E-1

1950

Paper

L. Szilard
1155 E 57th Str.
Chicago 37. Ill.

Vincent Dole
[MS.]

Paper on Chemostat

~~Expt Experiments on the mutat~~

experiments with

~~Unsp~~ Bacterial

Populations kept on the growth phase

~~plug under at~~ at ~~a subnormal~~

~~growth rate~~ subnormal growth-

~~rate.~~

Experiments with the Chemostat

~~on the mutation rates of~~ on the

~~fact ... mutations~~ pheno-

menon of mutations in bacteria. –

Lactate limitation on B/1t

Tryptophane ; what to expect

Curve on B/1t at 6 hours

fast strain   new curves for 37 in 25 °C

the fast strain

Experiments with the fast strain

for 1g $\tau = 172$ min (measured)

or $c_{1/2} = 1.2$ g/l (for 72 mins)

Temp coeff for ~~B/4~~ B/1 fast

~~rate~~ for high conc. of tryptophane

at 37 $\tau = 67.5$ min (100 γ/l

$c/2 = 0.55$ γ/l

at 25 °C ~~ex~~ ~~[illegible]~~

$\tau = 130$ min

$c/2 = 0.26$ γ/l

$\frac{130}{67.5} = 1.92$

~~[illegible]~~ (1.5, 3, 45 γ/l

for 12 °C

for 10 °C ~~take~~ 5/6 the root $\boxed{1.72}$

for slow B/1

at 25 °C $\tau = 135$ min [~~7.5~~ 5 γ/l ; ~~[illegible]~~ 30 γ/l]

~~concentration for t_2 value of τ is at 0.26 γ/l~~

~~double~~

~~B/1 slow [illegible] at τ min~~

~~at 0.9 γ/l~~

$C_{1/2} = 1.7$ γ/l

at 37 °C

$\tau = 70$ min

at same high conc of trypt (at 10 γ/l and 100 γ/l

172

Generation and time dep. 4

0.6 per gen

$$\begin{array}{r} 2.3 \\ 0.6 \\ \hline 1.7 \end{array}$$

3

2.4

a μ ~~[illegible]~~
mutation rate / per gen

Norwich Formula

$$x = \frac{k^*}{k_x}$$

$$m = \frac{aN}{1-r}\left(1 - e^{-(1-r)\frac{t}{\tau}}\right)$$

$$\frac{dm}{dt} = \frac{a}{2} \quad \text{what is } t$$

$$\frac{dm}{dt} =$$

In order to test a single cell ~~taken from~~ contained in the cell population ~~and to~~ one may proceed as follows. First a sample ~~of~~ (from the growth tube of the Chemostat is plated on agar plate ~~and~~ incubated ~~one~~ to obtain colonies and then one colony is picked to be tested for comparison with the parent strain. The test may be ~~[illegible]~~ ~~the control experiment~~ made as follows:

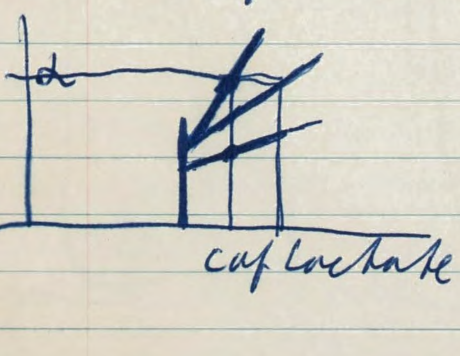
In a chemostat ~~under~~ with lactate as the controlling growth factor we inoculate the growth tube with a mixture of the parent strain and my ~~ot~~ mutant of the parent strain which is resistant to T6. The relative abundance of the ~~[illegible]~~ mutant strain should be large compared to relative abundance which would establish

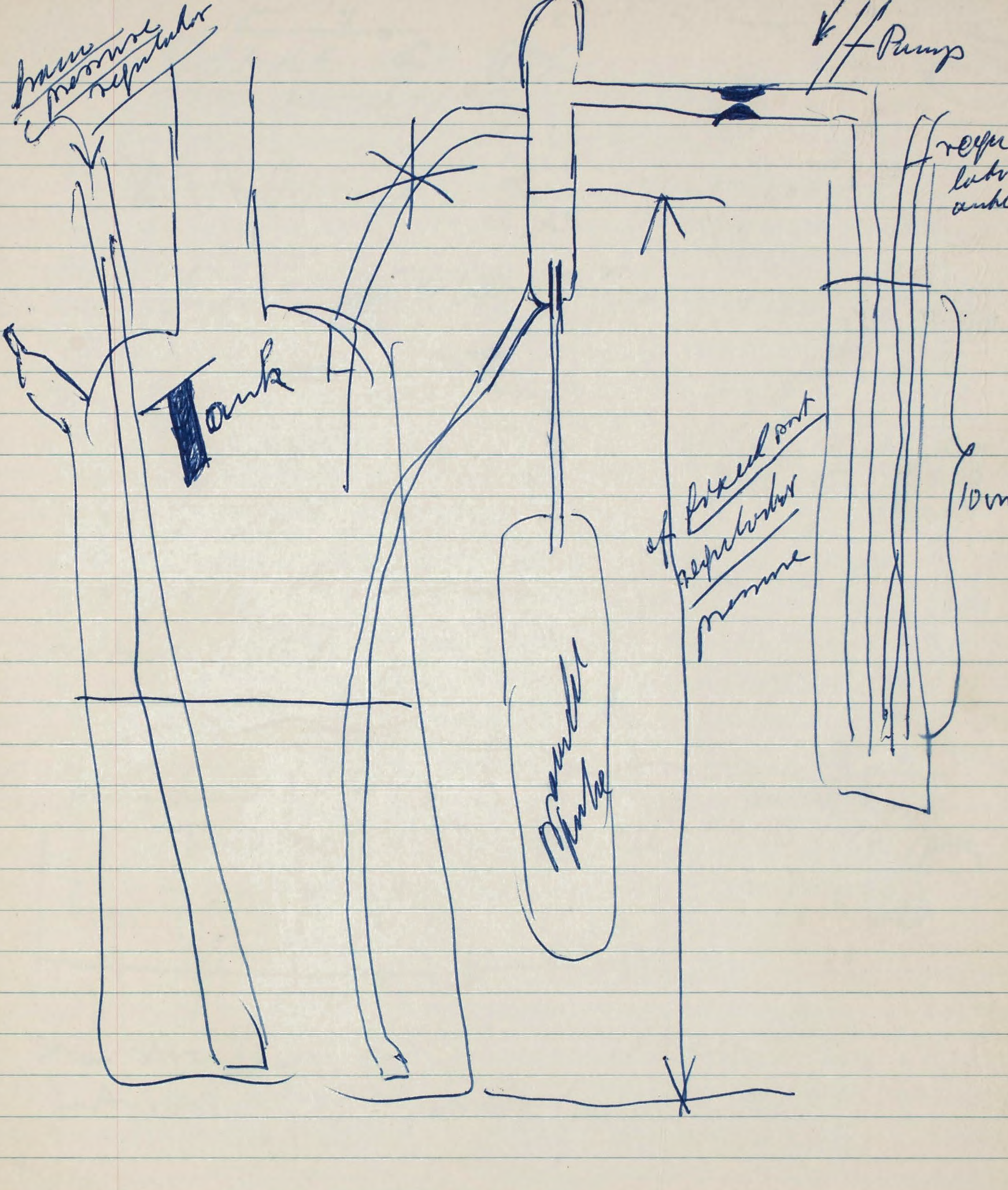
Add pt over a sufficiently long period of time 4

After a bacterial strain had grown in the Chemostat ~~with~~ ~~a [illegible] in amino-acid~~ with an amino-acid as the controlling growth factor and ~~and a [illegible]~~ and ~~with~~ with a generation time ~~[illegible]~~ τ large compared to ~~the minimal value of~~ the ~~the~~ gen time for high concentrations of that amino acid an appreciable ~~frac~~ fraction of the bacterial population should be ~~one or more~~ ~~[illegible]~~ at least an mutational step removed from the parent strain. ~~We~~ ~~what fraction of the population from~~ We could then ~~determine~~ experimentally determine ~~what fraction of the population~~ how ~~many generations have elapse~~ long it takes until a certain fraction ~~say 1/10~~ of the cell population ~~has become~~ is a mutant which grows appreciably slower than the parent strain, say having $\frac{\alpha^* - \alpha}{\alpha} > \frac{1}{300}$ if growing in the Chemostat ~~under [illegible] [illegible]~~ with lactate as the controlling growth factor.

itself through spontaneous mutations of the parent strain but diff should be small compared to 1. — Assuming that $\frac{\alpha^* - \alpha}{\alpha} = 1\%$ for the sake of argument and that we choose $\tau = 2$ hrs the relative abundance of the mutant will then fall by 1% for every two hours ~~or it will~~ i.e. it will fall to about $\frac{1}{e}$ in 200 hours.

This may now be compared ~~to~~ to the results obtained if the parent strain is replaced by the strain to be tested. If this "new" strain ~~has a growth rate which is smaller~~ grows appreciably slower than the ~~parent~~ ~~type~~ parent strain





Tank
Pump
10cm

per T_4

$5 \times 1.25\, 10^{-8}$/hour $= 37.5\, 10^{-8}$/~~hour~~ gen.

level $\dfrac{n^*}{n} = \dfrac{\alpha}{\alpha - \alpha^*} \dfrac{h}{\tau}\, \tau$

$\dfrac{n^*}{n} = \dfrac{\alpha}{\alpha - \alpha^*}\; 37.5\; 10^{-8}$

$\dfrac{\alpha}{\alpha - \alpha^*} = \dfrac{n^*}{2.5\, 10^{8} \times 10^{-8}} \qquad \dfrac{1}{37.5}$

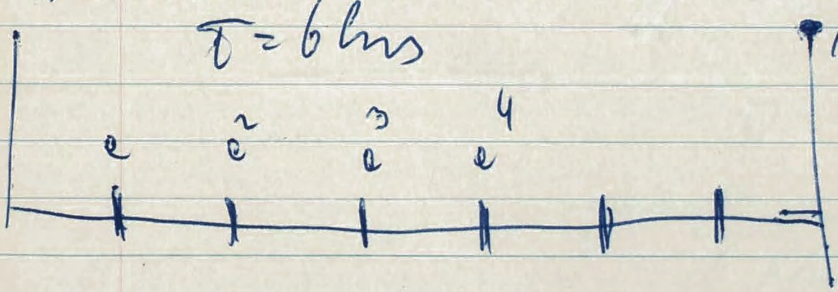
$= \dfrac{n^*}{2.5 \times 37.5}$

75.0
18.8
93.8 $\approx$ 100

$\dfrac{\alpha}{\alpha - \alpha^*} = 10$

or 10% difference or in 10 generations fall to $\frac{1}{e}$

Fluctuations



~~start~~ $h = 10^{-8}$/gen

2.3×8

16

18.4 gen

New strain gaining twice as fast appearing | 10^{-8} per six hours

Degeneration 4

$$\frac{df(n)}{dt} = \alpha f(n-1) - f(n)e^{-\beta n}$$

$\cancel{\frac{df(n)}{dt}}$

Total population rise $e^{\bar{\alpha} t}$

$$\frac{df(n)}{dt} = \alpha f(n-1) + \alpha_0 e^{-\beta n} f(n)$$

$$\frac{d}{dt}\frac{f(n)}{e^{\bar{\alpha} t}} = \frac{df(n)}{dt}\frac{1}{e^{\bar{\alpha} t}} - \frac{\bar{\alpha} f(n)}{e^{\bar{\alpha} t}}$$

$$0 = \frac{df(n)}{dt} - \bar{\alpha} f(n)$$

$$\bar{\alpha} f(n) = \alpha f(n-1) + \alpha_0 f(n) e^{-\beta n}$$

$$0 = \alpha f(n-1) + (\alpha_0 - \bar{\alpha}) f(n) e^{-\beta n}$$

$$0 = \alpha\left(-\frac{df}{dn} + f\right) + (\alpha_0 - \bar{\alpha}) f(n) e^{-\beta n}$$

λ would be if man's cells mutate 1/year ; 400 per 40 days or 10 per day or $\lambda \sim \alpha$

In order to converge $\dfrac{\bar{\alpha}}{\lambda} > 1$

$$\frac{df}{dn} = \Big\{ \overbrace{\frac{(\bar{\alpha} - \alpha_0)e^{-\beta n}}{\lambda} + \cdots}^{A} \Big\} f(n) \qquad 4$$

$$\ln f = A + c$$

$$f = C e^{A}$$

Repeat

$$\frac{df(n)}{dt} = \lambda f(n-1) + \alpha_0 e^{-\beta n} f(n)$$

$$\int f(n)\, dn = N$$

$$\frac{d}{dt} \frac{f(n)}{N e^{\bar{\alpha} t}} = 0$$

$$\frac{df}{dn} \times \frac{1}{e^{\bar{\alpha} t}} - f(n) \frac{\bar{\alpha}}{e^{2\bar{\alpha} t}} \quad e^{\bar{\alpha} t}$$

$$\frac{df}{dt} = \bar{\alpha} f(n)$$

$$\alpha_0 - \alpha_0 e^{-\beta n}$$

$$\bar{\alpha} f(n) = +\lambda \left[f(n) - \frac{df}{dn} \right] + \alpha_0 e^{-\beta n} f(n)$$

$$\lambda \frac{df}{dn} = \left[\alpha_0 e^{-\beta n} - \bar{\alpha} + \lambda \right] f(n)$$

$$\frac{1}{f} \frac{df}{dn} = \left[\frac{\alpha_0}{\lambda} e^{-\beta n} - \frac{\bar{\alpha}}{\lambda} + 1 \right] = [A]$$

$$f(n) = C e^{[A]}$$

let us put $\bar{\alpha} = \alpha_0 e^{-\beta n}$

$k = 0$

$\boxed{\begin{array}{l}\text{flows} \\ n = n\end{array}}$

ergo no information obtainable this way.

To check (1) $\frac{f(n)}{dt} = \bar{\alpha} f(n)$

(2) $\frac{df(n)}{dt} = k f(n-1) + \alpha_0 e^{-\beta n} f(n)$

$\bar{\alpha} f(n) = k f(n-1) + \alpha_0 e^{-\beta n} f(n)$

$k f(n-1) = \left(\bar{\alpha} - \alpha_0 e^{-\beta n}\right) f(n)$

$$\frac{f(n-1)}{f(n)} = \frac{\bar{\alpha} - \alpha_0 e^{-\beta n}}{k}$$

$$f(n) = \frac{k}{\bar{\alpha} - \alpha_0 e^{-\beta n}} f(n-1)$$

$n - 1 \geq 0$

W.2.B.N. $\bar{\alpha} > \alpha_0 e^{-\beta}$

H

$$-\lambda f(n-1) = \left[\alpha_0 e^{-\beta n} - \bar{\alpha}\right] f(n)$$

$$\frac{f(n-1)}{f(n)} = \frac{\bar{\alpha} - \alpha_0 e^{-\beta n}}{\lambda}$$

$$\frac{f(n)}{f(n-1)} = \frac{\lambda}{\bar{\alpha} - \alpha_0 e^{-\beta n}}$$

$$f(n) = \frac{\lambda}{\bar{\alpha} - \alpha_0 e^{-\beta n}} \cdot f(n-1)$$

It must be $\lambda < \bar{\alpha}$; (and $\bar{\alpha} < \alpha_0$)

Maximum at $1 = \dfrac{\lambda}{\bar{\alpha} - \alpha_0 e^{-\beta n}}$

or $\lambda = \bar{\alpha} - \alpha_0 e^{-\beta n}$ $\quad$ $\bar{\alpha} - \alpha_0 e^{-\beta n} = \lambda$

$$\frac{\bar{\alpha} - \lambda}{\alpha_0} = e^{-\beta n}$$

$$\frac{1}{\beta} \ln \frac{\alpha_0}{\bar{\alpha} - \lambda} = n$$

$\beta = \frac{1}{100}$ $\quad \ln[\,] = 1$ $\quad \boxed{n = 100}$

$$\frac{dn}{dt} = k - \frac{\Delta}{4} k \left(l + \frac{\Delta}{2}\right) + \frac{\Delta k}{4}\left(q + \frac{\Delta}{2}\right)$$

$$= k - \frac{\Delta}{4} k l + \frac{\Delta}{4} k q$$

for $q = 0$

$$\frac{dn}{dt} = k\left(1 - \frac{\Delta}{4} l\right)$$

$$z = x a + y b$$

$$x = \frac{n}{2}$$

$$\frac{dx}{dt} = -\frac{\Delta}{2}\frac{1}{2} \quad ; \quad a = k\left(l + \frac{\Delta}{2}\right)$$

$$\frac{dy}{dt} = +\frac{\Delta}{2}\frac{1}{2} \quad ; \quad b = k\left(q + \frac{\Delta}{2}\right)$$

$$y = \frac{1}{2}$$

$$\frac{dn}{dt} = -\frac{\Delta}{4} k\left(l + \frac{\Delta}{2}\right) + \frac{1}{2}k + \frac{\Delta}{4} k\left(q + \frac{\Delta}{2}\right) + \frac{1}{2}k$$

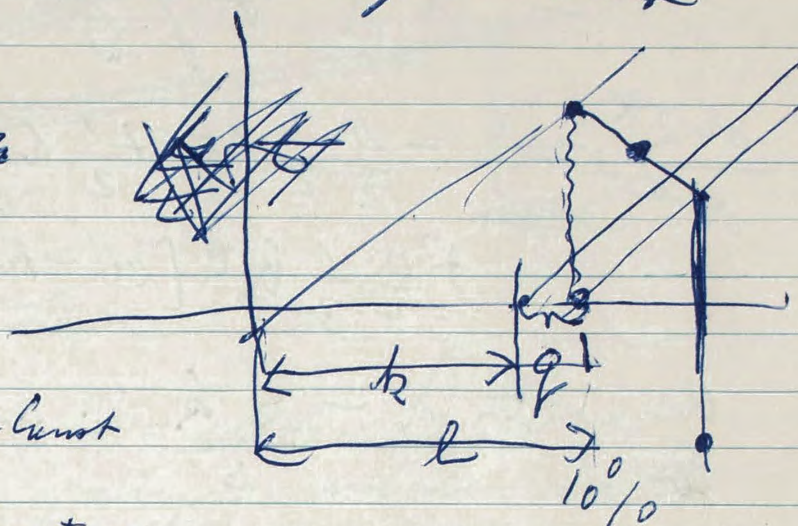
$$= k[q - l]\frac{\Delta}{4} + k$$

$\Delta = \frac{1}{4}$ $$= k\left[1 - \frac{l - q}{4\Delta}\right]$$

$$\frac{dn}{dt} = 0 \text{ of } q\Delta = \frac{k}{4}$$

$\Delta = 5/8 =$ 6 per

Transition in change-over 4



$\cancel{\alpha} = k\left(\frac{t}{\tau}\right)$

$\beta = k\left(\frac{t}{\tau}\right)$ + const

$k h$ + const $= 0$

$\beta = k\left(\frac{t}{\tau}\right) - k h$

$$z = \frac{x}{n} a + \frac{y}{n} b$$

mid point $\frac{l+m}{2} = l + \frac{m-l}{2}$

$\cancel{\ldots} + \frac{m-l}{2} \ldots l + \frac{m-l}{2}]$

$x = \frac{n}{2} e$

$\frac{dx}{dt} = \frac{n}{2} \frac{m-l}{2}$ $\quad m - l = \Delta$

$n = 1$ $\quad z = x a + y b$

$$\frac{dz}{dt} = \left(\frac{1}{2} \frac{\Delta}{2} a + \frac{1}{2} k\right)$$

$$\left(\frac{1}{2} \frac{\Delta}{2} b + \frac{1}{2} x\right)$$

$$z^* = x x^* + y y^*$$

$$\frac{dz^*}{dt} = -\frac{\Delta}{2}\frac{1}{2}\lambda t + \frac{1}{2}\lambda$$

$$+ \frac{\Delta}{2}\frac{1}{2}\left[\lambda t - \lambda k\right] + \frac{1}{2}\lambda$$

$$\frac{dz}{dt} = \lambda - \frac{\lambda k}{4}\Delta = \lambda\left(1 - \frac{k}{4}\Delta\right)$$

write $\frac{1}{\Delta}$ for Δ $= \lambda\left(1 - \frac{k}{4\Delta}\right)$

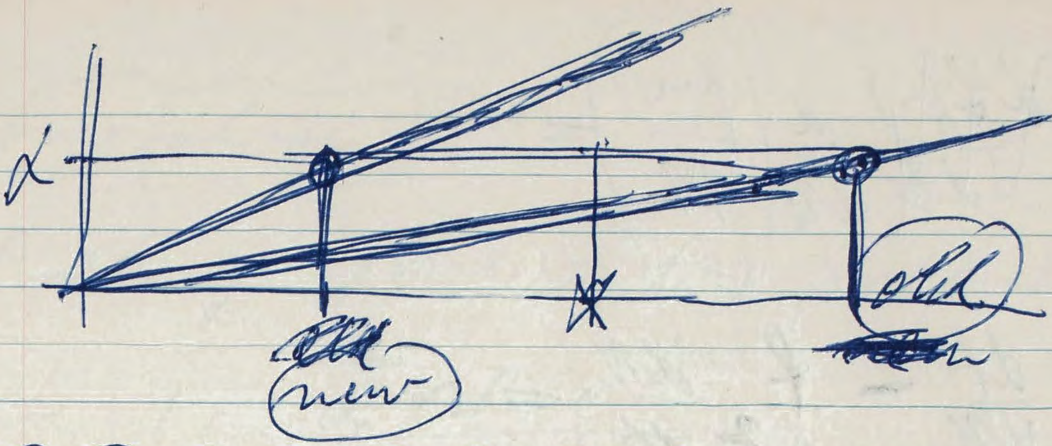
$$\frac{1}{\lambda}\left[\frac{dz}{dt}\right]_{x=\pi/2} = 1 - \frac{k}{4\Delta}$$

$$\frac{k}{4\Delta} = 1 - \frac{dz}{dt}\frac{1}{\lambda}$$

$$\frac{4\Delta}{k} = \frac{1}{1 - \frac{dz}{dt}/\lambda}$$

$$\Delta = \frac{k/4}{1 - \frac{dz}{dt}/\lambda}$$

W

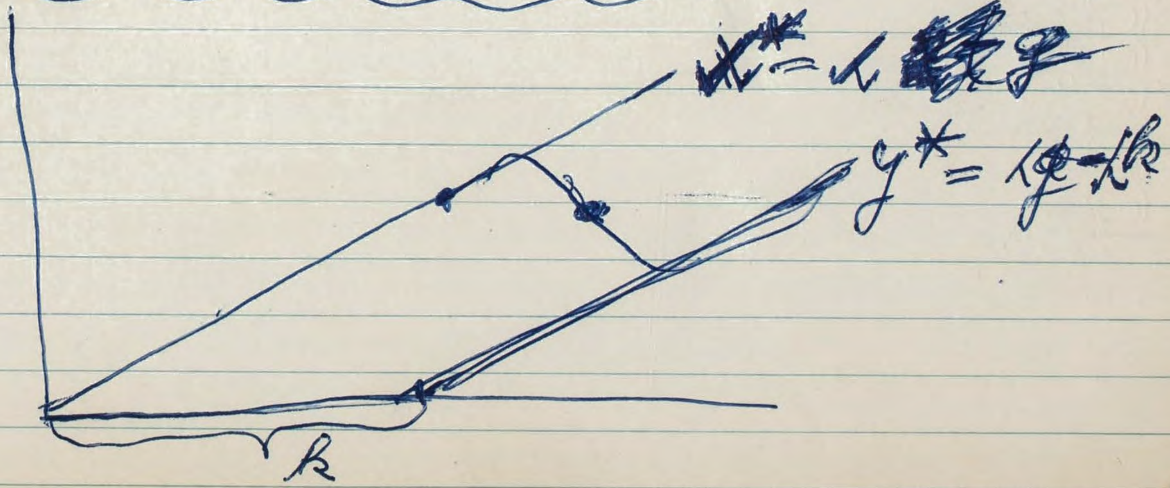


Write up: In above) case at half way point when both strains have a density of $\frac{n}{2}$ [$x + y = n$]

we have $\frac{1}{x}\frac{dx}{dt} = \frac{-\Delta}{2}$ [x is density of "parent strain"]

Whereas before the change over we have $\frac{1}{y}\frac{dy}{dt} = \Delta$ (as it should be

and after the change-over we have $\frac{1}{x}\frac{dx}{dt} = -\Delta$



$$\cancel{\frac{d f(x)}{dt}} \; \frac{d}{dt}\left(\frac{f(x)}{N}\right) = 0$$

$$\frac{1}{N}\frac{df}{dx} - \frac{f}{N^2}\frac{dN}{dt} = 0$$

$$\frac{df}{dx} = \frac{f}{\cancel{N}}\,\bar{\alpha}$$

If ~~ta~~ N

Deterioration

Putting $f(n-1) = f(n)$ (for maximum)

$$1 = \frac{\bar{\alpha} - \alpha_0 e^{-\beta n}}{\alpha}$$

$$f(n) = \frac{\alpha}{\bar{\alpha} - \alpha_0 e^{-\beta n}} f(n-1)$$

$$f(n-1) + \frac{df}{dn} = A$$

$$\frac{df}{dn} = \left[\frac{\alpha}{\bar{\alpha} - \alpha_0 e^{-\beta(n+1)}} - 1\right] f$$

$$\frac{\alpha - \bar{\alpha} + \alpha_0 e^{-\beta n}}{\alpha_0 - \alpha_0 e^{-\beta n}}$$

$$f = C e^{1 - \frac{\alpha}{\bar{\alpha} - \alpha_0 e^{-\beta n}}}$$

(2) $\bar{\alpha} < \alpha_0 f(0) + \alpha_0 \dfrac{\lambda e^{-\beta}}{\bar{\alpha} - \alpha_0 e^{-\beta}}$

$f(0) + f(1)$

$$\frac{\bar{\alpha}}{\alpha_0} < \frac{1 + \dfrac{\lambda}{\bar{\alpha} - \alpha_0 e^{-\beta}} e^{-\beta}}{1 + \dfrac{\lambda}{\bar{\alpha} - \alpha_0 e^{-\beta}}}$$

$$\frac{\bar{\alpha}}{\alpha_0} < \frac{\bar{\alpha}/\alpha_0 - e^{-\beta} + \lambda e^{-\beta}}{\bar{\alpha}/\alpha_0 - e^{-\beta} + \lambda}$$

or from (1) and (2)

$e^{-\beta} <$ ______

$$\frac{\bar{\alpha}}{\alpha} < \frac{ + \dfrac{\lambda e^{-\beta}}{\frac{\bar{\alpha}}{\alpha_0} - e^{-\beta}}}{ + \dfrac{\lambda/\alpha_0}{\frac{\bar{\alpha}}{\alpha_0} - e^{-\beta}}} \approx \frac{1 + \dfrac{\lambda(1-\beta)}{\frac{\bar{\alpha}}{\alpha_0} - 1 + \beta}}{1 + \dfrac{\lambda}{\frac{\bar{\alpha}}{\alpha_0} - 1 + \beta}}$$

$$\frac{\bar{\alpha}}{\alpha_0} < \frac{\frac{\bar{\alpha}}{\alpha_0} - 1 + \beta + \lambda/\alpha_0 - \lambda\beta/\alpha_0}{\frac{\bar{\alpha}}{\alpha_0} - 1 + \beta + \lambda/\alpha_0}$$

$f(0)$ If $\lambda = \bar{\alpha}$ 4

$$f(n) = \frac{\bar{\alpha}}{\bar{\alpha} - \alpha_0 e^{-\beta n}}$$

let us put $\bar{\alpha} = \alpha_0 e^{-\beta/2}$

$$f(n) = \frac{\alpha_0 e^{-\beta/2}}{\alpha_0 e^{-\beta/2} - \alpha_0 e^{-\beta n}} f(n-1)$$

$$f(n) = \frac{1}{1 - e^{-\beta(n-\frac{1}{2})}} f(n-1)$$

$$f(n) \equiv \frac{1}{+\beta(n-\frac{1}{2})} f(n-1)$$

$$\frac{\int f(n) e^{-\beta n} dn}{\int f(n)} \geqq e^{-\beta}$$

$$f(n) = \frac{\alpha}{\bar{\alpha} - \alpha_0 e^{-\beta n}} \times f(n-1)$$

$n \geqq 1$

For $n = 1$ we must have $\bar{\alpha} > \alpha_0 e^{-\beta}$ (1)

but $\bar{\alpha} < \dfrac{\alpha_0 f(0) + \alpha_0 e^{-\beta} f(1)}{f(0) + f(1)}$ (2)

$$\frac{\alpha}{\alpha_0} \angle K$$

$$\left\{ \frac{\alpha}{\alpha_0} - 1 + \beta > 0 \right\}$$

$$\frac{\alpha}{\alpha_0} - 1 + \beta < K - 1 + \beta$$

$$0 < B < K - 1 + \beta$$

$$\frac{1}{B} > \frac{1}{K-1+\beta}$$

$$K = \frac{1 + \frac{\lambda^*}{B} + \left[\frac{\lambda^* \lambda^*}{B(B+\beta)}\right] - \left[\quad\right] 2\beta \; \frac{\lambda^*}{B}\beta}{}$$

$$K = 1 - \frac{\left[2\frac{\lambda^*}{B}\frac{\lambda^*}{B+\beta} + \frac{\lambda^*}{B}\right]\beta}{1 + \frac{\lambda^*}{B} + \frac{\lambda^*}{B}\frac{\lambda^*}{B+\beta}}$$

$$K - 1 + \beta = \beta\left[1 - \frac{\frac{2\lambda^*\lambda^*}{B(B+\beta)} + \frac{\lambda^*}{B}}{1 + \frac{\lambda^*}{B} + \frac{\lambda^*\lambda^*}{B(B+\beta)}}\right]$$

$$K - 1 + \beta = \beta\left[\frac{1 - \frac{\lambda^*}{B}\frac{\lambda^*}{B+\beta}}{1 + \frac{\lambda^*}{B} + \frac{\lambda^*}{B}\frac{\lambda^*}{B+\beta}}\right]$$

$$1 - \frac{\lambda^*}{B}\frac{\lambda^*}{B+\beta} > 0$$

$$1 - \frac{\lambda^*}{K-1+\beta}\frac{\lambda^*}{K-1+2\beta} > 0$$

4

$$\frac{f(n)}{f(n-1)} = \frac{\lambda/\alpha_0}{\left\{\frac{\bar{\alpha}}{\alpha_0} - e^{-\beta}\right\}}$$

$\cancel{K} \; K B$

$$\bar{\lambda} = \frac{\alpha_0 \, 1 + \frac{\lambda/\alpha_0}{B}\alpha_0 . e^{-\beta}}{1 + \frac{\lambda/\alpha_0}{B}}$$

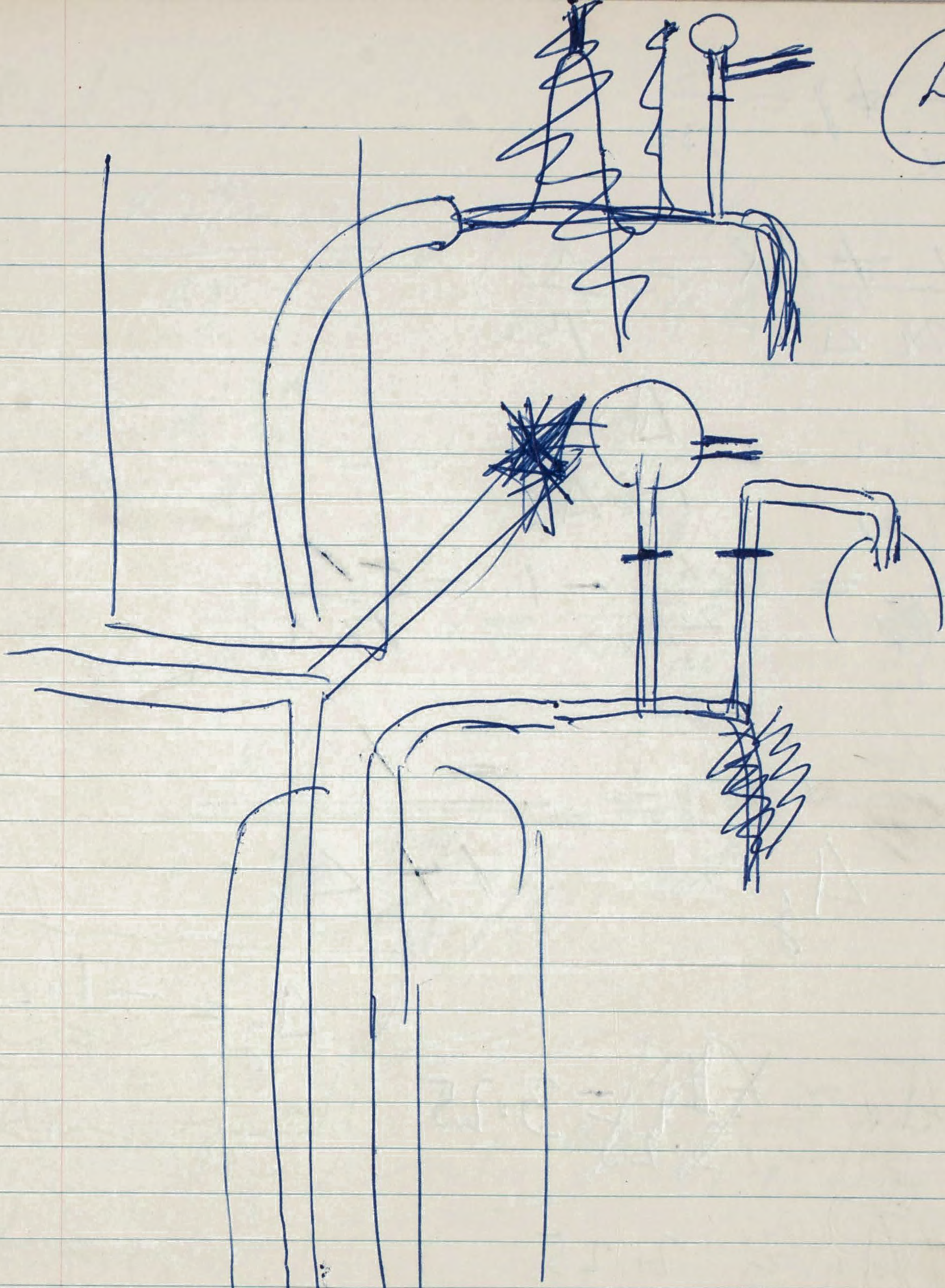
$$f(2) = \frac{\lambda}{\bar{\alpha} - \alpha_0 e^{-2\beta}} \times \frac{\lambda}{\bar{\alpha} - \alpha_0 e^{-\beta}} \times f(0)$$

$$f(2) = \frac{\lambda/\alpha_0}{\frac{\bar{\alpha}}{\alpha_0} - e^{-2\beta}} \times \frac{\lambda/\alpha_0}{\bar{\alpha}/\alpha_0 - e^{-\beta}} f(0)$$

$$\frac{\bar{\alpha}}{\alpha_0} \leq \frac{1 + \frac{\lambda/\alpha_0}{B}(1-\beta) + \frac{\lambda/\alpha_0}{B} \times \frac{\lambda/\alpha_0}{B+\beta}(1-2\beta)}{1 + \frac{\lambda/\alpha_0}{B} + \frac{\lambda/\alpha_0}{B}\,\frac{\lambda/\alpha_0}{B+\beta}}$$

$$\frac{\bar{\alpha}}{\alpha} > 1-\beta$$

$1-\beta <$



$$\frac{1}{\Delta x} \cancel{+} 1 = \frac{\beta_1}{\beta_2}$$

$$\frac{1 \cancel{+} \Delta x}{\cancel{\Delta x}\ \Delta x} = \frac{\beta_1}{\beta_2}$$

$$\frac{\beta_2}{\beta_1} = \frac{\Delta x}{1 \cancel{+} \Delta x}$$

$$\frac{1}{\Delta y} \cancel{\beta} = \frac{\Delta x}{1+\Delta_x} - 1 = \frac{-1}{1+\Delta x}$$

$$\frac{1}{\Delta_y} = \frac{-1}{1+\Delta_x}$$

$$\boxed{\Delta_y = -[1+\Delta_x]}$$

$\Delta_x = \cancel{+\Delta}\ \cancel{3.25} - 3.25$

$\Delta_y = 2.25$

to the 13 hours disappearance of x

Oct 2/50 H

$$\frac{d\,z^*/n}{dq} = \kappa\left(1 - \frac{k}{4\Delta y}\right)$$

$$\frac{1}{\kappa}\,\frac{d\,\frac{z^*}{n}}{dq} = 1 - \frac{k}{4\Delta y}$$

$$\frac{k}{4\Delta'} = 1 - \frac{1}{\kappa}\,\frac{d\,\frac{z^*}{n}}{dq}$$

$\kappa = \frac{28}{22}$

$$\frac{k/4}{1 - \frac{d\,z^*/n}{dq}/\kappa} = \Delta y$$

$$\frac{1}{\Delta x} = \frac{\beta_1}{\beta_2} - 1 \quad ; \quad \Delta x = \frac{\beta_2}{\beta_1 - \beta_2}$$

$$\frac{1}{\Delta y} = \frac{\beta_2}{\beta_1} - 1 \qquad \Delta y = \frac{\beta_1}{\beta_2 - \beta_1}$$

$$\frac{4\Delta y}{h} = \frac{1}{1-\Theta}$$

H

$$\frac{h}{4\Delta y} = 1-\Theta$$

$$\frac{d\gamma_n}{\lambda} = 1-\frac{h}{4\Delta y}$$

. order loose fall

$h > 4\Delta y$

$h = 70$ | -1 $70/8$ $= 9$ Div (41) and

$h = 44$ | 0 $= 11$ (42)

July 18th Oxygen (old) (54)

$h = 32$; $4y = 2.66$

from (1) and (2) and (3) $\left(\frac{f_2}{f_1} > 1\right)$

$$\frac{f_2}{f_1} - 1 = \frac{1}{b}$$

$$\frac{f_1}{f_2} - 1 = \frac{1}{a} \qquad \left(a < 0 \quad \cancel{|a| > 1}\right) \quad \text{o.k.}$$

(4) and we have $\boxed{\begin{array}{l} b = -(1+a) \\ a = -(1+b) \end{array}}$

$$\cancel{b = -\frac{a}{1+a}}$$

$$\cancel{\frac{f_1}{f_2-f_1} = -\left(1 + \frac{f_2}{f_1-f_2}\right)}$$

$$\cancel{-\left(\frac{f_1}{f_2-f_1} + \frac{f_2}{f_2-f_1}\right)}$$

$$\cancel{a = \frac{f_2}{f_1-f_2} = -\frac{f_1+\epsilon}{\epsilon}}$$

At midpoint we may write

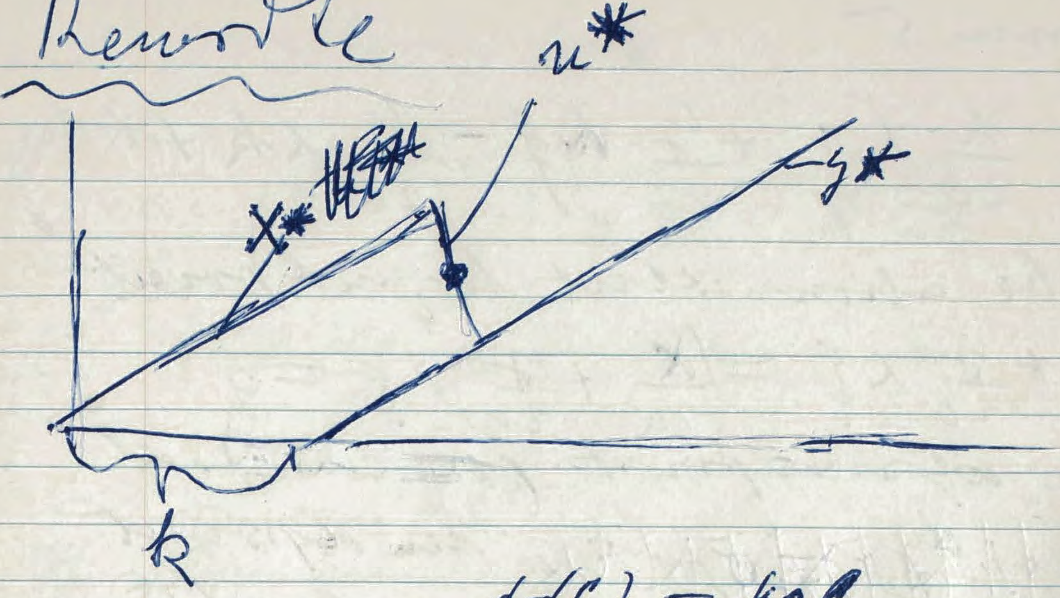
$$c = \frac{c_1+c_2}{2} \quad \text{and}$$

for y $\quad f_2 \frac{c_1+c_2}{2} - \frac{1}{\tau} = \frac{1}{y}\frac{dy}{dg}$

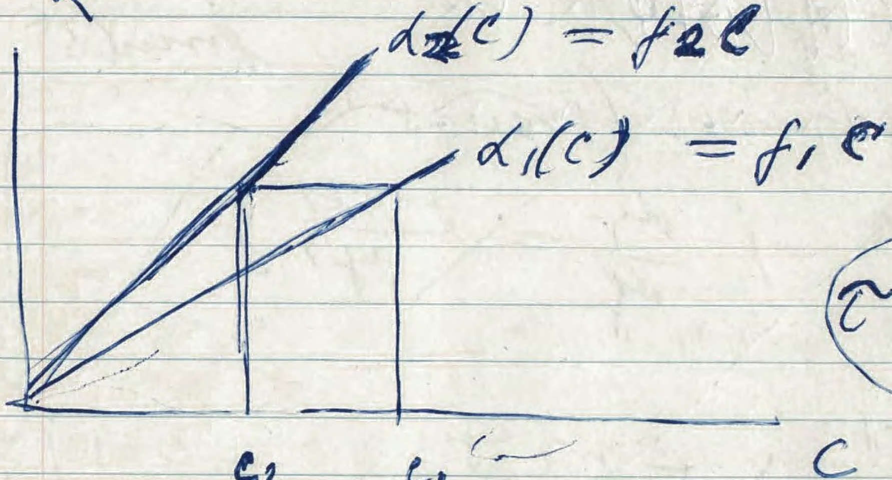
or from (2) $\quad \frac{1}{y}\frac{dy}{dg} = \frac{f_2-f_1}{2f_1} = \frac{1}{2b}$

(5) → or $\quad \frac{dy}{dg} = \frac{y}{2b}$

Renordle H



$\frac{t}{\tau} = \rho$



τ is washing out time

(1) $x = e^{\frac{g}{a}}$, $y = e^{\frac{g}{b}}$

for small x $(a<0)$! for small y $\rho = \frac{t}{\tau}$

(2) $c_1 = \frac{1}{\tau f_1}$; $c_2 = \frac{1}{\tau f_2}$

(3) for small y $f_2 c_1 - \frac{1}{\tau} = \frac{1}{y}\frac{dy}{dt}$

for small x $f_1 c_2 - \frac{1}{\tau} = \frac{1}{x}\frac{dx}{dt}$

and from 5

(7) $\frac{dn^*}{dg} = \frac{x}{2a}\lambda g + \frac{y}{2b}\lambda g - \frac{y}{2b}\lambda k + \lambda n$

It can be shown that for mod product

$\frac{x}{2a}\lambda g + \frac{y}{2b}\lambda g = \left(\frac{x}{2a} + \frac{y}{2b}\right)\lambda g = 0$

Because ~~at mod point (from 5)~~ at

~~[illegible]~~ mod product from (5)

~~at mod product (from 5)~~

$\cancel{\frac{dx}{dg} = \frac{f^1 - f^2}{2f^2}x \; ; \; \frac{dy}{dg} = \frac{f^2 - f^1}{2f^1}y}$

~~therefore~~

$\cancel{(9) \quad \frac{f^1 - f^2}{2f^2}x + \frac{f^2 - f^1}{2f^1}y = 0}$

~~and also~~ $\cancel{x + y = n}$

$\frac{dx}{dg} = \frac{x}{2a} \; ; \; \frac{dy}{dg} = \frac{y}{2b}$

and $\frac{dx}{dg} + \frac{dy}{dg} \equiv 0$

Therefore

(8) $\frac{dn^*}{dg} = -\frac{y}{2b}\lambda k + \lambda n$

and similarly ~~for x~~ H

for x

$f_1 \frac{c_1+c_2}{2} - \frac{1}{\tau} = \frac{1}{x}\frac{dx}{dt}$

giving

(5) $\frac{1}{x}\frac{dx}{dg} = \frac{f_1 - f_2}{2 f_2} = \frac{1}{2a}$

or $\frac{dx}{dg} = \frac{x}{2a}$

$x^*(g)$ is number of mutants per bacterium in original strain as function

y^* is number of mutants in new strain per bacterium

$n^* = x x^* + y y^*$ (where $x + y \equiv n$)

(6) and $x^* = \lambda g$; $y^* = \lambda g - \lambda k$

$\frac{dn^*}{dg} = \frac{dx}{dg} x^* + x \frac{dx^*}{dg} + \frac{dy}{dg} y^* + y \frac{dy^*}{dg}$

~~It can be shown that~~ (from 6)

(6a) $\frac{dn^*}{dg} = \frac{dx}{dg}\lambda g + \frac{dy}{dg}\lambda g - \frac{dy}{dg}\lambda k +$

$+ x\lambda + y\lambda$

$$l = \left(\frac{1}{2}\frac{f_1}{f_2} + \frac{1}{2}\right)\frac{1+f_2/f_1}{2}$$

$$l = \frac{1}{4}\left(\frac{f_1}{f_2} + 1\right)\left(1 + f_2/f_1\right) =$$

$$= \frac{1}{4}\left[\frac{f_1}{f_2} + 1 + 1 + \frac{f_2}{f_1}\right] \sim$$

$$\sim \frac{1}{4}\left[1+\varepsilon + 2 + 1 - \varepsilon\right]$$

21

$$x = n - y$$

$$n = \left((n-y)f_1 + y f_2\right)\frac{f_1+f_2}{2f_1 f_2}$$

$$n = \left\{ n f_1 + y(f_2 - f_1)\right\} \text{———}$$

$$2n\frac{f_1 f_2}{f_1+f_2} = n f_1 + y(f_2 - f_1)$$

$$n\left(\frac{2f_1 f_2}{f_1+f_2} - f_1\right) = n\frac{f_1 f_2 - f_1^2}{f_1+f_2} =$$

$$= n\frac{f_1(f_2 - f_1)}{f_1+f_2} = y(f_2 - f_1)$$

$$y = n\frac{f_1}{f_1+f_2}$$

~~Stop~~ 4

Question:
what is value of y at "mid-product"?

~~$aW = \frac{c_1 + c_2}{2} W + x$~~

$$nW = \left(\frac{dx}{dt} + y \frac{dy}{dt}\right) V$$

$$n\frac{W}{V} = x\,\alpha_1 + y\,\alpha_2$$

$$n\frac{W}{V} = x f_1 \frac{c_1 + c_2}{2} + y f_2 \frac{c_1 + c_2}{2}$$

$$x_1 + x_2 = n$$

$$\frac{n}{\bar{c}} = x f_1 \frac{\frac{1}{\bar{c} f_1} + \frac{1}{\bar{c} f_2}}{2} + y f_2 \frac{\frac{1}{\bar{c} f_1} + \frac{1}{\bar{c}}}{}$$

$$\left.\begin{aligned} n &= (x f_1 + y f_2)\frac{f_1 + f_2}{2 f_1 f_2} \\ n &= x + y \end{aligned}\right\} (21)$$

~~for $\frac{f_2}{f_1} \approx 1$ $x = \frac{n}{2}$ $y = \frac{n}{2}$~~

~~$n = \left(\frac{n}{2} + \frac{n}{2}\frac{f_2}{f_1}\right)\frac{f_1 + f_2}{2 f_1 f_2}$~~

$$4b+2 = \frac{k}{1 - \frac{1}{k}\frac{dx^*/x}{dg}}$$

$$b = \frac{k/4}{1-\frac{1}{k}\frac{dx^*/x}{dg}} - 1/2$$

$a =$

Question: is $\frac{d^2x^*}{dg^2} \equiv 0$ at "midpoint"? from (6a)

$$\frac{d^2x^*}{dg^2} = \cancel{\ldots}$$

$$= \frac{dx^3}{dg^2}\lambda g + \frac{dy^2}{dg^2}\lambda g - \frac{d^2y}{dg^2}\lambda k + \frac{dx}{dg}\lambda + \frac{dy}{dg}\lambda$$

~~midpoint~~

So

Answer No!

14

$$\boxed{y = n \frac{1}{1 + \frac{f_2}{f_1}} \quad \text{at midpoint}}$$

$$y = \frac{n}{1 + \frac{1}{6} + 1} = \frac{n}{2 + \frac{1}{6}}$$

and from (8)

$$\frac{dn^*}{dg} = -\frac{y}{26} \, v k + \lambda n$$

$$= -\frac{\cancel{6} n}{4b + 2} \lambda k + \lambda n$$

or

$$\frac{1}{\lambda} \frac{dn^*/n}{dg} = 1 - \frac{1}{4b+2} k$$

$$1 - \lambda \frac{dn^*/n}{dg} = \frac{1}{4b+2} k$$

$$0 = \left(\frac{dx}{dy}\delta_1 + \frac{dy}{dy}\delta_2\right) + (x\delta_1 + y\delta_2)\frac{dc}{dy}/c$$

$$\frac{dy}{dg} = y(\delta_2 c\tau - 1)$$

$$\frac{dx}{dg} = x(\delta_1 c\tau - 1)$$

$$x + y = n$$

$$\frac{d^2y}{dg^2} = \frac{dy}{dg}(\delta_2 c\tau - 1) + y\delta_2\tau\frac{dc}{dg}$$

$$\frac{d^2x}{dy^2} = \frac{dx}{dg}(\delta_1 c\tau - 1) + x\delta_1\tau\frac{dc}{dg}$$

$$\frac{d^2y}{dy^2} = y(\delta_2 c\tau - 1)^2 + y\delta_2\tau\frac{dc}{dy}$$

$$\frac{d^2x}{dp^2} = x(\delta_1 c\tau - 1)^2 + x\delta_1\tau\frac{dc}{dy}$$

$$\frac{dn^x}{dg} = \frac{dx}{dg}\lambda g + \frac{dy}{dp}\lambda g - \frac{dy}{dg}\lambda h + n$$

$$\frac{dy}{dt} = y\left\{f_2 c - \frac{1}{\tau}\right) \quad \frac{dy}{dp} = \tau y \left\{f_2 c - \frac{1}{\tau}\right\}$$

$$= y(f_2 c\tau - 1)$$

$$\frac{d^2 y}{dt^2} = \frac{dy}{dt}\left(f_2 c - \frac{1}{\tau}\right) + y f_2 \frac{dc}{dt}$$

$$\frac{n}{\tau} = x f_1 c + y f_2 c$$

$$0 = \left(\frac{dx}{dg} f_1 + \frac{dy}{dg} f_2\right) c + (x f_1 + y f_2)\frac{dc}{dg}$$

$$x + y = n$$

$$\frac{dx}{dg} + \frac{dy}{dg} = 0$$

$$0 = \left(\frac{dx}{dg} f_1 + \frac{dy}{dg} f_2\right) c + (x f_1 + y f_2)\frac{dc}{dp}$$

$$\frac{d^2 y}{dg^2} = \frac{dy}{dg}\left\{f_2 c\tau - 1\right\} + y f_2 \tau \frac{dc}{dp}$$

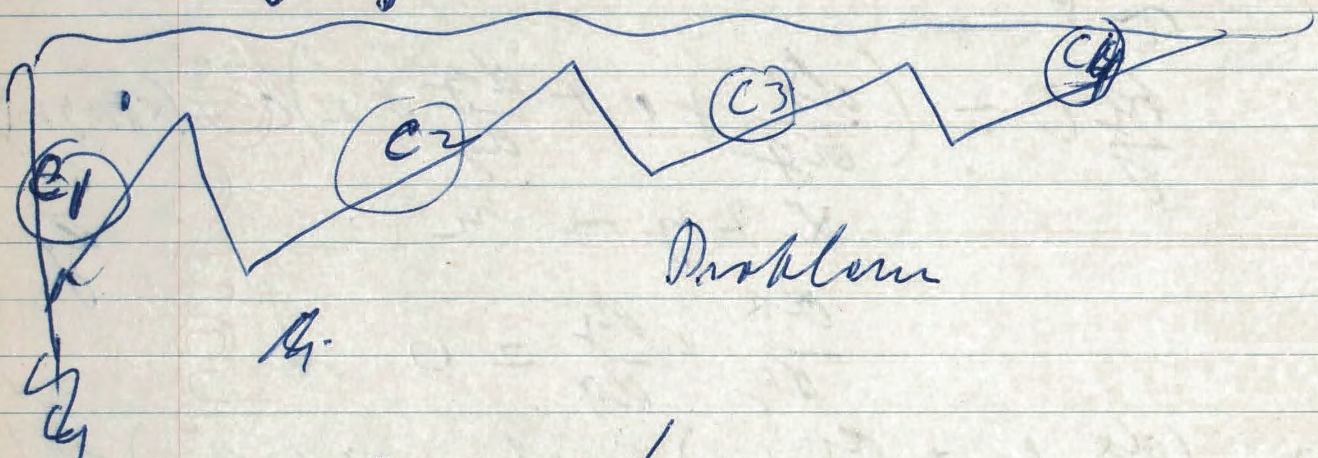
At Ausflachdan

$$\boxed{0 = \frac{d^2 x}{dg^2} + \frac{d^2 y}{dg^2} - \frac{d^2 y}{dg^2}\, k/g}$$

Checks:

$$b = \frac{f_1}{f_2 - f_1} \qquad \text{O.K.}$$

$$a = \frac{f_2}{f_1 - f_2}$$



Problem

$$c_i = \frac{1}{i f_i}$$

$$\frac{f_2}{f_1} - 1 = \frac{1}{b} \text{ (first row stroke, second strain rise)}$$

$$\frac{f_2}{f_1} = \frac{1}{b} + 1$$

$$\frac{f_3}{f_2} = \left(\frac{1}{b_2} + 1\right)$$

$$\frac{f_i}{f_1} = \left(\frac{b_1+1}{b_1}\right)\left(\frac{b_2+1}{b_2}\right)\left(\frac{b_{i-1}+1}{b_{i-1}}\right)$$

mutation rise of H

* strain goes over into y

which mutates at rate λ

$$\frac{d y^*}{dt} = \frac{\lambda}{\tau} y + \cancel{\left\{ \frac{dy}{} y^* - \frac{y^*}{c} \right\}} \text{ small?},$$

$$y = e^{\frac{t}{b\tau}}$$

$$\frac{dy^*}{dt} \approx \frac{\lambda}{\tau} e^{\frac{t}{b\tau}}$$

$$y^* \approx \frac{\lambda}{\tau} b t e^{\frac{t}{b\tau}}$$

$$\frac{d Z}{dt} = f(t) + \text{const} \times Z$$

continued ....

$$b = \frac{k/4}{1 - \frac{1}{\lambda} \frac{dn^*/n}{dg}} - 1/2$$

$$a = \left[\frac{k/4}{1 - \frac{1}{\lambda} \frac{dn^*/n}{dg}} + 1/2 \right]$$

Same move for a ~~[illegible]~~ $|a| > 1$

$$\frac{f_1}{f_2} - 1 = \frac{1}{a_1}$$

$$\frac{f_2}{f_3} - 1 = \frac{1}{a_2}$$

$$\frac{f_1}{f_i} = \frac{(a_1+1)(a_2+1)\cdots(a_{i-1}+1)}{a_1 a_2 \cdots a_{i-1}}$$

$$\frac{f_1}{f_i} - 1 = \frac{1}{A_i}$$

or

$$\frac{1}{A_i} = \frac{(\quad)(\quad)\cdots(\quad) - a_1 a_2 \cdots a_{i-1}}{a_1 a_2 \cdots a_{i-1}}$$

$$A_i = \frac{a_1 a_2 \cdots a_{i-1}}{(a_1+1)(a_2+1)\cdots(a_{i-1}+1) - a_1 a_2 \cdots a_{i-1}}$$

~~and since $a+1 = b$~~

$$\frac{f_i}{f_1} = \frac{1}{B_i} + 1 \equiv \frac{1+B_i}{B_i}$$

B_i is e^{g/B_i} gives rise for small values y of ~~first strain~~ strain "i" in original population

$$B_i = \frac{f'}{f_{i-1}}$$

or

$$\frac{B_i+1}{B_i} = \frac{(b_1+1)(b_2+1)\cdots(b_{i-1}+1)}{b_1\, b_2 \cdots b_{i-1}}$$

or

$$\frac{1}{B_i} = \frac{(b_1+1)\cdots(b_{i-1}+1) - b_1\cdots b_{i-1}}{b_1\cdots b_{i-1}}$$

$$B_i = \frac{b_1 b_2 \cdots b_{i-1}}{(b_1+1)(b_2+1)\cdots(b_{i-1}+1) - b_1 b_2 \cdots b_{i-1}}$$

formula requires, — [or
bother of stock / goes into log!]

— . — ; — : —

We shall prove that (4)

$$A_i = -(1+B_i) \qquad \left[B_i = -(1+A_i)\right]$$

for $$1+B_i = \frac{(b_1+1)(\quad)(\quad)}{(b_1+1)(\quad) \quad - b_1 b_2 \ldots b_{i-1}}$$

and

$$-A_i = \frac{a_1 a_2 \ldots}{a_1 a_2 \ldots \quad -(1+a_1)(1+a_2)(\quad)}$$

$$1+B_i = \frac{(-1)^{i-1} a_1 a_2 a_3 \ldots a_{i-1}}{(-1)^{i-1} a_1 a_2 a_3 \quad a_{i-1} - (-1)^{i-1}(1+a_1)(1+a_2)}$$

or $-A_i = 1+B_i$ W. 2. B.W.

Deviation to be expected

if ~~it~~ (stock) does not rise as fast (on account of saturation) as in stock 1 as formula requires

i.e. b_i observed > b_i calculated

~~a decay~~ Stock 1 should however decay in stock i as fast as

Rise of T_4 resistant H mutants of new strain by mutates at high rate by resistance

$$y = \cancel{e} = Ce^{g/b}$$ for small y

$$y = Ce^{\frac{g\tau}{b\tau}}$$

$$\cancel{\frac{dy^*}{dt}} \cancel{A\alpha}$$

$$\frac{dn^*}{dt} = \frac{a}{\tau} n + \frac{\cancel{g}1}{b\tau} n^*$$

$$\frac{dn^*}{dg} = a\,n + \frac{1}{b} n^*$$

$$\frac{dn^*}{dg} = a\,C_{onst}\,e^{g/b} + \frac{1}{b} n^*$$

[$y = \text{Const}\; e^{g/b}$
if for $g = 0$
$y = 1$
$\text{Const} = 1$

Solution

$$n^* = \left(C_{int} + \cancel{a}g\right) e^{\frac{g}{b}}$$

if $n^* = 0$
for $g = 0$ } then $C_{int} = 0$

$$n^* = a\,g\,e^{g/b}$$

( )

Mutations in Homo H

A Non-sexual reproduction

/ Animal giving m offspring

t in generations (gen time τ)

$$\frac{df(n)}{dt} = +\alpha\tau m\, f(n-1) \cancel{m\, f(n)}\, e^{-\beta n} - \alpha\tau\, m\, f(n)$$

$$\frac{df(n)}{dt} = \frac{\bar{a}}{a_0} m f(n)$$

$$[a_0 = 1]$$

$f(n)$ is distribution at birth of new generation.

Sexual reprod:

$$\sum_{k=0}^{k=n} f(n-k)\, f(n+k)$$

for $\frac{dn^*}{dg} = \frac{\lambda n}{e}$

we have

$$\frac{\lambda n}{e} = \lambda n \, e^{-(1-r)g}$$

$$(1-r)g = 1$$

$$g = \frac{1}{1-r} = \frac{1}{1-\frac{\alpha^*}{\alpha}}$$

$$g = \frac{\alpha}{\alpha-\alpha^*}$$

for $\frac{dn^*}{dg} = \lambda n e^{-1}$

To prove Novick Formula:

$\frac{t}{\tau} = g$ $\quad \frac{dn^*}{dg} = \frac{\lambda}{\tau} n - n^* \frac{w}{V} + n^* \alpha^* \quad \Big\| \quad \frac{dn^*}{dg} = \lambda n - n^* + n^* \frac{\alpha^*}{\alpha}$

$$\boxed{\frac{dn^*}{dg} = \lambda n - n^* \left(\frac{\alpha-\alpha^*}{\alpha}\right)}$$

$$\frac{dn^*}{dg} = \lambda n - n^* \left(\frac{\alpha-\alpha^*}{\alpha}\right)$$

$n^* = \frac{\alpha}{\alpha-\alpha^*} \lambda n (1-e)$ O.K.

Mutations with selection against mutant in chemostat H

Novick derived:

n^* (Number of mutants

n number of wild type "

λ mutation rate per gen

α growth rate

$$n^* = \frac{\lambda n}{1-r}\left(1 - e^{-(1-r)\frac{t}{\tau}}\right)$$

$\frac{\alpha^*}{\alpha}$

$$r = \frac{\alpha^*}{\alpha} \qquad n^* = \frac{\lambda n \alpha}{\alpha - \alpha^*}\left(1 - e^{-\frac{\alpha-\alpha^*}{\alpha}g}\right)$$

$r = \frac{\alpha^*}{\alpha}$

$$\frac{dn^*}{dg} = +\frac{\lambda n}{\cancel{1-r}}\,\cancel{(1-r)}\,e^{-(1-r)g}$$

$$\boxed{\frac{dn^*}{dg} = \lambda n\, e^{-(1-r)g}}$$

Read

The Respiratory Exchange of Animals and Man

Monographs of Biochemistry 1916

10 WE / hr. or $\boxed{2000}$ liter O_2 per hour 4/

10 ~~600~~ liter per hour

100 liter

2000 WE / day = 1/2 kg O_2 = 500 liter

250 liter air

100 liter air / day

~ 100 WE / hr ~ 1.2 WE / kg hr

per hour

20 liter O_2 per hour per man

2/7 liter O_2 per hour / kg (for man)

Bee at rest 18 °C

30 (mm)^3 per gm per minute

cockroaches at 15 °C 100 (mm)^3 per hour per gm

or 1/20 th of Bee

but man is 50 times less than Bee

Drosophila 3 mg O_2 per gm per hour

The Principles of Insect physiology
V. B. Wigglesworth
~~Methuen~~ Methuen & Co Ltd London
36. Essex Street, Strand W.C.

Bee 100 mg will burn sugar
at the rate of 10 mg/hour in flight.

[Carbohydrate 1 liter of O_2 ~ 5.~~047~~ cal

Bee at rest 9.1 calories per kg per hr (18°C)

30 cmm O_2 per min ~~per gm~~
300×6 = 1800 cmm = 1.8 cm³ O_2 / gm per hr
or 1.8 liter O_2 per kg per hr
or about 9 small calories. —

Man ~~2000~~ 30 [illegible] WE/day kg
or 1.2 WE/kg hr

Read Fox HM Simmonds B G.
J. Exp. Biol 10 (1933): 67–74;
12 (1935) 179–84; 14 210–218;
Nature 138 (1936) 1015

Oct 15th

Ext 201

Henry Katzenstein [4500]
Univ. Conn. Storrs, Conn.
of.

1130
VERNON ROYAL LINE
U. S. A.