). \qquad (6.28)$$

6.3 The actual maximum specific growth rate and lag time

Consider the Baranyi model for bacterial growth, viz.

$$p(0) = p_0 \tag{6.29}$$

$$x(0) = x_0 \tag{6.30}$$

$$p'(t) = \mu\, p(t) \tag{6.31}$$

$$x'(t) = \mu \frac{p(t)}{K + p(t)} x(t) \left(1 - \frac{x(t)}{x_{max}}\right) \tag{6.32}$$

The solution is as follows

$$x(t) = \frac{x_{max}\,(K + p_0 \exp(\mu t))}{C + p_0 \exp(\mu t)} \tag{6.33}$$

where $C = (K + p_0)\, x_{max} / x_0 - p_0$

Let $y(t) = \ln(x(t))$.

$$y(t) = \ln\left(\frac{x_{max}\,(K + p_0 \exp(\mu t))}{C + p_0 \exp(\mu t)}\right) \tag{6.34}$$

$$y'(t) = -\left(\frac{(K - C)\mu p_0 \exp(\mu t)}{(K + p_0 \exp(\mu t))(C + p_0 \exp(\mu t))}\right) \tag{6.35}$$

The maximum specific growth rate is defined as the maximum value of y'(t). To obtain this result solve y''(t) =0 for t. Which gives

$$t^* = \frac{1}{2\mu} \ln\left(C\, K / {p_0}^2\right) \tag{6.36}$$

$$y'(t^*) = -\mu\left(\frac{(K - C)\sqrt{CK}}{(K + \sqrt{CK})(C + \sqrt{CK})}\right) = \mu\left(\frac{\sqrt{C} - \sqrt{K}}{\sqrt{C} + \sqrt{K}}\right) \tag{6.37}$$

$$y(t^*) = \ln\left(\frac{x_{max}\,(K + \sqrt{CK})}{C + \sqrt{CK}}\right) \tag{6.38}$$

$$\lambda = t^* - \frac{1}{\mu_{max}}\,[y(t^*) - y_0] =$$

$$\frac{1}{2\mu}\,ln\,(C\,K/p_0^2) + ln\left(\frac{x_{max}\,(K + \sqrt{CK})}{C + \sqrt{CK}}\right)\left(\frac{(K + \sqrt{CK})(C + \sqrt{CK})}{\mu(K - C)\sqrt{CK}}\right) \tag{6.39}$$

Which can remarkably differ from the potential $\mu_{max} = \mu$ and potential $\lambda = \log\,(1 + K_z/P_0)/\mu$ estimates. Care must be taken, as from the striking difference between the actual and the potential maximum specific growth rate can result in misleading conclusion for the derived time lag parameter. Therefore – as the lag is not a model parameter – it should not be computed in the same way as for the two-phase model. To visualise this discrepancy see *fig 6.3*

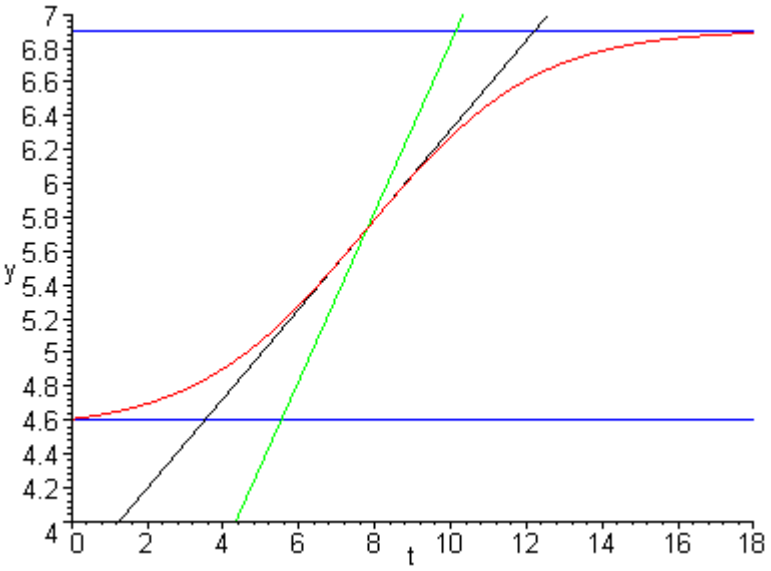

Fig 6.3 Red graph illustrates the growth curve (μ = 5, K = 15, p_0= 1, x_{max} = 1000, x_0 = 100), green line is for the potential maximum specific growth rate, black one represents the actual maximum specific rate.

6.4 Model Extension

Return to the model mentioned in [Baranyi, 2002]. There is striking inconsistency between this and the 2–phase Baranyi model (i.e. where the stationary phase neglected, namely eliminating the $[1 - x(t) / x_{max}]$ factor from the differential equation). It is that in the deterministic model it is assumed that the initial derivative of y(t) can be positive, in this case: $\mu \frac{p_0}{1 + p_0}$. On the other hand in the stochastic model y'(0) = 0. To eliminate this contradiction let us consider an upgraded stochastic model. Here the lag time distribution will be the linear combination of a discrete (dirac delta distribution, concentrated on point zero) and a continuous distribution. In formula:

$$P(\tau = 0) = v \qquad P(\tau \le t \mid \tau > 0) = F(t) \qquad F'(t) = f(t) \tag{6.40}$$

Therefore the stochastic process X(t) is of the form

$$X(t) = \sum_{i=1}^{N} [\, I(t < \tau_i) + \exp(\mu(t-\tau_i))\, I(t \ge \tau_i) \,] =$$

$$\sum_{i=1}^{N} [\, I(t < \tau_i) + \exp(\mu t)\, I(\tau_i = 0) + \exp(\mu(t-\tau_i))\, I(t \ge \tau_i > 0) \,] \tag{6.41}$$

Taking expectation yields

$$x(t) = E[X(t)] = N[\, (1 - v)\,[1 - F(t)] + \exp(\mu t)\, v + (1 - v)\int_0^t \exp(\mu(t - s)) f(s)\, ds \,] \tag{6.42}$$

$$y(t) = y_0 + \mu t + \ln\left(\exp(-\mu t)\,[1 - F(t)](1 - v) + v + (1 - v)\int_0^t \exp(-\mu s) f(s)\, ds \right) \tag{6.43}$$

$$y'(t) = \mu - \frac{\mu \exp(-\mu t)\,[1 - F(t)]\,(1 - v)}{\exp(-\mu t)\,[1 - F(t)]\,(1 - v) + v + (1 - v)\int_0^t \exp(-\mu s)\, f(s)\, ds} =$$

$$\mu - \frac{\mu \exp(-\mu t)\,[1 - F(t)]\,(1 - v)}{\exp\,(y(t) - \mu t - y_0)} = \tag{6.44}$$

$$y\,'(t) = \mu - \frac{\mu\,[1 - F(t)]\,(1 - v)}{x(t) / x_0} \tag{6.45}$$

Whence – along the same lines as above –

$$F(t) = \frac{1}{1 - v}\left((1 - v) + \frac{x'(t)}{\mu x_0} - \frac{x(t)}{x_0}\right) \tag{6.46}$$

.

Thus the distribution function of τ , denote with

$$F_\tau(t) = v + (1 - v)\,F(t) = \left(1 + \frac{x'(t)}{\mu x_0} - \frac{x(t)}{x_0}\right) \tag{6.47}$$

It states that this generalisation in the distribution function does not effect the formula, only the growth curve.

Moreover, the lag remains the same, as

$$\lambda = -\frac{1}{\mu}\left(v + (1 - v)\int_0^\infty \exp(-\mu s) f(s)\,ds\right) = -\frac{1}{\mu}\ln E[\exp(-\mu\tau)]. \tag{6.48}$$

6.5 Stochastic interpretation of the Baranyi model

Let us consider the three–phase Baranyi model for bacterial growth

$$p(0) = p_0 \tag{6.49}$$

$$x(0) = x_0 \tag{6.50}$$

$$p'(t) = \mu\, p(t) \tag{6.51}$$

$$x'(t) = \mu \frac{p(t)}{K + p(t)} x(t) \left(1 - \frac{x(t)}{x_{max}}\right) \tag{6.52}$$

Let us suggest a more general form of its two phased version

$$H(0) = h_0 \tag{6.53}$$

$$x(0) = x_0 \tag{6.54}$$

$$x'(t) = \mu\, H(t)\, x(t) \tag{6.55}$$

Where H(t) is a distribution function (of a non–negative random variable, τ), same as in the above chapter. I.e. $P(\tau = 0) = h_0$, $P(\tau \leq s \mid \tau > 0) = F(s)$ and $F'(t) = f(t)$. On rearranging we have

$$y'(t) = \mu\, H(t) \tag{6.56}$$

which integrates to give

$$y(t) = \mu \int_0^t H(s)\, ds + y_0 = y_0 + \mu \int_0^t P(\tau \leq s) ds =$$

$$y_0 + \mu \int_0^t P(\tau = 0) + P(0 < \tau \leq s) ds = \tag{6.57}$$

$$= y_0 + \mu \int_0^t h_0 + (1 - h_0) \int_0^s f(u)du\, ds = y_0 + \mu h_0 t + \mu(1 - h_0) \int_0^t \int_0^s f(u)du\, ds. \tag{6.58}$$

Applying Fubini's theorem yields

$$y(t) = y_0 + \mu h_0 t + \mu(1 - h_0) \int_0^t \int_u^t f(u)ds\, du = y_0 + \mu h_0 t + \mu(1 - h_0) \int_0^t f(u)(t - u)du = \tag{6.59}$$

$$= y_0 + \mu t - \mu(1 - h_0)[1 - F(t)] - \mu(1 - h_0) \int_0^t u\, f(u)du = E\,[y_0 + \mu(t - \tau)\, I(\tau \le t)] \tag{6.60}$$

Therefore in this model the logarithm of the growth curve can be considered as a stochastic process

$$Y(t) = y_0 + \mu(t - \tau)\, I(\tau \le t). \tag{6.61}$$

Where the individual lag time is clearly

$$E[\tau] = \int_0^\infty [1 - H(s)]ds \tag{6.62}$$

.

6.6 Stochastic justification of the deterministic pure birth process

Let us consider the following cell growth model. Each cell's interevent time between two divisions is exponentially distributed, with parameter μ. We do not violate generality on assuming that cells of same generation have the same interevent time. Thus the stochastic process – with one initial cell – is of the form

$$X(t) = 1 + \sum_{n=1}^{\infty} 2^{n-1} I(t > \Gamma_{n,\mu}) \tag{6.63}$$

where $\Gamma_{n,\mu}$ is a random variable of gamma distribution (p.d.f. is $\frac{1}{\Gamma(n)} \mu^n s^{n-1} e^{-\mu s}$), as the sum of n independent, exponentially (with same parameter, μ) distributed variables is $\Gamma_{n,\mu}$. The deterministic model is derived by taking expectation, namely

$$x(t) = E[X(t)] = 1 + \sum_{n=1}^{\infty} 2^{n-1} \int_0^t \frac{1}{\Gamma(n)} \mu^n s^{n-1} e^{-\mu s} ds = \tag{6.64}$$

with Fubini's theorem

$$= 1 + \int_0^t \mu e^{-\mu s} \sum_{n=1}^{\infty} \frac{(2\mu s)^{n-1}}{(n-1)!} ds = 1 + \int_0^t \mu e^{\mu s} ds = e^{\mu t} \tag{6.65}$$

Which is the deterministic pure birth process.

6.7 A stochastic process with the same deterministic counterpart

Suppose that each cell goes through a lag phase (the length of which is a random variable, denoted by τ, with p.d.f. *f* and df *F*) then follows a pure cell division process described in the previous section. Hence the combined process is

$$X(t) = 1 + \sum_{n=1}^{\infty} 2^{n-1} I(t > \tau + \Gamma_{n,\mu}) \tag{6.66}$$

The following formula will be used to compute the density function of the sum of two independent, nonnegative random variables.

$$h(t) = (f \otimes g)(t) = \int_0^t f(s)g(t-s)ds \tag{6.67}$$

where *f* and *g* are the respective density functions of random variables *X* and *Y* and *h* is the probability density function of *(X+Y)*.

Theorem The induced deterministic model agrees with the formerly introduced one (6.1)

$$y(t) = \log(x(t)) = y_0 + \mu t + \ln\left(\exp(-\mu t)(1 - F(t)) + \int_0^t \exp(-\mu s) f(s)\, ds \right) \tag{6.68}$$

Proof

Along the same lines, the induced deterministic model

$$x(t) = E[X(t)] = 1 + \sum_{n=1}^{\infty} 2^{n-1} \int_0^t \int_0^u \frac{1}{\Gamma(n)} \mu^n s^{n-1} e^{-\mu s} f(u-s)ds\, du = \tag{6.69}$$

On interchanging the sum and the double integral

$$= 1 + \int_0^t \int_0^u \mu e^{\mu s} f(u-s)\, ds\, du = \tag{6.70}$$

interchanging the order of integrations

$$= 1 + \int_0^t \mu e^{\mu s} \int_s^t f(u-s)du\, ds = \tag{6.71}$$

$$= 1 + \int_0^t \mu e^{\mu s} \int_s^t f(u-s)du\, ds = 1 + \int_0^t \mu e^{\mu s} F(t-s)\, ds = \tag{6.72}$$

By partial integration

$$1 - F(t) + \int_0^t e^{\mu s} f(t-s)ds \tag{6.73}$$

Hence

$$y(t) = \log(x(t)) = y_0 + \mu t + \ln\left(\exp(-\mu t)(1 - F(t)) + \int_0^t \exp(-\mu s) f(s)\, ds\right) \tag{6.74}$$

♦

Now compute the coefficient variation (CV(t)) of this process to analyse its stability.

Theorem The coefficient variation of the model tends to infinity as time increases.

Proof

$$\mathrm{Var}[X(t)] = \mathrm{Var}[X(t) - 1] =$$

$$N\left\{E\left[\left(\sum_{n=1}^{\infty} 2^{n-1} I(t > \tau + \Gamma_{n,\mu})\right)^2\right] - E^2\left[\sum_{n=1}^{\infty} 2^{n-1} I(t > \tau + \Gamma_{n,\mu})\right]\right\} \tag{6.75}$$

$$E\left[\left(\sum_{n=1}^{\infty} 2^{n-1} I(t > \tau + \Gamma_{n,\mu})\right)^2\right] = \tag{6.76}$$

$$= E\left[2 \sum_{n<m} 2^{n-1} I(t > \tau + \Gamma_{n,\mu})\, 2^{m-1} I(t > \tau + \Gamma_{m,\mu}) + \sum_{n=1}^{\infty} 2^{2n-2} I(t > \tau + \Gamma_{n,\mu})\right] = \tag{6.77}$$

$$= E\left[2 \sum_{m=1}^{\infty} \sum_{n=1}^{m-1} 2^{n+m-2} I(t > \tau + \Gamma_{m,\mu}) + \sum_{n=1}^{\infty} 2^{2n-2} I(t > \tau + \Gamma_{n,\mu})\right] = \tag{6.78}$$

$$= E\left[2 \sum_{m=1}^{\infty} 2^{m-1} I(t > \tau + \Gamma_{m,\mu}) \sum_{n=1}^{m-1} 2^{n-1} + \sum_{n=1}^{\infty} 2^{2n-2} I(t > \tau + \Gamma_{n,\mu})\right] = \tag{6.79}$$

$$= E\left[2 \sum_{m=1}^{\infty} 2^{m-1} I(t > \tau + \Gamma_{m,\mu})(2^{m-1} - 1) + \sum_{n=1}^{\infty} 2^{2n-2} I(t > \tau + \Gamma_{n,\mu})\right] = \tag{6.80}$$

$$= E\left[3 \sum_{m=1}^{\infty} 2^{2m-2}\, I(t > \tau + \Gamma_{m,\mu}) - \sum_{m=1}^{\infty} 2^{m}\, I(t > \tau + \Gamma_{m,\mu}) \right] = \tag{6.81}$$

$$3\mu \int_0^t \int_0^u e^{-\mu s} \sum_{m=1}^{\infty} \frac{(4\mu s)^{m-1}}{(m-1)!} f(u-s)\, ds\, du - 2\mu \int_0^t \int_0^u e^{-\mu s} \sum_{m=1}^{\infty} \frac{(2\mu s)^{m-1}}{(m-1)!} f(u-s)\, ds\, du = \tag{6.82}$$

$$= 3\mu \int_0^t \int_0^u e^{3\mu s} f(u-s)\, ds\, du - 2\mu \int_0^t \int_0^u e^{\mu s} f(u-s)\, ds\, du = \tag{6.83}$$

$$= 3\mu \int_0^t e^{3\mu s} F(t-s)\, ds - 2\mu \int_0^t e^{\mu s} F(u-s)\, ds \tag{6.84}$$

Thus

$$Var[X(t)] = N\left\{ E\left[\left(\sum_{n=1}^{\infty} 2^{n-1}\, I(t > \tau + \Gamma_{n,\mu}) \right)^2 \right] - E^2\left[\sum_{n=1}^{\infty} 2^{n-1}\, I(t > \tau + \Gamma_{n,\mu}) \right] \right\} =$$

$$= N\left\{ 3\mu \int_0^t e^{3\mu s} F(t-s)\, ds + 1 - \left(\mu \int_0^t e^{\mu s} F(u-s)\, ds + 1 \right)^2 \right\} \tag{6.85}$$

$$CV(t) = \frac{1}{\sqrt{N}} \left(\frac{(1 - F(t)) + e^{3\mu t} \int_0^t e^{-3\mu s} f(s)\, ds}{\left((1 - F(t)) + e^{\mu t} \int_0^t e^{-\mu s} f(s)\, ds \right)^2} - 1 \right)^{\frac{1}{2}} \tag{6.86}$$

♦

This unfortunately tends to infinity as the time increases. This indicates that we have to be more careful with the estimates according to the model proposed earlier.

6.8 Time–lag distribution

Revisit the model where each cell after a shoulder period, τ, grow exponentially. We are to define time–lag within the stochastic model and find its approximate distribution (with the help of computer simulations).

$$X(t) = \sum_{i=1}^{N} I(t \le \tau_i) + I(t > \tau_i) \exp(\mu(t-\tau_i)) =$$

$$= \sum_{i=0}^{N} \left\{ I(\tau_i^* \le t < \tau_{i+1}^*)[\,(N - i) + \sum_{j=1}^{i} \exp(\mu(t-\tau_i))] \right\} \qquad (6.87)$$

where τ_i^* is the i–th smallest random variable within the τ–sample. $\tau_0^* = 0$ and $\tau_{N+1}^* = \infty$.

Which is for $t > \tau_N^*$ is of the form

$$X(t) = \sum_{j=1}^{N} \exp(\mu(t-\tau_i)) = N \exp(\mu t) \frac{1}{N} \sum_{j=1}^{N} \exp(-\mu\tau_i) \qquad (6.88)$$

$$Y(t) = \log (X(t)) = y_0 + \mu \left[t - \frac{1}{\mu} \ln \left(\frac{1}{N} \sum_{j=1}^{N} \exp(-\mu\tau_i) \right) \right] \qquad (6.89)$$

Thus the population lag is

$$\lambda = -\frac{1}{\mu} \ln \left(\frac{1}{N} \sum_{j=1}^{N} \exp(-\mu\tau_i) \right) \qquad (6.90)$$

Important to note that the individual time–lag distribution differs remarkably from the aggregate lag distribution. However we can express the probability density function of λ in integral form, the explicit formula gives no clue for the shape of the distribution and its computation is cumbersome even for N = 2. Therefore we can have much more straightforward results by computer simulation. According to the outcome, it was suggested by [Wu, 2000] that regardless of the individual time–lag distribution family the aggregate lag follows normal distribution. *Fig 6.4* gives an illustration of the distribution of population time-lag with gamma distributed individual time-lag. Same

results can be drawn from other individual lag distributions, like exponential, or normal.

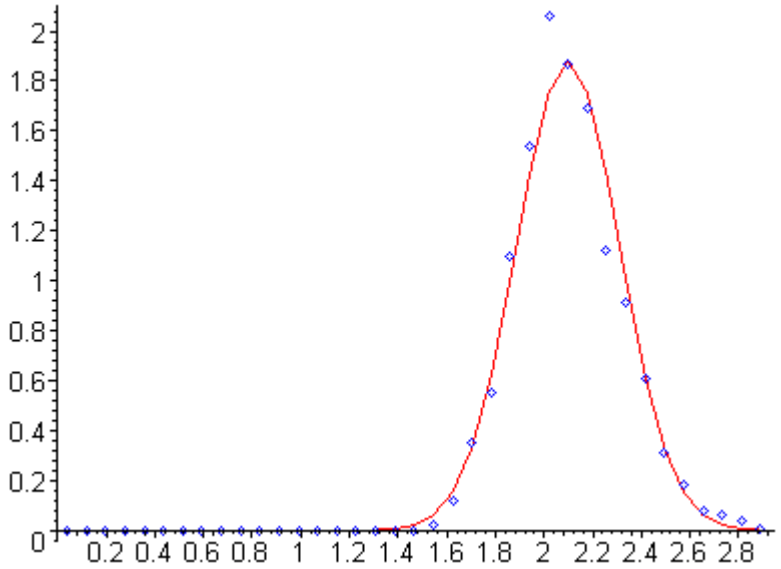

Fig 6.4 The red line represents the fitted normal distribution's density function and the blue dots are the normalised frequency curve drawn from the sample. Here the sample size is 1500, the initial population 32, the individual lag follows gamma distribution ($\Gamma_{3,1}$), $\mu = 1$.

Moreover, it must be expressed that the estimate for the common lag derived from this model, E[λ] deviates from the one gained from the deterministic model. The reason lies in the fact that LAG (E[Y(t)]) $\neq$ E[LAG (Y(t)], where LAG is the time–lag operator of a (stochastic/deterministic) process. In our case it is equivalent to the discrepancy between

$$-\frac{1}{\mu}\ln\{E[\exp(-\mu\tau)]\} \qquad \text{and} \qquad -\frac{1}{\mu}\,E\left[\ln\left(\frac{1}{N}\sum_{j=1}^{N}\exp(-\mu\tau_i)\right)\right] \tag{6.91}$$

This difference does not manifest itself only in the change of shape, but also in the expectation. Although in case of exponentially distributed individual lag, with expectation 1, the aggregate lag reduces to 0.7. Also in case of gamma distribution, the lag of a single cell is to be 3, while the expected common lag turns out to be 2.2. Where the individual lag was assumed to be normally distributed the joint lag diminished to 0.9 from 1.

In accord with simulation results, it is quite straightforward to show that the individual lag exceeds the population lag.

Theorem $E[\tau] \geq -\frac{1}{\mu}\ E\left[\ln\left(\frac{1}{N}\sum_{j=1}^{N}\exp(-\mu\tau_i)\right)\right]$

Proof

As the logarithm function is concave, thus

$$-\frac{1}{\mu}\ln\left(\frac{1}{N}\sum_{j=1}^{N}\exp(-\mu\tau_i)\right) \leq -\frac{1}{\mu}\left(\frac{1}{N}\sum_{j=1}^{N}\ln(\exp(-\mu\tau_i))\right) = \frac{1}{N}\sum_{j=1}^{N}\tau_i \qquad (6.92)$$

Taking expectation completes the proof. ♦

This result was verified by laboratory experiments (see [Robinson, 2001])

Furthermore, the following theorem holds.

Theorem The lag derived from the stochastic model is longer than the time lag in the deterministic sense. Translated into mathematical formula

$$-\frac{1}{\mu}\ln\{E[\exp(-\mu\tau)]\} \leq -\frac{1}{\mu}\ E\left[\ln\left(\frac{1}{N}\sum_{j=1}^{N}\exp(-\mu\tau_i)\right)\right] \qquad (6.93)$$

Proof

As the logarithm function is concave, $E[\ln(X)] \leq \ln(E[X])$, for any positive random variable. Applied in this case,

$$E\left[\ln\left(\frac{1}{N}\sum_{j=1}^{N}\exp(-\mu\tau_i)\right)\right] \leq \ln\left(E\left[\frac{1}{N}\sum_{j=1}^{N}\exp(-\mu\tau_i)\right]\right) = \ln(E[\exp(-\mu\tau)]) \qquad (6.94)$$

♦

Another aspect of the difference in the two lag models is that the one proposed earlier does not depend on the initial inoculum size. However it seems to be logical to expect smaller time–lag for larger inoculum size, by simulation we can show that it does not hold precisely in general. See *Fig 6.2* for simulation results.

Despite this discouraging fact, it can be shown that

Theorem $\lambda(2N) < \lambda(N)$.

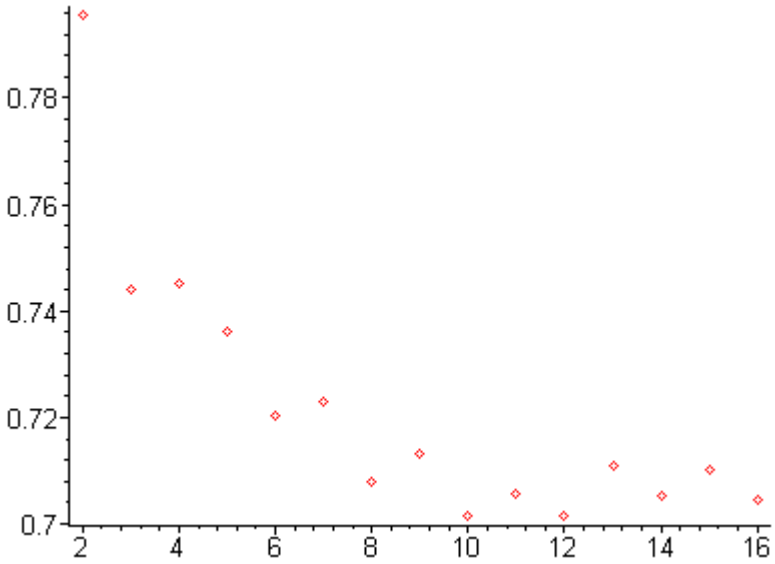

Fig 6.5. Population time–lag values plotted against the initial cell number, N. Individual lag was adjusted to be exponentially distributed with parameter value 1.

Proof

It is equivalent to prove that

$$E\left[\ln\left(\frac{1}{2N}\sum_{j=1}^{2N}\exp(-\mu\tau_i)\right)\right] \geq E\left[\ln\left(\frac{1}{N}\sum_{j=1}^{N}\exp(-\mu\tau_i)\right)\right] \qquad (6.95)$$

For simplification in formula let us introduce some notations.

$$X_i := \exp(-\mu\tau_i),\ Y_n := \sum_{i=1}^{n} X_i \text{ and } Y_n' := \sum_{i=n+1}^{2n} X_i \qquad (6.96)$$

Furthermore let H(t) be the distribution function , and h(t) the pdf of random variable Y_N (and of Y_N' as well).

On rearrangement, it remains to be proven

$$E\left[\ln\left(\frac{Y_{2N}}{Y_N}\right)\right] \geq \ln(2)$$

Let us juggle with the left hand side

$$E\left[\ln\left(\frac{Y_{2N}}{Y_N}\right)\right] = E\left[\ln\left(1+\frac{Y_N'}{Y_N}\right)\right] = \qquad (6.97)$$

$$\int_0^N \int_0^N \ln\left(1 + \frac{x}{y}\right) h(x)\, h(y)\, dx\, dy = \tag{6.98}$$

$$\int_0^N \int_0^y \left[\ln\left(1 + \frac{x}{y}\right) + \ln\left(1 + \frac{y}{x}\right)\right] h(x)\, h(y)\, dx\, dy = \tag{6.99}$$

$$\int_0^N \int_0^y \left[\ln\left(2 + \frac{x}{y} + \frac{y}{x}\right)\right] h(x)\, h(y)\, dx\, dy = \tag{6.100}$$

It is clear that for $0 < a$, $a + \frac{1}{a} \geq 2$. (Use the inequality for arithmetic and geometric means.) Thus

$$\int_0^N \int_0^y \left[\ln\left(2 + \frac{x}{y} + \frac{y}{x}\right)\right] h(x)\, h(y)\, dx\, dy \geq \int_0^N \int_0^y 2\ln(2)\, h(x)\, h(y)\, dx\, dy = \tag{6.101}$$

$$\ln(2) \int_0^N 2\, H(y)\, h(y)\, dy = \ln(2)\,[H^2(N) - H(0)] = \ln(2) \tag{6.102}$$

♦

Theorem

$$L(\mu) = -\frac{1}{\mu}\, E\left[\ln\left(\frac{1}{N}\sum_{j=1}^{N} \exp(-\mu\tau_i)\right)\right] \tag{6.103}$$

is monotone decreasing in μ. Namely, the time lag in this model decreases as the maximum specific growth rate increases.

Proof

It is sufficient if $L'(\mu)$ turns out to be negative. For shortening, use the notation X_i for $\exp(-\mu\tau_i)$ and

$$Z_i := \frac{X_i}{\sum_{j=1}^{N} X_j}. \tag{6.104}$$

Then

$$-L'(\mu) = \frac{1}{\mu} E\left[\frac{\sum_{i=1}^{N}(-\tau_i \exp(-\mu\tau_i))}{\sum_{i=1}^{N} X_i}\right] - \frac{1}{\mu^2} E\left[\ln\left(\frac{1}{N}\sum_{i=1}^{N} X_i\right)\right] = \tag{6.105}$$

$$\frac{1}{\mu^2} E\left[\sum_{i=1}^{N} \ln(X_i) \frac{X_i}{\sum_{j=1}^{N} X_j} - \ln\left(\frac{1}{N}\sum_{i=1}^{N} X_i\right)\right] = \tag{6.106}$$

$$\frac{1}{\mu^2} E\left[\sum_{i=1}^{N} \ln\left(\frac{X_i}{\sum_{j=1}^{N} X_j}\right) \frac{X_i}{\sum_{j=1}^{N} X_j} + \ln(N)\right] = \tag{6.107}$$

$$= \frac{1}{\mu^2}\left\{N\, E\left[\frac{1}{N}\sum_{i=1}^{N} Z_i \ln(Z_i)\right] + \ln(N)\right\} \tag{6.108}$$

G(s) = s ln(s) is convex (as was shown earlier) for s > 0. Hence

$$\frac{1}{N}\sum_{i=1}^{N} G(Z_i) \geq G\left(\frac{1}{N}\sum_{i=1}^{N} Z_i\right) \tag{6.109}$$

Therefore – using the property $\sum_{i=1}^{N} Z_i = 1$ – it gives

$$-L'(\mu) = \frac{1}{\mu^2}\left\{N\, E\left[\frac{1}{N}\sum_{i=1}^{N} Z_i \ln(Z_i)\right] + \ln(N)\right\} \geq \frac{1}{\mu^2}\left\{N\, E\left[\frac{1}{N}\ \ln\,(1/N)\right] + \ln(N)\right\} = 0. \tag{6.110}$$

♦

6.9 Detection time as a mean to quantify population lag

It is wide spread to measure population lag by the means of detection time or doubling time. However it is not a one–to one mapping, we can deduce from one the other reasonably well. If the approximation of time lag is required to be measured within an arbitrary accuracy level, it can be done by increasing the detection level. In other words, if we choose high enough detection level (say qN, where the N represents the initial inoculum), then the formula $\lambda = T_{d,q} - \ln(q)/\mu$ represents an excellent approximation for the real time lag. Where $T_{d,q}$ is the detection time for the level *q*, i.e. $T_{d,q} = \inf \{ t > 0 : X(t) \geq qN \}$

Proof

If q is large enough, then $T_{d,q}$ will be large enough to be greater than τ_N^* with considerably good chance (in terms of probability level). Thus $T_{d,q}$ can be substituted by the following conditional random variable

$$T_{d,q} \approx (T_{d,q} \mid T_{d,q} > \tau_N^*) = \inf \{ t > 0 : X(t) \geq qN \} = \qquad (6.111)$$

$$\inf \left\{ t > 0 : Y(t) = \ln(N) + \mu \left[t - \frac{1}{\mu} \ln \left(\frac{1}{N} \sum_{j=1}^{N} \exp(-\mu \tau_i) \right) \right] \geq \ln(qN) \right\} = \lambda - \frac{\ln(q)}{\mu} \qquad (6.112)$$

♦

6.10 Revisiting population lag distribution

However normal approximation showed a reasonably good fit for the frequency distributions (gained from simulation), it has to be analysed more carefully with more sophisticated mathematical consideration. In this chapter the central limit theorem will be applied to gain a deeper understanding of the time lag distribution.

Theorem Let $X_1, X_2, \ldots$ be independent, identically distributed random variables, with common expectation m and variance v^2. Then

$$\frac{1}{v\sqrt{N}}\left(\sum_{i=1}^{N} X_i - Nm\right) \xrightarrow{d} Y \qquad (N \to \infty) \tag{6.113}$$

where Y follows standard normal distribution.♦

Remark (Berry–Eseen Theorem) Moreover the speed of convergence can be calculated, as for every X, with a finite absolute third moment, there exists a constant C, such that

$$\sup_z \left| p\left(\frac{1}{v\sqrt{N}}\left(\sum_{i=1}^{N} X_i - Nm\right) < z\right) - \Phi(z)\right| < \frac{C\, E|X|^3}{\sqrt{N}} \tag{6.114}$$

♦

Using this fundamental theorem for $X_i := \exp(-\mu\tau_i)$, we gain that for relatively large N values

$$\frac{1}{N}\sum_{i=1}^{N} X_i \overset{d}{\approx} N(m, v^2/N) \tag{6.115}$$

holds.

Therefore the population lag has the following approximate probability density function

$$f(t) = \mu\sqrt{\frac{N}{2\pi}}\frac{1}{v}\exp\left\{-\frac{N}{2v^2}\left(e^{-\mu t} - m\right)^2\right\}\exp(-\mu t) \tag{6.116}$$

For instance, in case when the individual lag, τ, is exponentially distributed with expectation α, then

$$m = (1 + \alpha\mu)^{-1} \tag{6.117}$$

$$v^2 = (1 + 2\alpha\mu)^{-1} - (1 + \alpha\mu)^{-2} \tag{6.118}$$

However this distribution function emerges only in the limit, provides better approximation (in least square sense) than the best normal distribution even for small N values such as N = 8, 16, 32, 64. This can be verified by simulation.

In the following plots blue dots represent the relative frequency gained from the simulation, where the individual lag is exponentially distributed (mean value = 1), μ was set to be 1, while the sample size was 1500, and N = 8, 16, 32, 64 cells were unleashed to grow at time zero. Black curve show the newly introduced distribution, while red one the formerly used normal distribution curve.

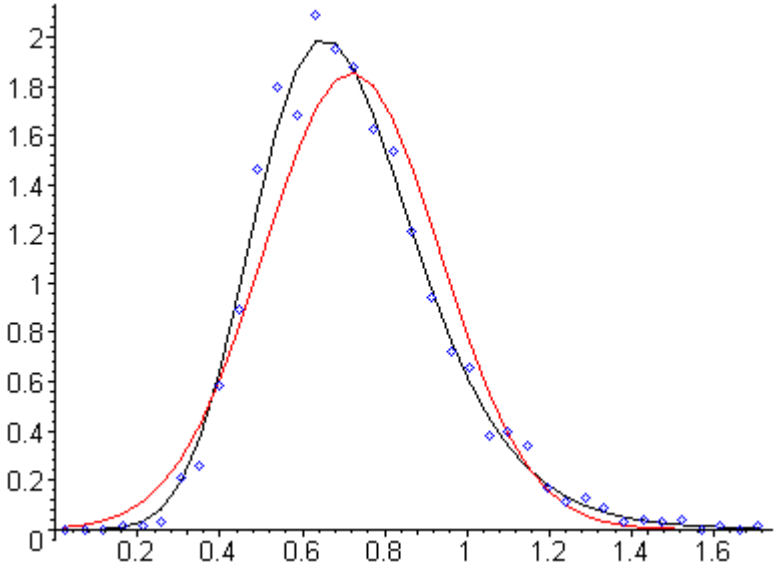

Fig 6.6 N = 8. The summed squared difference between the simulated frequencies and the normal approximation was 1.0149, while with the new approach it was reduced to give 0.1594.

Just one further argument against normal distribution is the range of the random variable. It is clear that time-lag can not be negative, which is not reflected in normal distribution's approximation, as with this assumption there is a positive probability that the population lag will turn out to be negative, which is a nonsense. These evidences and arguments along with other papers, strongly contradicts theories emerged in [Wu, 2000].

Note that this suggests that individual lag cannot be elicited from the population lag, however it can be drawn from the (expected) growth curve itself [6.1].

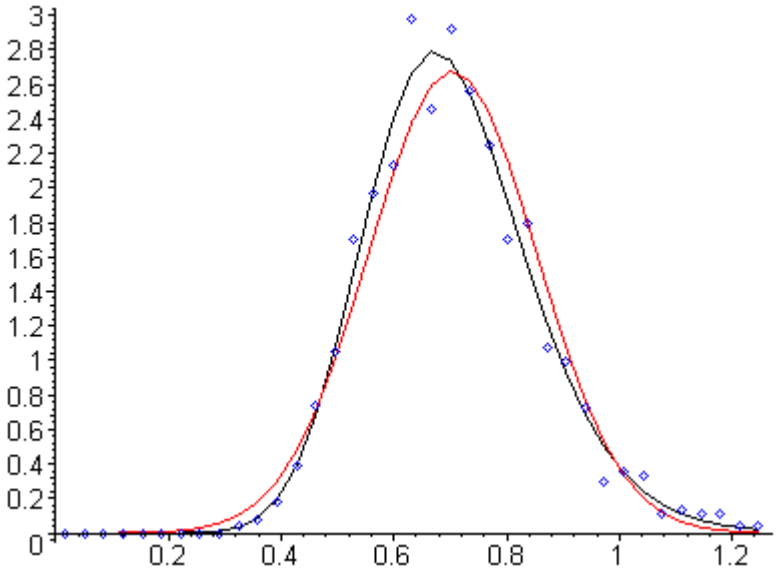

Fig 6.7 N = 16. The respective deviations from the simulation are 1.1496 and 0.5376

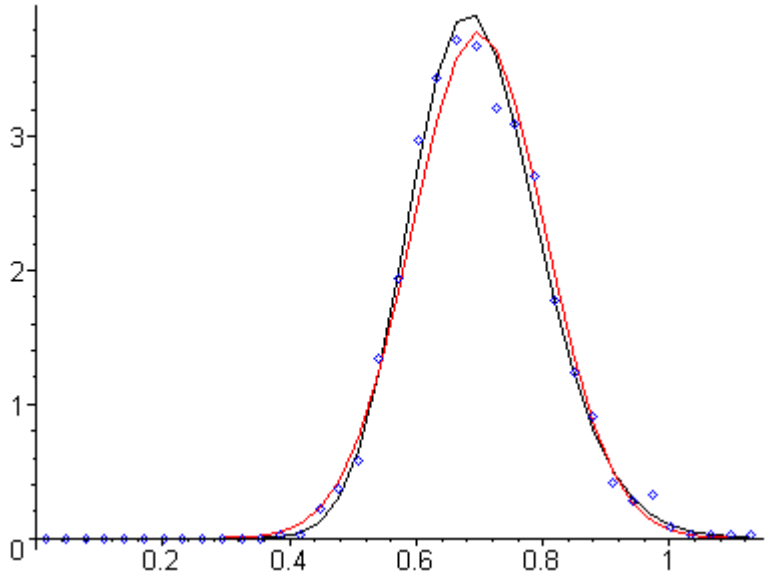

Fig 6.8 N = 32. The discrepancy 0.7656 and 0.4269, respectively

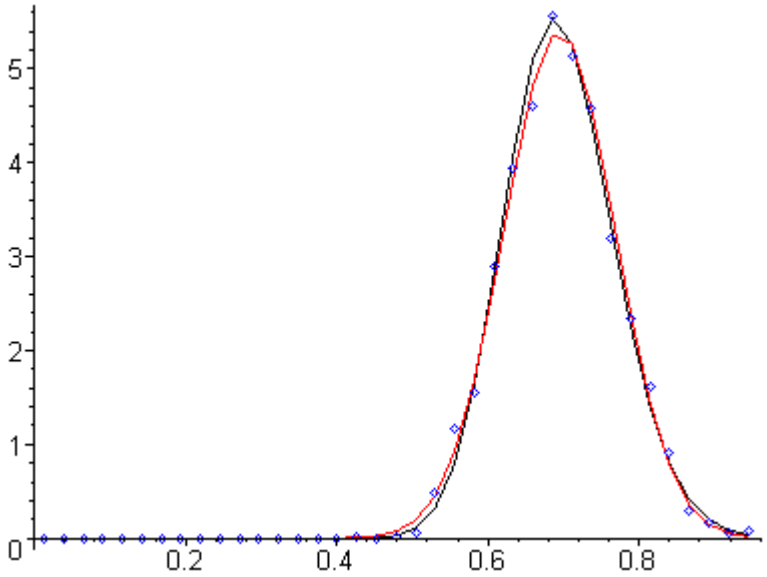

Fig 6.9 N = 64. At this initial inoculum size approximations melted almost into one. No significant difference can be detected in goodness of fit.

6.11 Bayesian approach in stochastic modelling

In the models proposed so far in the literature, the maximum specific growth rate was treated as a constant value. In contrast with this, other papers assumed the growth rate to be normally distributed. [see. Wu, 2000] The two most common candidates for individual cell time-lag's distribution were exponential [Baranyi, 2001] and normal [Wu, 2000]. It is recommended to assume that each cell after an adaptation period will start to grow exponentially when only the first two growth phase is examined. Moreover the growth curve (plotted against time, on log scale) tends to a shifted linear plot, where the shift is considered to be the population time-lag. In this section it will be proven that under fixed psychological circumstances (without external stimuli) the growth rate is fixed for cells of same attributes and can not follow normal distribution.

Let τ be a random variable, which represents the individual lag, and μ is another random variable for the maximum specific growth rate. Finally – as usual – assume that after the shoulder period (τ) a cells starts to grow exponentially with parameter μ. First, τ is supposed to be exponentially distributed (with parameter v). Then

$$X(t) = \sum_{i=1}^{N} I(t \le \tau_i) + I(t > \tau_i) \exp(\mu_i (t-\tau_i)) \qquad (6.119)$$

Let us calculate x(t) =E[X(t)] to explore its deterministic property! The used distributions are: $\tau \sim \exp(v)$ and $\mu \sim N(m,w^2)$

$$\frac{x(t)}{N} = (1 - F(t)) + \int_{0}^{t}\int_{-\infty}^{\infty} \exp(u(t-s)) \frac{1}{\sqrt{2\pi}w} \exp(-(u-m)^2/(2w^2))\ v \exp(-vs)\, du\, ds \qquad (6.120)$$

Reshape the second term

$$\int_{0}^{t}\int_{-\infty}^{\infty} \exp(u(t-s)) \frac{1}{\sqrt{2\pi}w} \exp(-(u - m)^2/(2w^2))\ v \exp(-vs)\, du\, ds = \qquad (6.121)$$

$$\int_{0}^{t} v \exp(-vs) \exp(\ ([(t - s)w^2 + m]^2 - m^2) / (2w^2)) \int_{-\infty}^{\infty} H(u,s)\, du\, ds \qquad (6.122)$$

Where $H(u,s) = \frac{1}{\sqrt{2\pi}w} \exp(-(u - [(t-s)w^2 + m])^2/(2w^2))$, which is a pdf, thus integrated over the whole range gives one.

$$(6.122) = \int_0^t v \exp(-vs) \exp(([(t - s)w^2 + m]^2 - m^2) / (2w^2)) ds = \tag{6.123}$$

$$\int_0^t v \exp(-vs) \exp((t - s)^2 w^2 /2 + (t - s)m) ds = \tag{6.124}$$

$$v \exp(-vt) \int_0^t \exp(vy) \exp(y^2 w^2 /2 + ym) dy \tag{6.125}$$

Where y was substituted for t – s.

$$S(t):= \int_0^t \exp((v+m) y) \exp(y^2 w^2 /2) dy \tag{6.126}$$

To obtain a reasonable linear limit function for x(t), as t tends to infinity, we need to find an exponent q, such that $R(t):= \exp(qt) S(t)$

$\lim_{t\to\infty} R(t) = b \in \mathbf{R}$

but $R'(t) = q R(t) + \exp(qt) \exp((v+m)t) \exp (t^2 w^2 /2)$, which goes to infinity as t increases, contradicting to the fact that function R has a finite limit at infinity. It is easy to verify in the same way that this growth is not polynomial at all!

Now, check the other possibility, when – alike the growth rate – individual lag follows normal distribution. Taking expectation yields ($\tau \sim N(n,v^2)$ and $\mu \sim N(m,w^2)$)

$$\frac{x(t)}{N} - (1 - F(t)) = \tag{6.127}$$

$$\int_{-\infty}^{t}\int_{-\infty}^{\infty} \exp(u(t-s))\frac{1}{\sqrt{2\pi}w}\exp(-(u-m)^2/(2w^2))\frac{1}{\sqrt{2\pi}v}\exp(-(s-n)^2/(2v^2))\,du\,ds= \quad (6.128)$$

$$\int_{-\infty}^{t} \exp(\,(t-s)^2w^2/2 + (t-s)m)\frac{1}{\sqrt{2\pi}v}\exp(-(s-n)^2/(2v^2))\,ds = \quad (6.129)$$

$$\int_{-\infty}^{t} P(s)\,ds\,\frac{1}{\sqrt{1-v^2w^2}}\exp\left\{\frac{1}{2}\frac{n^2w^2+w^2t^2+2mt-2nw^2t-2nm+m^2v^2}{1-w^2v^2}\right\} \quad (6.130)$$

Where $P(s) := \sqrt{\frac{1/v^2-w^2}{2\pi}}\exp\left\{-\frac{1}{2}(1/v^2-w^2)\left[s-\frac{n/v^2-w^2t-m}{1/v^2-w^2}\right]^2\right\}$, a probability density function, when$1/v^2 - w^2 > 0$. Therefore lim P(t) =1 (as t goes off to infinity). On examining the asymptotic properties of

$$\frac{1}{\sqrt{1-v^2w^2}}\exp\left\{\frac{1}{2}\frac{n^2w^2+w^2\mathbf{t^2}+2mt-2nw^2t-2nm+m^2v^2}{1-w^2v^2}\right\} \quad (6.131)$$

for large t values, one finds that y(t) = log(x(t)) tends to a shifted parabolic function. This conclusion yields to contradiction again.

Reached this stage, we have to widen our scope to richer families of non negative distributions [van Boekel, 2002] and revisit our assumptions about the asymptotically linear nature of the log-scaled growth curve. This is the real challenge for biomathematicians in the future…

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