# Optimal Dynamic Instability of Microtubules 2.0

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These notes follow up on the paper

Peskin CS
Optimal dynamic instability of microtubules
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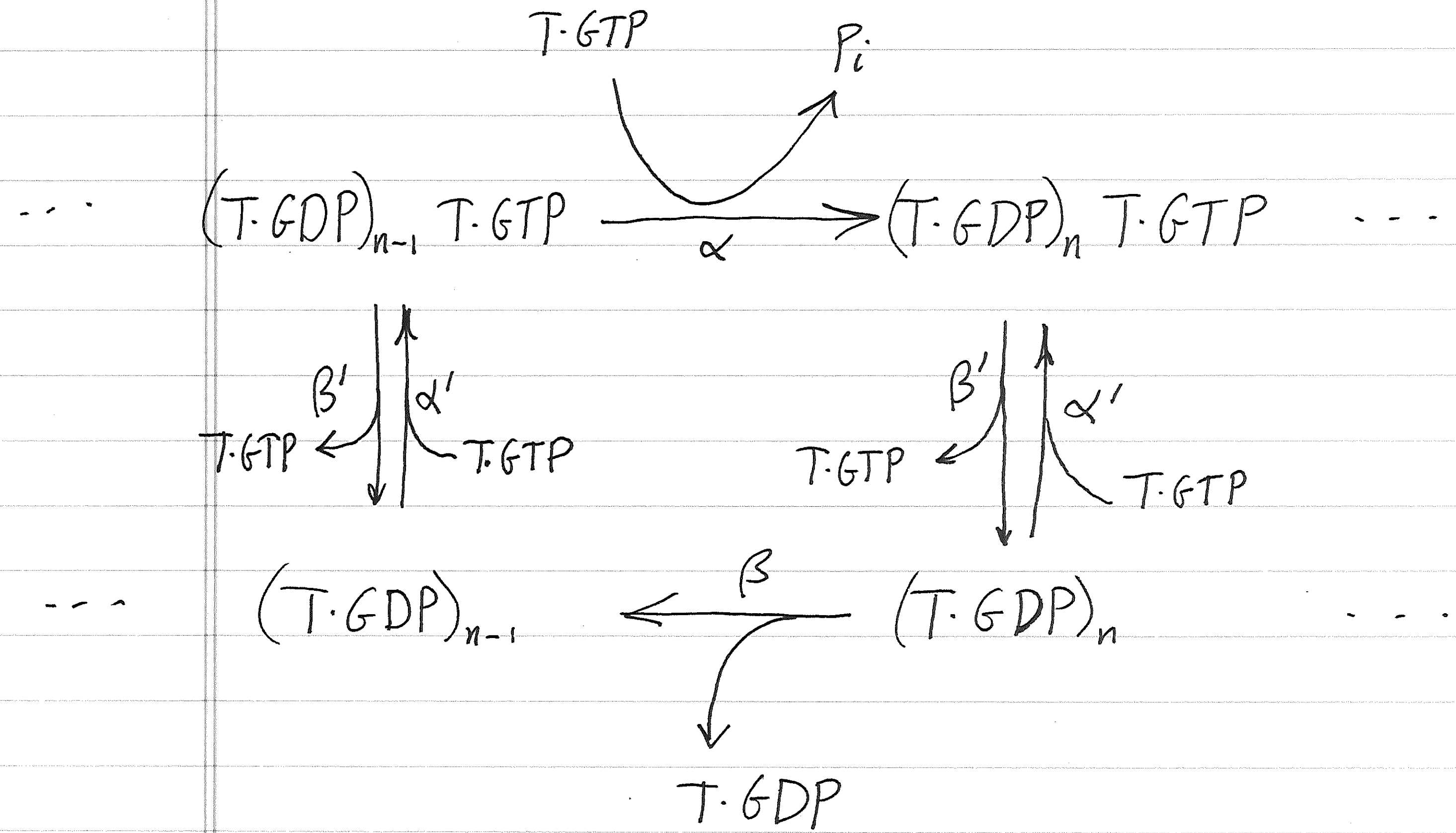
III 633-642, 1998

Here, we consider a more relevant optimization problem: to maximize the probability of success in hitting a target on a trial, divided by the metabolic cost per trial.

CS Peskin




$$
\begin{tikzcd}
A_1 \arrow[r, "\alpha"] \arrow[d, shift right, "\beta'"'] & A_2 \arrow[r, "\alpha"] \arrow[d, shift right, "\beta'"'] & A_3 \arrow[r, "\alpha"] \arrow[d, shift right, "\beta'"'] & \cdots \arrow[r, "\alpha"] & A_{n+1} \arrow[r, "\alpha"] \arrow[d, shift right, "\beta'"'] & {} \\
B_0 \arrow[u, shift right, "\alpha'"'] & B_1 \arrow[l, "\beta"] \arrow[u, shift right, "\alpha'"'] & B_2 \arrow[l, "\beta"] \arrow[u, shift right, "\alpha'"'] & \cdots \arrow[l, "\beta"] & B_n \arrow[l, "\beta"] \arrow[u, shift right, "\alpha'"'] & {} \arrow[l, "\beta"]
\end{tikzcd}
$$

Steady-state probabilities

$p_n$ = probability that system is in state $A_n$, $n \geq 1$

$q_n$ = probability that system is in state $B_n$, $n \geq 0$

$$1 = \sum_{n=1}^{\infty} p_n + \sum_{n=0}^{\infty} q_n$$

$$\begin{tikzcd}
\cdots & A_n \arrow[r, "\alpha"] \arrow[d, shift right, "\beta'"'] & A_{n+1} \arrow[d, shift right, "\beta'"'] & \cdots \\
\cdots & B_{n-1} \arrow[u, shift right, "\alpha'"'] & B_n \arrow[l, "\beta"'] \arrow[u, shift right, "\alpha'"'] & \cdots
\end{tikzcd}$$

let $u_n = \alpha p_n = \beta q_n \qquad n \geq 1$

Also:

$$\alpha p_n + \alpha' q_n = (\alpha + \beta') p_{n+1}$$

$$u_n + \frac{\alpha'}{\beta} u_n = \left(1 + \frac{\beta'}{\alpha}\right) u_{n+1}$$

$$u_{n+1} = \left( \frac{1 + \frac{\alpha'}{\beta}}{1 + \frac{\beta'}{\alpha}} \right) u_n$$

For a normalizable solution

$$1 + \frac{\alpha'}{\beta} < 1 + \frac{\beta'}{\alpha}$$

$$0 < \beta\beta' - \alpha\alpha'$$

i.e., depolymerization must be dominant over polymerization

Let

$$r = \frac{1 + \frac{\alpha'}{\beta}}{1 + \frac{\beta'}{\alpha}} < 1$$

$$\left.\boxed{\begin{aligned} u_n &= u_1 r^{n-1} \\ p_n &= \frac{u_1}{\alpha} r^{n-1} \\ q_n &= \frac{u_1}{\beta} r^{n-1} \end{aligned}}\right\} \quad n \geq 1$$

$$\alpha' q_0 = \beta' p_1 + \beta q_1$$

$$= \left(\frac{\beta'}{\alpha} + 1\right) u_1$$

$$\boxed{q_0 = \frac{1}{\alpha'}\left(1 + \frac{\beta'}{\alpha}\right) u_1}$$

Note that

$$1-r = 1 - \frac{1+\frac{\alpha'}{\beta}}{1+\frac{\beta'}{\alpha}} = \frac{\frac{\beta'}{\alpha} - \frac{\alpha'}{\beta}}{1+\frac{\beta'}{\alpha}} = \frac{\beta\beta' - \alpha\alpha'}{\beta(\alpha+\beta')}$$

To find $u_1$, use

$$\frac{\alpha'}{\alpha'+\beta'} = \sum_{n=1}^{\infty} p_n = \frac{u_1}{\alpha(1-r)}$$

$$u_1 = \frac{\alpha\alpha'}{\alpha'+\beta'} \frac{\beta\beta'-\alpha\alpha'}{\beta(\alpha+\beta')}$$

Thus

$$p_n = \frac{\alpha'}{\alpha'+\beta'} \frac{\beta\beta'-\alpha\alpha'}{\beta(\alpha+\beta')} r^{n-1} \qquad n \geq 1$$

$$\gamma_n = \frac{\alpha\alpha'}{\alpha'+\beta'} \frac{\beta\beta'-\alpha\alpha'}{\beta^2(\alpha+\beta')} r^{n-1} \qquad n \geq 1$$

$$\gamma_0 = \frac{\cancel{\alpha+\beta'}}{\cancel{\alpha\alpha'}} \frac{\cancel{\alpha\alpha'}}{\alpha'+\beta'} \frac{\beta\beta'-\alpha\alpha'}{\beta\cancel{(\alpha+\beta')}} = \frac{\beta\beta'-\alpha\alpha'}{\beta(\alpha'+\beta')}$$

Check :

$$\gamma_0 + \sum_{n=1}^{\infty}(p_n + q_n) = \frac{\beta\beta' - \alpha\alpha'}{\beta(\alpha'+\beta')}\left[1 + \frac{\alpha'}{\alpha+\beta'}\left(1+\frac{\alpha}{\beta}\right)\sum_{n=1}^{\infty} r^{n-1}\right]$$

$$= \frac{\beta\beta' - \alpha\alpha'}{\beta(\alpha'+\beta')}\left[1 + \frac{\alpha'}{\beta}\left(\frac{\alpha+\beta}{\alpha+\beta'}\right)\frac{1}{1-r}\right]$$

$$= \frac{\beta\beta' - \alpha\alpha'}{\beta(\alpha'+\beta')}\left[1 + \frac{\alpha'}{\cancel{\beta}}\,\frac{\alpha+\beta}{\cancel{\alpha+\beta'}}\,\frac{\cancel{\beta(\alpha+\beta')}}{\beta\beta' - \alpha\alpha'}\right]$$

$$= \frac{\beta\beta' - \alpha\alpha'}{\beta(\alpha'+\beta')}\left[\frac{\beta\beta' - \alpha\alpha' + \alpha\alpha' + \alpha'\beta}{\beta\beta' - \alpha\alpha'}\right]$$

$$= \frac{\beta\beta' - \alpha\alpha'}{\beta(\alpha'+\beta')}\,\frac{\beta(\beta'+\alpha')}{\beta\beta' - \alpha\alpha'} = 1 \checkmark$$

$$E[N|N>0] = \frac{\sum_{n=1}^{\infty} n(p_n+q_n)}{\sum_{n=1}^{\infty}(p_n+q_n)}$$

$$= \frac{\sum_{n=1}^{\infty} n r^{n-1}}{\sum_{n=1}^{\infty} r^{n-1}} = \frac{\frac{d}{dr}\sum_{n=0}^{\infty} r^n}{\sum_{n=0}^{\infty} r^n}$$

$$= \frac{\frac{d}{dr}\left(\frac{1}{1-r}\right)}{\left(\frac{1}{1-r}\right)} = \frac{\left(\frac{1}{1-r}\right)^2}{\left(\frac{1}{1-r}\right)} = \frac{1}{1-r}$$

$$= \frac{\beta(\alpha+\beta')}{\beta\beta'-\alpha\alpha'}$$

If $\alpha'=\alpha$ and $\beta'=\beta$, $E[N|N>0] = \frac{\beta\cancel{(\alpha+\beta)}}{(\beta-\alpha)\cancel{(\beta+\alpha)}} = \frac{\beta}{\beta-\alpha}$

$$= \frac{1}{1-\left(\frac{\alpha}{\beta}\right)}$$

If $\beta=\infty$, $E[N|N>0] = 1+\frac{\alpha}{\beta'}$

supersensitive

not so sensitive

Chemical energy expenditure in constructing microtubules.

Assume that 1 unit of chemical energy is used to add each subunit, regardless of whether that is done through normal growth

$$A_n \xrightarrow{\alpha} A_{n+1}$$

or through rescue

$$B_n \xrightarrow{\alpha'} A_{n+1}$$

Then the steady-state rate at which chemical energy is expended is given by

$$\dot{W} = \left(\frac{\alpha'}{\alpha'+\beta'}\right)\alpha + \left(\frac{\beta'}{\alpha'+\beta'}\right)\alpha'$$

$$= \frac{\alpha'(\alpha+\beta')}{\alpha'+\beta'}$$

<u>cycles per unit time</u> :

Birth of a microtubule is the process $B_0 \xrightarrow{\alpha'} A_1$

~~Th~~ In the steady state, the number of these events per unit time (for a given nucleation site) is

$$\dot{c} = \alpha' g_0 = \frac{\alpha'}{\beta} \frac{\beta\beta' - \alpha\alpha'}{(\alpha' + \beta')}$$

Over a long period of time $t$, the amount of work done is $\dot{w}t$ and the number of cycles accomplished is $\dot{c}t$. Therefore, the work per cycle is

$$W_{cycle} = \frac{\dot{w}}{\dot{c}} = \frac{\frac{\alpha'(\alpha + \beta')}{\alpha' + \beta'}}{\frac{\alpha'}{\beta} \frac{\beta\beta' - \alpha\alpha'}{\alpha' + \beta'}}$$

$$= \frac{\alpha'\beta(\alpha + \beta')}{\alpha'(\beta\beta' - \alpha\alpha')}$$

$$= \frac{\beta(\alpha + \beta')}{\beta\beta' - \alpha\alpha'} = E[N | N > 0] \quad (!)$$

On a given cycle, let $P_n$ = probability that the microtubule grows to length at least $n$.

$$\begin{tikzcd}
\text{START} \arrow[r] & A_1 \arrow[r, "\alpha"] \arrow[d, "\beta'"'] & \cdots \arrow[r, "\alpha"] & A_j \arrow[r, "\alpha"] \arrow[d, shift right, "\beta'"'] & \cdots \arrow[r, "\alpha"] & A_{n-1} \arrow[r, "\alpha"] \arrow[d, shift right, "\beta'"'] & \text{STOP} \\
& \text{Stop} & \cdots \arrow[l, "\beta"] & B_{j-1} \arrow[l, "\beta"] \arrow[u, shift right, "\alpha'"'] & \cdots \arrow[l, "\beta"] & B_{n-2} \arrow[l, "\beta"] \arrow[u, shift right, "\alpha'"'] &
\end{tikzcd}$$

$$\frac{dp_1}{dt} = -(\alpha+\beta')p_1$$

$$\frac{dp_j}{dt} = \alpha p_{j-1} + \alpha' q_{j-1} - (\alpha+\beta')p_j \qquad j = 2\cdots(n-1)$$

$$\frac{dq_j}{dt} = \beta q_{j+1} + \beta' p_{j+1} - (\alpha'+\beta)q_j \qquad j = 1\cdots(n-2)$$

with boundary condition $q_{n-1} = 0$

Initial conditions: $p_1(0) = 1$, $p_j(0) = 0$, $j = 2\cdots(n-1)$

Output is

$$P_n = \int_0^\infty \alpha p_{n-1}(t)\,dt$$

let $\bar{\circ}$ denote $\int_0^\infty \circ \, dt$

We have $p_1(t) = e^{-(\alpha+\beta')t}$

and therefore $\bar{p}_1 = \left(\frac{1}{\alpha+\beta'}\right)$

Integrating the equations gives

$$0 = \alpha \bar{p}_{j-1} + \alpha' \bar{q}_{j-1} - (\alpha+\beta')\bar{p}_j \qquad j=2\cdots(n-1)$$

$$0 = \beta \bar{q}_{j+1} + \beta' \bar{p}_{j+1} - (\alpha'+\beta)\bar{q}_j \qquad j=1\cdots(n-2)$$

with

$$\bar{q}_{n-1} = 0$$

Solving the first of these equations for $\bar{q}_{j-1}$ gives

$$\bar{q}_{j-1} = \frac{(\alpha+\beta')}{\alpha'}\bar{p}_j - \left(\frac{\alpha}{\alpha'}\right)\bar{p}_{j-1} \qquad j=2\cdots(n-1)$$

Shifting indices

$$\bar{q}_j = \left(\frac{\alpha+\beta'}{\alpha'}\right)\bar{p}_{j+1} - \left(\frac{\alpha}{\alpha'}\right)\bar{p}_j \qquad j=1\cdots(n-2)$$

In the second equation, shift $j$ down by 1:

$$0 = \beta \bar{q}_j + \beta' \bar{p}_j - (\alpha'+\beta)\, \bar{q}_{j-1} \qquad j = 2 \cdots (n-1)$$

Substitute the above formulae for $\bar{q}_{j-1}$ and $\bar{q}_j$ into this equation, and note that the result is only valid for $j = 2, \cdots, (n-2)$

$$0 = \beta \left[ \frac{\alpha+\beta'}{\alpha'} \bar{p}_{j+1} - \frac{\alpha}{\alpha'} \bar{p}_j \right] + \beta' \bar{p}_j$$

$$- (\alpha'+\beta) \left[ \frac{\alpha+\beta'}{\alpha'} \bar{p}_j - \frac{\alpha}{\alpha'} \bar{p}_{j-1} \right]$$

$$j = 2, \cdots, (n-2)$$

For $j = n-1$, we have

$$0 = \cancel{\beta \bar{q}_{n-1}} + \beta' \bar{p}_{n-1} - (\alpha'+\beta)\, \bar{q}_{n-2}$$

$$= \beta' \bar{p}_{n-1} - (\alpha'+\beta) \left[ \frac{\alpha+\beta'}{\alpha'} \bar{p}_{n-1} - \left(\frac{\alpha}{\alpha'}\right) \bar{p}_{n-2} \right]$$

$$= \left( \beta' - \frac{(\alpha'+\beta)(\alpha+\beta')}{\alpha'} \right) \bar{p}_{n-1} + \frac{(\alpha'+\beta)\alpha}{\alpha'} \bar{p}_{n-2}$$

Multiplying by $\alpha'$, we get

$$0 = (\alpha+\beta')\beta \bar{p}_{j+1}$$
$$- (\alpha\beta - \alpha'\beta' + (\alpha'+\beta)(\alpha+\beta'))\bar{p}_j$$
$$+ (\alpha'+\beta)\alpha \bar{p}_{j-1} \qquad j = 2 \cdots (n-2)$$

$$0 = -( \quad -\alpha'\beta' + (\alpha'+\beta)(\alpha+\beta'))\bar{p}_{n-1}$$
$$+ (\alpha'+\beta)\alpha' \bar{p}_{n-2}$$

We can make the last equation look like the typical equation (for $j = n-1$) by artificially introducing $\bar{p}_n$ such that

$$0 = (\alpha+\beta')\beta \bar{p}_n - \alpha\beta \bar{p}_{n-1}$$

Then we have the tridiagonal system

$$0 = (\alpha+\beta')\beta \bar{p}_{j+1} - (\alpha\beta - \alpha'\beta' + (\alpha'+\beta)(\alpha+\beta'))\bar{p}_j + (\alpha'+\beta)\alpha \bar{p}_{j-1}$$
$$\text{for } j = 2 \cdots (n-1)$$

with boundary conditions

$$\bar{p}_1 = \frac{1}{\alpha+\beta'} \qquad \bar{p}_n = \frac{\alpha}{\alpha+\beta'}\bar{p}_{n-1}$$

The equation (without the boundary conditions) has solutions of the form $z^j$ provided that

$$0 = (\alpha+\beta')\beta\, z^2 - \left(\alpha\beta - \alpha'\beta' + (\alpha'+\beta)(\alpha+\beta')\right)z + (\alpha'+\beta)\alpha$$

$$= (z-1)\left((\alpha+\beta')\beta\, z - (\alpha'+\beta)\alpha\right)$$

<u>check</u>

$$= (\alpha+\beta')\beta\, z^2 - \left[(\alpha+\beta')\beta + (\alpha'+\beta)\alpha\right] + (\alpha'+\beta)\alpha$$

But

$$(\alpha+\beta')\beta + (\alpha'+\beta)\alpha = 2\alpha\beta + \alpha\alpha' + \beta\beta'$$

and

$$\left(\alpha\beta - \alpha'\beta' + (\alpha'+\beta)(\alpha+\beta')\right) = \alpha\beta - \cancel{\alpha'\beta'} + \alpha'\alpha + \beta'\beta + \alpha\beta + \cancel{\alpha'\beta'}$$

$$= 2\alpha\beta + \alpha\alpha' + \beta\beta' \quad \checkmark$$

Thus, the roots are $z = 1$ and $z = \dfrac{(\alpha'+\beta)\alpha}{(\alpha+\beta')\beta}$

$$= \frac{1 + \frac{\alpha'}{\beta}}{1 + \frac{\beta'}{\alpha}} \equiv r$$

The general solution, without considering the boundary conditions is

$$\bar{p}_j = X + Y r^j$$

$$X + Yr = \frac{1}{\alpha + \beta'}$$

$$X + Y r^n = \frac{\alpha}{\alpha+\beta'}\left(X + Y r^{n-1}\right)$$

or: $$X \frac{\beta'}{\alpha+\beta'} + Y r^{n-1}\left(r - \frac{\alpha}{\alpha+\beta'}\right) = 0$$

But $$r - \frac{\alpha}{\alpha+\beta'} = \frac{\alpha'+\beta}{\beta}\,\frac{\alpha}{\alpha+\beta'} - \frac{\alpha}{\alpha+\beta'}$$

$$= \left(\frac{\alpha'+\beta}{\beta} - 1\right)\frac{\alpha}{\alpha+\beta'}$$

$$= \frac{\alpha'}{\beta}\,\frac{\alpha}{\alpha+\beta'}$$

Thus, we have the pair of linear equations

$$X + Yr = \frac{1}{\alpha+\beta'}$$

$$X\beta\beta' + Yr^{n-1}\alpha\alpha' = 0$$

$$X = \frac{\frac{r^{n-1}\alpha\alpha'}{\alpha+\beta'}}{r^{n-1}\alpha\alpha' - r\beta\beta'} = -\frac{\left(\frac{r^{n-2}\alpha\alpha'}{\alpha+\beta'}\right)}{\beta\beta' - r^{n-2}\alpha\alpha'}$$

$$Y = \frac{-\frac{\beta\beta'}{\alpha+\beta'}}{r^{n-1}\alpha\alpha' - r\beta\beta'} = +\frac{\left(\frac{r^{-1}\beta\beta'}{\alpha+\beta'}\right)}{\beta\beta' - r^{n-2}\alpha\alpha'}$$

$$\bar{p}_j = X + Yr^j$$

$$\bar{p}_{n-1} = X + Yr^{n-1}$$

$$P_n = \alpha\bar{p}_{n-1} = \frac{\alpha}{\alpha+\beta'}r^{n-2}\left(\frac{\beta\beta' - \alpha\alpha'}{\beta\beta' - r^{n-2}\alpha\alpha'}\right)$$

$$= \frac{\alpha}{\alpha+\beta'}\,\frac{\beta\beta' - \alpha\alpha'}{\beta\beta' r^{2-n} - \alpha\alpha'}$$

We seek to maximize

$$\frac{P_n}{W_{cycle}} = \frac{\dfrac{\alpha}{\alpha+\beta'}\left(\dfrac{\beta\beta' - \alpha\alpha'}{\beta\beta' r^{2-n} - \alpha\alpha'}\right)}{\dfrac{\beta(\alpha+\beta')}{\beta\beta' - \alpha\alpha'}}$$

$$= \frac{\alpha}{\beta(\alpha+\beta')^2}\,\frac{(\beta\beta' - \alpha\alpha')^2}{(\beta\beta' r^{2-n} - \alpha\alpha')}$$

$$= \frac{\cancel{\alpha}}{\cancel{\beta\alpha^2}\left(1+\frac{\beta'}{\alpha}\right)^2}\,\frac{\cancel{(\alpha\beta)^2}}{\cancel{(\alpha\beta)}}\,\frac{\left(\frac{\beta'}{\alpha} - \frac{\alpha'}{\beta}\right)^2}{\frac{\beta'}{\alpha} r^{2-n} - \frac{\alpha'}{\beta}}$$

$$= \frac{\left(\frac{\beta'}{\alpha} - \frac{\alpha'}{\beta}\right)^2}{\left(1+\frac{\beta'}{\alpha}\right)^2\left[\frac{\beta'}{\alpha}\left(\frac{1+\frac{\beta'}{\alpha}}{1+\frac{\alpha'}{\beta}}\right)^{n-2} - \frac{\alpha'}{\beta}\right]}$$

$$= \frac{\left(\frac{\beta'}{\alpha} - \frac{\alpha'}{\beta}\right)^2\left(1+\frac{\alpha'}{\beta}\right)^{n-2}}{\left(1+\frac{\beta'}{\alpha}\right)^2\left[\frac{\beta'}{\alpha}\left(1+\frac{\beta'}{\alpha}\right)^{n-2} - \frac{\alpha'}{\beta}\left(1+\frac{\alpha'}{\beta}\right)^{n-2}\right]}$$

Let $\theta = \frac{\beta'}{\alpha}$ , $\varphi = \frac{\alpha'}{\beta}$

so $\theta > \varphi \geq 0$

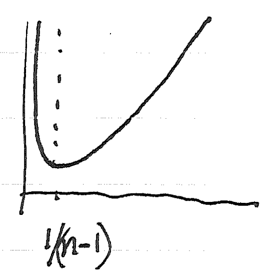
equality to allow $\beta = \infty$

Then we seek to <u>minimize</u>

$$f_n(\theta, \varphi) = \frac{(1+\theta)^2 \left[ \theta (1+\theta)^{n-2} - \varphi (1+\varphi)^{n-2} \right]}{(\theta - \varphi)^2 (1+\varphi)^{n-2}}$$

$$= \frac{\theta (1+\theta)^n}{(\theta-\varphi)^2 (1+\varphi)^{n-2}} - \frac{(1+\theta)^2 \varphi}{(\theta - \varphi)^2}$$

$$f_n(\theta, 0) = \frac{\theta (1+\theta)^n}{\theta^2} = \frac{(1+\theta)^n}{\theta}$$




This has a minimum at $\theta$ given by

$$\theta n (1+\theta)^{n-1} - (1+\theta)^n = 0$$

$$\theta n = 1 + \theta$$

$$\boxed{\theta_0 = \frac{1}{n-1}}$$

To show that $(\theta_0, 0)$ really is a local minimum (keeping in mind the constraint $\varphi \geq 0$), we need to evaluate $(\partial f/\partial\varphi)(\theta_0, 0)$

$$f_n(\theta,\varphi) = \theta(1+\theta)^n(\theta-\varphi)^{-2}(1+\varphi)^{2-n} - (1+\theta)^2\varphi(\theta-\varphi)^{-2}$$

$$\frac{\partial f_n}{\partial\varphi} = \theta(1+\theta)^n\, 2(\theta-\varphi)^{-3}(1+\varphi)^{2-n}$$
$$+\theta(1+\theta)^n(\theta-\varphi)^{-2}(2-n)(1+\varphi)^{1-n}$$
$$-(1+\theta)^2(\theta-\varphi)^{-2} - (1+\theta)^2\varphi\, 2(\theta-\varphi)^{-3}$$

$$\frac{\partial f_n}{\partial\varphi}(\theta,0) = 2\theta^{-2}(1+\theta)^n + (2-n)\theta^{-1}(1+\theta)^n$$
$$-(1+\theta)^2\left(\theta^{-2}\right)$$

$$\frac{\partial f_n}{\partial\varphi}\left(\frac{1}{n-1}, 0\right) = \left[2(n-1)^2 + (2-n)(n-1)\right]\left(\frac{n}{n-1}\right)^n$$
$$-\left(\frac{n}{n-1}\right)^2(n-1)^2$$

$$= (n^2-n)\left(\frac{n}{n-1}\right)^n - (n-1)^2\left(\frac{n}{n-1}\right)^2$$
$$= n(n-1)\left(\frac{n}{n-1}\right)^n - n^2 = n^2\left[\left(\frac{n-1}{n}\right)\left(\frac{n}{n-1}\right)^n - 1\right]$$

$$\frac{\partial f_n}{\partial \varphi}\left(\frac{1}{n-1}, 0\right) = n^2\left[\left(\frac{n}{n-1}\right)^{n-1} - 1\right] > 0$$

In fact

$$\frac{\partial f_n}{\partial \varphi}\left(\frac{1}{n-1}, 0\right) \sim n^2(e-1)$$

Let $\theta = \frac{x}{n}$ , $\varphi = \frac{y}{n}$

Then

$$g(x,y) = \lim_{n\to\infty} \frac{f_n(\frac{x}{n}, \frac{y}{n})}{n}$$

$$= \frac{xe^{x-y} - y}{(x-y)^2}$$

We seek $(x,y)$ to minimize $g$ subject to $x > y \geq 0$

Note that

$$g(x,y) = \frac{(x-y)e^{(x-y)} + y(e^{x-y} - 1)}{(x-y)^2}$$

We can think of this as a function of $x-y$ ~~and~~ and $y$.

The constraints are $x-y > 0$ and $y \geq 0$

Clearly, for any fixed $(x-y)$, we ~~[illegible]~~ minimize $g$

by setting $y=0$.

With $y=0$, we have

$$g(x,0) = \frac{xe^x}{x^2} = \frac{e^x}{x} \quad , x>0$$

$$\frac{d}{dx} g(x,0) = \frac{xe^x - e^x}{x^2} = \frac{e^x}{x^2}(x-1)$$

So the minimum occurs at $x=1$.

This shows that for large $n$ the global minimum occurs at

$$\theta = \frac{1}{n} \qquad \varphi = 0$$

That is

$$\frac{\beta'}{\alpha} = \frac{1}{n} \qquad \frac{\alpha'}{\beta} = 0 \iff \beta = \infty \text{ with } \alpha' \text{ finite}$$