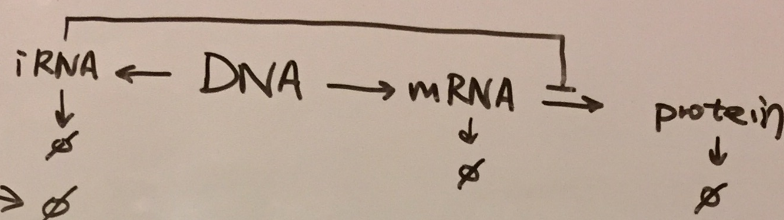

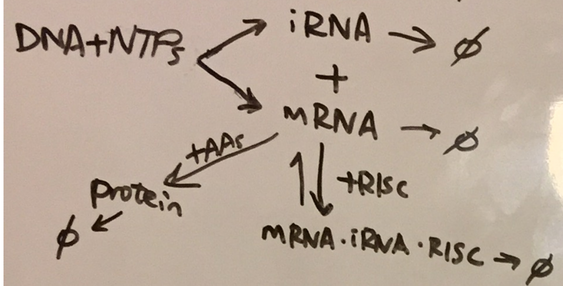

$$\begin{cases}
DNA + NTP_s \xrightarrow{K_1} DNA + mRNA \\
DNA + NTP_s \xrightarrow{K_2} DNA + iRNA \\
mRNA + AA_s \xrightarrow{K_3} mRNA + protein \\
mRNA + iRNA + RISC_s \underset{f}{\overset{h}{\rightleftharpoons}} mRNA \cdot iRNA \cdot RISC_s \\
mRNA \xrightarrow{\gamma_1} \phi \\
iRNA \xrightarrow{\gamma_1} \phi \\
mRNA \cdot iRNA \cdot RISC \xrightarrow{\gamma_2} \phi \\
protein \xrightarrow{\gamma_3} \phi
\end{cases}$$

$$\begin{cases}
K_1 = k_1 [DNA][NTP_s] \\
K_2 = k_2 [DNA][NTP_s] \\
K_3 = k_3 [AA_s] \\
H = h [RISC_s]
\end{cases}$$

$h > f$, $\gamma_2 > \gamma_1$, iRNA & mRNA same γ

[DNA], [NTPs], [AA], [RISCs] → maintained!

Let $x = [iRNA]$

$y = [mRNA]$

$z = [mRNA \cdot iRNA \cdot RISCs]$

$w = [protein]$

Deterministic:

$$\begin{cases}
\frac{dx}{dt} = K_2 - \gamma_1 x + fz - Hxy & ① \\
\frac{dy}{dt} = K_1 - \gamma_1 y + fz - Hxy & ② \\
\frac{dz}{dt} = (-f - \gamma_2) z + Hxy & ③ \\
\frac{dw}{dt} = K_3 y - \gamma_3 w & ④
\end{cases}$$

$K_5 = f + \gamma_2$

$K_4 = K_1 + K_2$

Nondimensionalize.

K_1, K_2, K_4	$\sim NT^{-1}$
t	$\sim T$
x, y, z, w	$\sim N$
$k_3, f, \gamma_2, \gamma_1, \gamma_3$	$\sim T^{-1}$
H	$\sim N^{-1}T^{-1}$

$u = \frac{y}{x+y}$

$\tau = \gamma_3 t$, $d\tau = \gamma_3 dt$

$\boxed{\text{Attempt 1}}$

① + ②:

$$\frac{d(x+y)}{dt} = K_1 + K_2 + 2fz - 2Hxy - \gamma_1(x+y)$$

Let $u = \frac{y}{x+y}$, i.e. fraction of coding RNA in all free/unbounded RNA

$$\frac{du}{dt} = \frac{d\left(\frac{y}{x+y}\right)}{dt} = \frac{y'(x+y) - (x+y)'y}{y^2} = \frac{(K_1 - \gamma_1 y + fz - Hxy)(x+y) - (K_4 + 2fz - 2Hxy - \gamma_1(x+y))y}{y^2}$$

$$= \left(K_1 x - \cancel{\gamma_1 y x} + fzx - Hx^2y + \cancel{K_1 y} - \cancel{\gamma_1 y^2} + \cancel{fzy} - \cancel{Hxy^2} - K_1 y - \cancel{K_2 y} - \cancel{2fzy} + \cancel{2Hxy^2} + \cancel{\gamma_1 xy} + \cancel{\gamma_1 y^2}\right)\frac{1}{y^2}$$

$$= \left(K_1 x + fzx - Hx^2y - K_1 y - fzy + Hxy^2\right)/y^2$$

$$= \frac{x-y}{y^2}(K_1 + fz - Hxy)$$

$$= \frac{1}{x+y}\frac{1-2u}{u^2}\left(K_1 + fz - H(x+y)u(1-u)\right)$$

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$\boxed{\text{Attempt 2}}$

$$\frac{d(x+y)}{d\tau} = \frac{K_4}{\gamma_3} + \frac{2f}{\gamma_3} z + (x+y)\left(-\frac{2H}{\gamma_3}u(1-u) - \frac{\gamma}{\gamma_3}\right)$$

$$\frac{dz}{d\tau} = \frac{K_5}{\gamma_3} z + (x+y)\frac{H}{\gamma_3}u(1-u)$$

$$\frac{dw}{d\tau} = \frac{K_3}{\gamma_3}(x+y)u - w$$

Here, to simplify, let's assume $f=0$, irreversible RNA interference.

Then:

Let:

$\ell = x+y$

$$\begin{cases} \dfrac{d\ell}{d\tau} = \dfrac{K_4}{\gamma_3} + \left(-\dfrac{2H}{\gamma_3}u(1-u) - \dfrac{\gamma}{\gamma_3}\right)\ell \\ \dfrac{du}{d\tau} = \dfrac{1-2u}{u^2}\dfrac{1}{\gamma_3 \ell}\left[K_1 - Hu(1-u)\ell\right] \\ \dfrac{dz}{d\tau} = \dfrac{H}{\gamma_3}u(1-u)\ell \\ \dfrac{dw}{d\tau} = \dfrac{K_3}{\gamma_3}u\ell - w \end{cases}$$

$r = \frac{r_1}{K_1} y$, $dr = \frac{r_1}{K_1} dy$, $\tau = r_3 t$, $d\tau = r_3 dt$,

$\therefore \frac{dr}{d\tau} = \frac{r_1}{K_1 r_3} \frac{dy}{dt} = \frac{r_1 \cancel{K_1}}{r_3 \cancel{K_1}} - \frac{r_1}{r_3} r - \cancel{H x \frac{K_1}{r_1} r}\ H \frac{K_2}{r_1 r_3} v r$

(Attempt 3)

$s = \frac{r_1 r_3}{K_1 K_3} w$, $ds = \frac{r_1 r_3}{K_1 K_3} dw$

$\therefore \frac{ds}{d\tau} = \frac{r_1}{K_1 K_3} \frac{dw}{dt} = r - s$

$v = \frac{r_1}{K_2} x$, $dv = \frac{r_1}{K_2} dx$

$\therefore \frac{dv}{d\tau} = \frac{r_1}{K_2 r_3} \frac{dx}{dt} = \frac{r_1}{r_3} - \frac{r_1}{r_3} v - H \frac{K_1}{r_1 r_3} v r$

$q = r_2 H z$, $dq = r_2 H dz$

$\therefore \frac{dq}{d\tau} = \frac{r_2 H}{r_3} \frac{dz}{dt} = -\frac{r_2}{r_3} q + \frac{r_2 H^2}{r_3} \cdot \frac{K_2 K_1}{r_1^2} v r$

To sum up:

$$\begin{cases} \frac{dv}{d\tau} = \epsilon_1 (1 - v - H_1 v r) = f(v, r) \\ \frac{dr}{d\tau} = \epsilon_2 (1 - r - H_2 v r) = g(v, r) \\ \frac{dq}{d\tau} = \epsilon_3 (-q + H_3 v r) \\ \frac{ds}{d\tau} = r - s \end{cases}$$

set $f(v^*, r^*) = g(v^*, r^*) = 0$

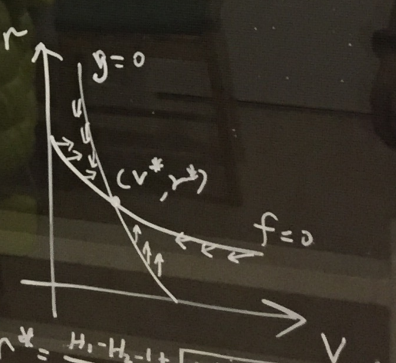
$v^* = \frac{1}{1 + H_1 r^*}$, plug into $g(v, r)$

$r^* = \frac{1}{1 + H_2 \frac{1}{1 + H_1 r^*}} = \frac{1 + H_1 r^*}{1 + H_1 r^* + H_2}$

$H_1 r^{*2} + (1 + H_2 - H_1) r^* - 1 = 0$

1 positive real s.s. (ignore negative)

Stable



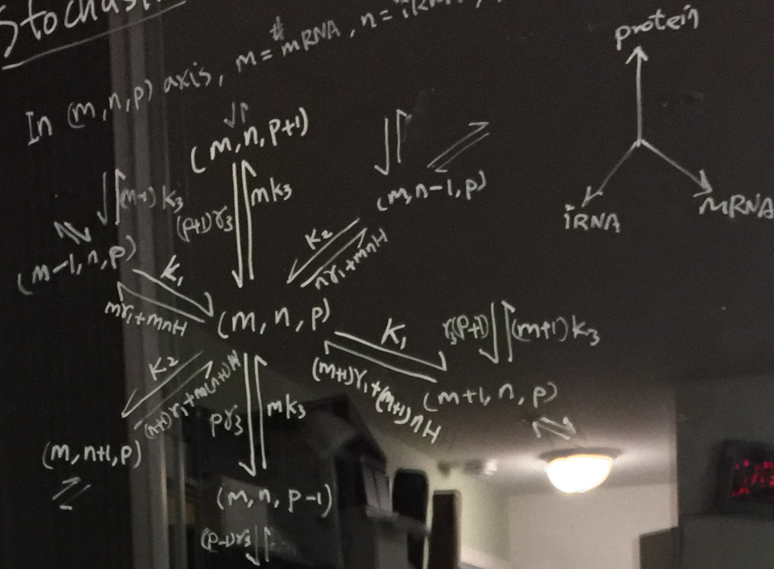
$r^* = \frac{H_1 - H_2 - 1 + \sqrt{(-H_1 + H_2 + 1)^2 + 4H_1}}{2H_1}$

$v^* = \frac{H_2 - H_1 - 1 + \sqrt{(-H_2 + H_1 + 1)^2 + 4H_2}}{2H_2}$

$\therefore s^* = r^* + (-r^*) e^{-\tau}$

Stochastic:

In (m,n,p) axis, $m = \#\text{mRNA}$, $n = \#\text{iRNA}$, $p = \#\text{protein}$



state-transition diagram for PGF

$P_M(m)$?

$P_N(n)$?

$P_{M,N,P}(m,n,p)$?

$\downarrow$

$P_p(p)$?

CME:

$$\frac{dP(m,n,p)}{dt} = k_2 P(m,n-1,p) + k_1 P(m-1,n,p) + mk_3 P(m,n,p-1) + [(n+1)\gamma_1 + m(n+1)H]P(m,n+1,p) + (p+1)\gamma_3 P(m,n,p+1) + [(m+1)\gamma_1 + (m+1)nH]P(m+1,n,p) - P(m,n,p)(k_2 + p\gamma_3 + k_1 + mk_3 + n\gamma_1 + mnH + m\gamma_1 + mnH)$$

$$\frac{dP(0,n,p)}{dt} = k_2 P(0,n-1,p) + (n+1)\gamma_1 P(0,n+1,p) + (p+1)\gamma_3 P(0,n,p+1) + (\gamma_1 + nH)P(1,n,p) - P(0,n,p)(k_2 + p\gamma_3 + k_1 + n\gamma_1)$$

$$\frac{dP(m,0,p)}{dt} = k_1 P(m-1,0,p) + mk_3 P(m,0,p-1) + (\gamma_1 + mH)P(m,1,p) + (p+1)\gamma_3 P(m,0,p+1) + (m+1)\gamma_1 P(m+1,0,p) - P(m,0,p)(k_2 + p\gamma_3 + k_1 + mk_3 + m\gamma_1)$$

$$\frac{dP(m,n,0)}{dt} = k_2 P(m,n-1,0) + k_1 P(m-1,n,0) + [(n+1)\gamma_1 + m(n+1)H]P(m,n+1,0) + \gamma_3(m,n,1) + [(m+1)\gamma_1 + (m+1)nH]P(m+1,n,0) - P(m,n,0)(k_2 + k_1 + mk_3 + n\gamma_1 + mnH + m\gamma_1 + mnH)$$

To sur

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