(* Kramers–Moyal expansion of a chemical master equation system modelling physical and genetic oDNA dynamics *)

(* includes compartmentalisation, replication difference δ, gene conversion bias ϵ, degradation cluster ndf (fused) and nd (fragmented) *)

```
(* stoichiometric matrix, reaction rates, and species *)

(* wf, mf, ws, ms = wildtype fused,
mutant fused, wildtype single, mutant single *)
(* we'll also call these W1, M1, W2, M2 *)

s = Transpose[{{1, 0, 0, 0}, {0, 1, 0, 0},
    {-ndf, 0, 0, 0}, {0, -ndf, 0, 0}, {0, 0, 1, 0}, {0, 0, 0, 1},

    {2, 0, -1, 0}, {0, 2, 0, -1}, {0, 0, -nd, 0}, {0, 0, 0, -nd},

    {2, 0, -2, 0}, {1, 0, -1, 0}, {0, 2, 0, -2}, {0, 1, 0, -1},

    {-1, 0, 1, 0}, {0, -1, 0, 1},

    {-2, 0, 2, 0}, {0, -2, 0, 2}, {-1, -1, 1, 1},

    {0, 1, 0, -1}, {1, 0, -1, 0}, {1, 1, -1, -1},

    {-1, 1, 0, 0}, {1, -1, 0, 0}}];

barerates =
  {λw W1[t], λm M1[t], νf W1[t] / ndf, νf M1[t] / ndf, β1 λw W2[t], β1 λm M2[t],

   (1 - β1) λw W2[t], (1 - β1) λm M2[t], ν W2[t] / nd, ν M2[t] / nd,

   αfuse W2[t] (W2[t] - 1) / 2, αfuse W1[t] W2[t],
   αfuse M2[t] (M2[t] - 1) / 2, αfuse M1[t] M2[t],

   αfrag β2 W1[t], αfrag β2 M1[t],

   αfrag (1 - β2) W1[t] (W1[t] - 1) / 2,
   αfrag (1 - β2) M1[t] (M1[t] - 1) / 2, αfrag (1 - β2) W1[t] M1[t],

   αfuse W1[t] M2[t], αfuse M1[t] W2[t], αfuse W2[t] M2[t],

   κ W1[t] M1[t], (κ + ϵ) M1[t] W1[t]
  };

r = {W1[t], M1[t], W2[t], M2[t]};

(* implement relaxed replication *)
```

```
rates = barerates /. λw → (λ + δ) (1 - α (W1[t] + W2[t] + M1[t] + M2[t])) /.
   λm → λ (1 - α (W1[t] + W2[t] + M1[t] + M2[t]))
```

$$\Big\{(\delta+\lambda)\,\text{W1}[t]\,(1-\alpha\,(\text{M1}[t]+\text{M2}[t]+\text{W1}[t]+\text{W2}[t])),\ \lambda\,\text{M1}[t]\,(1-\alpha\,(\text{M1}[t]+\text{M2}[t]+\text{W1}[t]+\text{W2}[t])),\ \frac{\nu\text{f W1}[t]}{\text{ndf}},\ \frac{\nu\text{f M1}[t]}{\text{ndf}},\ \beta1\,(\delta+\lambda)\,\text{W2}[t]\,(1-\alpha\,(\text{M1}[t]+\text{M2}[t]+\text{W1}[t]+\text{W2}[t])),\ \beta1\,\lambda\,\text{M2}[t]\,(1-\alpha\,(\text{M1}[t]+\text{M2}[t]+\text{W1}[t]+\text{W2}[t])),\ (1-\beta1)\,(\delta+\lambda)\,\text{W2}[t]\,(1-\alpha\,(\text{M1}[t]+\text{M2}[t]+\text{W1}[t]+\text{W2}[t])),\ (1-\beta1)\,\lambda\,\text{M2}[t]\,(1-\alpha\,(\text{M1}[t]+\text{M2}[t]+\text{W1}[t]+\text{W2}[t])),\ \frac{\nu\,\text{W2}[t]}{\text{nd}},\ \frac{\nu\,\text{M2}[t]}{\text{nd}},\ \frac{1}{2}\,\alpha\text{fuse}\,(-1+\text{W2}[t])\,\text{W2}[t],\ \alpha\text{fuse W1}[t]\,\text{W2}[t],\ \frac{1}{2}\,\alpha\text{fuse}\,(-1+\text{M2}[t])\,\text{M2}[t],\ \alpha\text{fuse M1}[t]\,\text{M2}[t],\ \alpha\text{frag}\,\beta2\,\text{W1}[t],\ \alpha\text{frag}\,\beta2\,\text{M1}[t],\ \frac{1}{2}\,\alpha\text{frag}\,(1-\beta2)\,(-1+\text{W1}[t])\,\text{W1}[t],\ \frac{1}{2}\,\alpha\text{frag}\,(1-\beta2)\,(-1+\text{M1}[t])\,\text{M1}[t],\ \alpha\text{frag}\,(1-\beta2)\,\text{M1}[t]\,\text{W1}[t],\ \alpha\text{fuse M2}[t]\,\text{W1}[t],\ \alpha\text{fuse M1}[t]\,\text{W2}[t],\ \alpha\text{fuse M2}[t]\,\text{W2}[t],\ \kappa\,\text{M1}[t]\,\text{W1}[t],\ (\epsilon+\kappa)\,\text{M1}[t]\,\text{W1}[t]\Big\}$$

```
(* example parameterisation for use later *)

params = {δ → 0, ϵ → 0, αfuse → 0.005, αfrag → 0.01,
    α → 1 / 1000, κ → 0.002, ν → 1, νf → 1, λ → 2, β1 → 0, β2 → 0};

(* number of species and reactions *)

nt = Length[r]
nr = Length[barerates]
```

4

24

```
(* matrices A and B in the Fokker-
 Planck equation arising from the system size expansion *)
```

```
avector = s.rates
```

```
{-αfrag β2 W1[t] - νf W1[t] - αfrag (1 - β2) M1[t] W1[t] -
   κ M1[t] W1[t] + (ϵ + κ) M1[t] W1[t] - αfrag (1 - β2) (-1 + W1[t]) W1[t] +
   αfuse M1[t] W2[t] + αfuse M2[t] W2[t] + αfuse W1[t] W2[t] +
   αfuse (-1 + W2[t]) W2[t] + (δ + λ) W1[t] (1 - α (M1[t] + M2[t] + W1[t] + W2[t])) +
   2 (1 - β1) (δ + λ) W2[t] (1 - α (M1[t] + M2[t] + W1[t] + W2[t])),
  -αfrag β2 M1[t] - νf M1[t] - αfrag (1 - β2) (-1 + M1[t]) M1[t] +
   αfuse M1[t] M2[t] + αfuse (-1 + M2[t]) M2[t] - αfrag (1 - β2) M1[t] W1[t] +
   κ M1[t] W1[t] - (ϵ + κ) M1[t] W1[t] + αfuse M2[t] W1[t] +
   αfuse M2[t] W2[t] + λ M1[t] (1 - α (M1[t] + M2[t] + W1[t] + W2[t])) +
   2 (1 - β1) λ M2[t] (1 - α (M1[t] + M2[t] + W1[t] + W2[t])),
  αfrag β2 W1[t] + αfrag (1 - β2) M1[t] W1[t] + αfrag (1 - β2) (-1 + W1[t]) W1[t] -
   ν W2[t] - αfuse M1[t] W2[t] - αfuse M2[t] W2[t] - αfuse W1[t] W2[t] -
   αfuse (-1 + W2[t]) W2[t] - (1 - β1) (δ + λ) W2[t] (1 - α (M1[t] + M2[t] + W1[t] + W2[t])) +
   β1 (δ + λ) W2[t] (1 - α (M1[t] + M2[t] + W1[t] + W2[t])),
  αfrag β2 M1[t] + αfrag (1 - β2) (-1 + M1[t]) M1[t] - ν M2[t] - αfuse M1[t] M2[t] -
   αfuse (-1 + M2[t]) M2[t] + αfrag (1 - β2) M1[t] W1[t] - αfuse M2[t] W1[t] -
   αfuse M2[t] W2[t] - (1 - β1) λ M2[t] (1 - α (M1[t] + M2[t] + W1[t] + W2[t])) +
   β1 λ M2[t] (1 - α (M1[t] + M2[t] + W1[t] + W2[t]))}
```

```
bmatrix = s.DiagonalMatrix[rates].Transpose[s]
```

```
{{αfrag β2 W1[t] + ndf νf W1[t] + αfrag (1 - β2) M1[t] W1[t] +
    κ M1[t] W1[t] + (ϵ + κ) M1[t] W1[t] + 2 αfrag (1 - β2) (-1 + W1[t]) W1[t] +
    αfuse M1[t] W2[t] + αfuse M2[t] W2[t] + αfuse W1[t] W2[t] +
    2 αfuse (-1 + W2[t]) W2[t] + (δ + λ) W1[t] (1 - α (M1[t] + M2[t] + W1[t] + W2[t])) +
    4 (1 - β1) (δ + λ) W2[t] (1 - α (M1[t] + M2[t] + W1[t] + W2[t])),
   αfrag (1 - β2) M1[t] W1[t] - κ M1[t] W1[t] - (ϵ + κ) M1[t] W1[t] + αfuse M2[t] W2[t],
   -αfrag β2 W1[t] - αfrag (1 - β2) M1[t] W1[t] -
    2 αfrag (1 - β2) (-1 + W1[t]) W1[t] - αfuse M1[t] W2[t] -
    αfuse M2[t] W2[t] - αfuse W1[t] W2[t] - 2 αfuse (-1 + W2[t]) W2[t] -
    2 (1 - β1) (δ + λ) W2[t] (1 - α (M1[t] + M2[t] + W1[t] + W2[t])),
   -αfrag (1 - β2) M1[t] W1[t] - αfuse M2[t] W2[t]},
  {αfrag (1 - β2) M1[t] W1[t] - κ M1[t] W1[t] - (ϵ + κ) M1[t] W1[t] + αfuse M2[t] W2[t],
   αfrag β2 M1[t] + ndf νf M1[t] + 2 αfrag (1 - β2) (-1 + M1[t]) M1[t] +
    αfuse M1[t] M2[t] + 2 αfuse (-1 + M2[t]) M2[t] + αfrag (1 - β2) M1[t] W1[t] +
    κ M1[t] W1[t] + (ϵ + κ) M1[t] W1[t] + αfuse M2[t] W1[t] +
    αfuse M2[t] W2[t] + λ M1[t] (1 - α (M1[t] + M2[t] + W1[t] + W2[t])) +
    4 (1 - β1) λ M2[t] (1 - α (M1[t] + M2[t] + W1[t] + W2[t])),
   -αfrag (1 - β2) M1[t] W1[t] - αfuse M2[t] W2[t],
   -αfrag β2 M1[t] - 2 αfrag (1 - β2) (-1 + M1[t]) M1[t] - αfuse M1[t] M2[t] -
    2 αfuse (-1 + M2[t]) M2[t] - αfrag (1 - β2) M1[t] W1[t] - αfuse M2[t] W1[t] -
    αfuse M2[t] W2[t] - 2 (1 - β1) λ M2[t] (1 - α (M1[t] + M2[t] + W1[t] + W2[t]))},
  {-αfrag β2 W1[t] - αfrag (1 - β2) M1[t] W1[t] - 2 αfrag (1 - β2) (-1 + W1[t]) W1[t] -
    αfuse M1[t] W2[t] - αfuse M2[t] W2[t] - αfuse W1[t] W2[t] - 2 αfuse (-1 + W2[t])
     W2[t] - 2 (1 - β1) (δ + λ) W2[t] (1 - α (M1[t] + M2[t] + W1[t] + W2[t])),
   -αfrag (1 - β2) M1[t] W1[t] - αfuse M2[t] W2[t],
   αfrag β2 W1[t] + αfrag (1 - β2) M1[t] W1[t] +
    2 αfrag (1 - β2) (-1 + W1[t]) W1[t] + nd ν W2[t] + αfuse M1[t] W2[t] +
    αfuse M2[t] W2[t] + αfuse W1[t] W2[t] + 2 αfuse (-1 + W2[t]) W2[t] +
    (1 - β1) (δ + λ) W2[t] (1 - α (M1[t] + M2[t] + W1[t] + W2[t])) +
    β1 (δ + λ) W2[t] (1 - α (M1[t] + M2[t] + W1[t] + W2[t])),
   αfrag (1 - β2) M1[t] W1[t] + αfuse M2[t] W2[t]},
  {-αfrag (1 - β2) M1[t] W1[t] - αfuse M2[t] W2[t],
   -αfrag β2 M1[t] - 2 αfrag (1 - β2) (-1 + M1[t]) M1[t] - αfuse M1[t] M2[t] -
    2 αfuse (-1 + M2[t]) M2[t] - αfrag (1 - β2) M1[t] W1[t] - αfuse M2[t] W1[t] -
    αfuse M2[t] W2[t] - 2 (1 - β1) λ M2[t] (1 - α (M1[t] + M2[t] + W1[t] + W2[t])),
   αfrag (1 - β2) M1[t] W1[t] + αfuse M2[t] W2[t],
   αfrag β2 M1[t] + 2 αfrag (1 - β2) (-1 + M1[t]) M1[t] + nd ν M2[t] + αfuse M1[t] M2[t] +
    2 αfuse (-1 + M2[t]) M2[t] + αfrag (1 - β2) M1[t] W1[t] + αfuse M2[t] W1[t] +
    αfuse M2[t] W2[t] + (1 - β1) λ M2[t] (1 - α (M1[t] + M2[t] + W1[t] + W2[t])) +
    β1 λ M2[t] (1 - α (M1[t] + M2[t] + W1[t] + W2[t]))}}
```

```
(* f is fragmented proportion;
n is total copy number; h is mutant proportion *)
(* here we compute various derivatives for their analysis *)
```

```
fdef = (W2[t] + M2[t]) / (W1[t] + W2[t] + M1[t] + M2[t]);
ndef = (W1[t] + W2[t] + M1[t] + M2[t]);
hdef = (M1[t] + M2[t]) / (W1[t] + W2[t] + M1[t] + M2[t]);
gradn = Simplify[D[ndef, {r}]];
gradh = Simplify[D[hdef, {r}]];
gradf = Simplify[D[fdef, {r}]];
```

```
hessianf = Simplify[Table[
    Table[D[D[fdef, r[[i]]], r[[j]]], {i, 1, Length[r]}], {j, 1, Length[r]}]];
hessiann = Simplify[Table[Table[D[D[ndef, r[[i]]], r[[j]]], {i, 1, Length[r]}],
    {j, 1, Length[r]}]];
hessianh = Simplify[Table[Table[D[D[hdef, r[[i]]], r[[j]]],
     {i, 1, Length[r]}], {j, 1, Length[r]}]];
```

```
(* atilde is the Ito-transformed A in the F-
 P equation for the corresponding quantity *)
```

```
atildef = Simplify[gradf.avector + 1 / 2 Tr[hessianf.bmatrix]];
atilden = Simplify[gradn.avector + 1 / 2 Tr[hessiann.bmatrix]];
atildeh = Simplify[gradh.avector + 1 / 2 Tr[hessianh.bmatrix]];
```

```
atildefsub =
 Simplify[(atildef /. M1[t] → (1 - f) h n /. M2[t] → f h n /. W1[t] → (1 - f) (1 - h) n /.
     W2[t] → f (1 - h) n) /. {h → h[t], n → n[t], f → f[t]}]
atildensub = Simplify[(atilden /. M1[t] → (1 - f) h n /. M2[t] → f h n /.
      W1[t] → (1 - f) (1 - h) n /. W2[t] → f (1 - h) n) /. {h → h[t], n → n[t], f → f[t]}]
atildehsub = Simplify[(atildeh /. M1[t] → (1 - f) h n /. M2[t] → f h n /.
      W1[t] → (1 - f) (1 - h) n /. W2[t] → f (1 - h) n) /. {h → h[t], n → n[t], f → f[t]}]
```

$$\frac{1}{n[t]}\Big(\alpha\mathrm{frag}\, n[t]\ (-1+2\,\beta 2+n[t]-\beta 2\, n[t])+ f[t]^2\ \left(\mathrm{nd}\,\nu-\mathrm{ndf}\,\nu\mathrm{f}+(\nu-\nu\mathrm{f})\ n[t]+(\alpha\mathrm{frag}-\alpha\mathrm{frag}\,\beta 2)\ n[t]^2\right)+ f[t]\ \big(2\,\delta-2\,\beta 1\,\delta+2\,\lambda-2\,\beta 1\,\lambda-\mathrm{nd}\,\nu+\mathrm{ndf}\,\nu\mathrm{f}+(\alpha\mathrm{frag}+\alpha\mathrm{fuse}-2\,\alpha\mathrm{frag}\,\beta 2- 2\,\delta-2\,\alpha\,\delta+2\,\beta 1\,\delta+2\,\alpha\,\beta 1\,\delta-2\,\lambda-2\,\alpha\,\lambda+2\,\beta 1\,\lambda+2\,\alpha\,\beta 1\,\lambda-\nu+\nu\mathrm{f})\ n[t]- (\alpha\mathrm{fuse}-2\,\alpha\mathrm{frag}\ (-1+\beta 2)+2\,\alpha\ (-1+\beta 1)\ (\delta+\lambda))\ n[t]^2+2 (-1+\beta 1)\ \delta\, h[t]\ (-1+n[t])\ (-1+\alpha\, n[t])\big)\Big)$$

$$n[t]\ (\delta+\lambda-\nu\mathrm{f}+(-\nu+\nu\mathrm{f})\ f[t]-\alpha\,\delta\, n[t]-\alpha\,\lambda\, n[t]+\delta\, h[t]\ (-1+\alpha\, n[t]))$$

$$-\frac{1}{n[t]}(-1+h[t])\ h[t]\ \left(\delta-(1+\alpha)\ \delta\, n[t]+\left(\alpha\,\delta-\epsilon+2\,\epsilon\, f[t]-\epsilon\, f[t]^2\right)\ n[t]^2\right)$$

(*** neutral case ***)

```
FullSimplify[atildehsub /. δ → 0 /. ϵ → 0]
```

0

```
(* three simultaneous ODEs. separation of timescales -- assume n,
f equilibrate more quickly *)
```

```
dhdt = Simplify[atildehsub /. n[t] → n]
```

$$-\frac{1}{n}\left(\delta-n\ (1+\alpha)\ \delta+n^2\ \left(\alpha\,\delta-\epsilon+2\,\epsilon\, f[t]-\epsilon\, f[t]^2\right)\right)\ (-1+h[t])\ h[t]$$

```
FullSimplify[dhdt /. δ → 0 /. ϵ → 0]
```

0

```
(* btildes are the Ito-transformed B in the F-P equations for each quantity *)
```

```
btildef = Simplify[gradf.bmatrix.gradf]
btilden = Simplify[gradn.bmatrix.gradn]
btildeh = Simplify[gradh.bmatrix.gradh]
```

$$
\begin{aligned}
&-\frac{1}{(M1[t]+M2[t]+W1[t]+W2[t])^4}\\
&\Big((M2[t]+W2[t])\,((M1[t]+W1[t])\,(\alpha\text{frag}\,(-1+\beta2)\,M1[t]\,W1[t]-\alpha\text{fuse}\,M2[t]\,W2[t])-\\
&\quad (M2[t]+W2[t])\,(-(\alpha\text{frag}\,(-1+\beta2)+\epsilon+2\,\kappa)\,M1[t]\,W1[t]+\alpha\text{fuse}\,M2[t]\,W2[t])+\\
&\quad (M1[t]+W1[t])\,(-\alpha\text{frag}\,\beta2\,M1[t]+2\,\alpha\text{frag}\,(-1+\beta2)\,(-1+M1[t])\,M1[t]-\\
&\qquad \alpha\text{fuse}\,M1[t]\,M2[t]-2\,\alpha\text{fuse}\,(-1+M2[t])\,M2[t]+\\
&\qquad \alpha\text{frag}\,(-1+\beta2)\,M1[t]\,W1[t]-\alpha\text{fuse}\,M2[t]\,W1[t]-\alpha\text{fuse}\,M2[t]\,W2[t]-\\
&\qquad 2\,(1-\beta1)\,\lambda\,M2[t]\,(1-\alpha\,(M1[t]+M2[t]+W1[t]+W2[t]))))-(M2[t]+W2[t])\\
&\quad (\alpha\text{frag}\,\beta2\,M1[t]+\text{ndf}\,\nu\text{f}\,M1[t]-2\,\alpha\text{frag}\,(-1+\beta2)\,(-1+M1[t])\,M1[t]+\\
&\qquad \alpha\text{fuse}\,M1[t]\,M2[t]+2\,\alpha\text{fuse}\,(-1+M2[t])\,M2[t]-\alpha\text{frag}\,(-1+\beta2)\,M1[t]\,W1[t]+\\
&\qquad \kappa\,M1[t]\,W1[t]+(\epsilon+\kappa)\,M1[t]\,W1[t]+\alpha\text{fuse}\,M2[t]\,W1[t]+\\
&\qquad \alpha\text{fuse}\,M2[t]\,W2[t]+\lambda\,M1[t]\,(1-\alpha\,(M1[t]+M2[t]+W1[t]+W2[t]))+\\
&\qquad 4\,(1-\beta1)\,\lambda\,M2[t]\,(1-\alpha\,(M1[t]+M2[t]+W1[t]+W2[t])))))-\\
&(M1[t]+W1[t])\,\Big((M1[t]+W1[t])\,(-\alpha\text{frag}\,(-1+\beta2)\,M1[t]\,W1[t]+\alpha\text{fuse}\,M2[t]\,W2[t])+\\
&\quad (M2[t]+W2[t])\,(-\alpha\text{frag}\,(-1+\beta2)\,M1[t]\,W1[t]+\alpha\text{fuse}\,M2[t]\,W2[t])+\\
&\quad (M1[t]+W1[t])\,\Big(-2\,\alpha\text{frag}\,(-1+\beta2)\,W1[t]^2+\\
&\qquad W2[t]\,(-2\,\alpha\text{fuse}+\delta+\lambda+\text{nd}\,\nu+(\alpha\text{fuse}-\alpha\,(\delta+\lambda))\,M1[t]+\\
&\qquad\quad (\alpha\text{fuse}-\alpha\,(\delta+\lambda))\,M2[t]+2\,\alpha\text{fuse}\,W2[t]-\alpha\,\delta\,W2[t]-\alpha\,\lambda\,W2[t])-\\
&\qquad W1[t]\,(\alpha\text{frag}\,(2-3\,\beta2)+\alpha\text{frag}\,(-1+\beta2)\,M1[t]+(-\alpha\text{fuse}+\alpha\,(\delta+\lambda))\,W2[t])\Big)-\\
&\quad (M2[t]+W2[t])\,(-\alpha\text{frag}\,\beta2\,W1[t]+\alpha\text{frag}\,(-1+\beta2)\,M1[t]\,W1[t]+\\
&\qquad 2\,\alpha\text{frag}\,(-1+\beta2)\,(-1+W1[t])\,W1[t]-\alpha\text{fuse}\,M1[t]\,W2[t]-\\
&\qquad \alpha\text{fuse}\,M2[t]\,W2[t]-\alpha\text{fuse}\,W1[t]\,W2[t]-2\,\alpha\text{fuse}\,(-1+W2[t])\,W2[t]-\\
&\qquad 2\,(1-\beta1)\,(\delta+\lambda)\,W2[t]\,(1-\alpha\,(M1[t]+M2[t]+W1[t]+W2[t]))))\Big)+\\
&(M2[t]+W2[t])\,((M1[t]+W1[t])\,(\alpha\text{frag}\,(-1+\beta2)\,M1[t]\,W1[t]-\alpha\text{fuse}\,M2[t]\,W2[t])-\\
&\quad (M2[t]+W2[t])\,(-(\alpha\text{frag}\,(-1+\beta2)+\epsilon+2\,\kappa)\,M1[t]\,W1[t]+\alpha\text{fuse}\,M2[t]\,W2[t])+\\
&\quad (M1[t]+W1[t])\,(-\alpha\text{frag}\,\beta2\,W1[t]+\alpha\text{frag}\,(-1+\beta2)\,M1[t]\,W1[t]+\\
&\qquad 2\,\alpha\text{frag}\,(-1+\beta2)\,(-1+W1[t])\,W1[t]-\alpha\text{fuse}\,M1[t]\,W2[t]-\\
&\qquad \alpha\text{fuse}\,M2[t]\,W2[t]-\alpha\text{fuse}\,W1[t]\,W2[t]-2\,\alpha\text{fuse}\,(-1+W2[t])\,W2[t]-\\
&\qquad 2\,(1-\beta1)\,(\delta+\lambda)\,W2[t]\,(1-\alpha\,(M1[t]+M2[t]+W1[t]+W2[t])))-\\
&\quad (M2[t]+W2[t])\,(\alpha\text{frag}\,\beta2\,W1[t]+\text{ndf}\,\nu\text{f}\,W1[t]-\alpha\text{frag}\,(-1+\beta2)\,M1[t]\,W1[t]+\\
&\qquad \kappa\,M1[t]\,W1[t]+(\epsilon+\kappa)\,M1[t]\,W1[t]-2\,\alpha\text{frag}\,(-1+\beta2)\,(-1+W1[t])\,W1[t]+\\
&\qquad \alpha\text{fuse}\,M1[t]\,W2[t]+\alpha\text{fuse}\,M2[t]\,W2[t]+\alpha\text{fuse}\,W1[t]\,W2[t]+2\,\alpha\text{fuse}\\
&\qquad\ (-1+W2[t])\,W2[t]+(\delta+\lambda)\,W1[t]\,(1-\alpha\,(M1[t]+M2[t]+W1[t]+W2[t]))+\\
&\qquad 4\,(1-\beta1)\,(\delta+\lambda)\,W2[t]\,(1-\alpha\,(M1[t]+M2[t]+W1[t]+W2[t])))))+\\
&(M1[t]+W1[t])\,\Big(2\,\alpha\text{frag}\,(-1+\beta2)\,M1[t]^3+M1[t]^2\,((-\alpha\text{fuse}+2\,\alpha\text{frag}\,(-1+\beta2)+\alpha\,\lambda)\\
&\qquad M2[t]+\alpha\text{frag}\,(2-3\,\beta2+4\,(-1+\beta2)\,W1[t]+2\,(-1+\beta2)\,W2[t]))+\\
&\quad M1[t]\,\Big((-3\,\alpha\text{fuse}+\alpha\,(3-2\,\beta1)\,\lambda)\,M2[t]^2+\alpha\text{frag}\,(2-3\,\beta2+2\,(-1+\beta2)\,W1[t])\\
&\qquad (W1[t]+W2[t])+M2[t]\,(2\,\alpha\text{frag}+2\,\alpha\text{fuse}-3\,\alpha\text{frag}\,\beta2-\lambda-\text{nd}\,\nu-2\,(\alpha\text{frag}+\\
&\qquad\quad \alpha\text{fuse}-\alpha\text{frag}\,\beta2-\alpha\,\lambda)\,W1[t]+(-3\,\alpha\text{fuse}+\alpha\,(3-2\,\beta1)\,\lambda)\,W2[t])\Big)-\\
&\quad M2[t]\,\Big(2\,(\alpha\text{fuse}+\alpha\,(-1+\beta1)\,\lambda)\,M2[t]^2+(\alpha\text{fuse}-\alpha\,\lambda)\,W1[t]^2+\\
&\qquad 2\,W2[t]\,(-\alpha\text{fuse}+\lambda-\beta1\,\lambda+(\alpha\text{fuse}+\alpha\,(-1+\beta1)\,\lambda)\,W2[t])+\\
&\qquad W1[t]\,(-2\,\alpha\text{fuse}+\lambda+\text{nd}\,\nu+(3\,\alpha\text{fuse}+\alpha\,(-3+2\,\beta1)\,\lambda)\,W2[t])+\\
&\qquad M2[t]\,((3\,\alpha\text{fuse}+\alpha\,(-3+2\,\beta1)\,\lambda)\,W1[t]+\\
&\qquad\quad 2\,(-\alpha\text{fuse}+\lambda-\beta1\,\lambda+2\,(\alpha\text{fuse}+\alpha\,(-1+\beta1)\,\lambda)\,W2[t])))\Big)\Big)\Big)
\end{aligned}
$$

$$
\begin{aligned}
&\text{ndf}\,\nu\text{f}\,M1[t]+\text{nd}\,\nu\,M2[t]+\text{ndf}\,\nu\text{f}\,W1[t]+\\
&\ \text{nd}\,\nu\,W2[t]+\lambda\,M1[t]\,(1-\alpha\,(M1[t]+M2[t]+W1[t]+W2[t]))+\\
&\ (1-\beta1)\,\lambda\,M2[t]\,(1-\alpha\,(M1[t]+M2[t]+W1[t]+W2[t]))+\\
&\ \beta1\,\lambda\,M2[t]\,(1-\alpha\,(M1[t]+M2[t]+W1[t]+W2[t]))+\\
&\ (\delta+\lambda)\,W1[t]\,(1-\alpha\,(M1[t]+M2[t]+W1[t]+W2[t]))+\\
&\ (1-\beta1)\,(\delta+\lambda)\,W2[t]\,(1-\alpha\,(M1[t]+M2[t]+W1[t]+W2[t]))+\\
&\ \beta1\,(\delta+\lambda)\,W2[t]\,(1-\alpha\,(M1[t]+M2[t]+W1[t]+W2[t]))
\end{aligned}
$$

$$\frac{1}{(\mathrm{M1}[t]+\mathrm{M2}[t]+\mathrm{W1}[t]+\mathrm{W2}[t])^4}\Big(-\mathrm{M1}[t]^3\left((-\epsilon-2\kappa+\alpha(\delta+\lambda))\,\mathrm{W1}[t]+\alpha(\delta+\lambda)\,\mathrm{W2}[t]\right)+\mathrm{M1}[t]^2\Big((2(\epsilon+2\kappa)-\alpha(\delta+2\lambda))\,\mathrm{W1}[t]^2+\mathrm{W2}[t]\,(\delta+\lambda+\mathrm{nd}\,\nu-3\alpha(\delta+\lambda)\,\mathrm{M2}[t]-\alpha(\delta+2\lambda)\,\mathrm{W2}[t])+\mathrm{W1}[t]\,(\delta+\lambda+\mathrm{ndf}\,\nu f+(2(\epsilon+2\kappa)-3\alpha(\delta+\lambda))\,\mathrm{M2}[t]+2(\epsilon+2\kappa-\alpha(\delta+2\lambda))\,\mathrm{W2}[t])\Big)+\mathrm{M2}[t]\Big(-\alpha(\delta+\lambda)\,\mathrm{M2}[t]^2(\mathrm{W1}[t]+\mathrm{W2}[t])-(\mathrm{W1}[t]+\mathrm{W2}[t])^2(-\lambda-\mathrm{nd}\,\nu+\alpha\lambda\,\mathrm{W1}[t]+\alpha\lambda\,\mathrm{W2}[t])+\mathrm{M2}[t]\Big(-\alpha(\delta+2\lambda)\,\mathrm{W1}[t]^2+\mathrm{W1}[t]\,(\delta+\lambda+\mathrm{ndf}\,\nu f-2\alpha(\delta+2\lambda)\,\mathrm{W2}[t])+\mathrm{W2}[t]\,(\delta+\lambda+\mathrm{nd}\,\nu-\alpha(\delta+2\lambda)\,\mathrm{W2}[t])\Big)\Big)+\mathrm{M1}[t]\Big(-(\mathrm{W1}[t]+\mathrm{W2}[t])^2(-\lambda-\mathrm{ndf}\,\nu f-(\epsilon+2\kappa-\alpha\lambda)\,\mathrm{W1}[t]+\alpha\lambda\,\mathrm{W2}[t])+\mathrm{M2}[t]^2((\epsilon+2\kappa-3\alpha(\delta+\lambda))\,\mathrm{W1}[t]-3\alpha(\delta+\lambda)\,\mathrm{W2}[t])+2\,\mathrm{M2}[t]\Big((\epsilon+2\kappa-\alpha(\delta+2\lambda))\,\mathrm{W1}[t]^2+\mathrm{W2}[t]\,(\delta+\lambda+\mathrm{nd}\,\nu-\alpha(\delta+2\lambda)\,\mathrm{W2}[t])+\mathrm{W1}[t]\,(\delta+\lambda+\mathrm{ndf}\,\nu f+(\epsilon+2\kappa-2\alpha(\delta+2\lambda))\,\mathrm{W2}[t])\Big)\Big)\Big)$$

```
(* vp = "v prime" -- this is d V'(h) / dt *)
```

```
dvpdtNeutral = FullSimplify[
  Simplify[btildeh /. δ → 0 /. ϵ → 0 /. M1[t] → (1 - f) h n /. M2[t] → f h n /.
     W1[t] → (1 - f) (1 - h) n /. W2[t] → f (1 - h) n] / (h (1 - h))]
FullSimplify[dvpdtNeutral /. νf → 0]
FullSimplify[dvpdtNeutral /. νf → ν /. nd → 1 /. ndf → 1]
```

$$\frac{2(-1+f)^2 n\kappa+\lambda-n\alpha\lambda+f\,\mathrm{nd}\,\nu+\mathrm{ndf}\,\nu f-f\,\mathrm{ndf}\,\nu f}{n}$$

$$\frac{2(-1+f)^2 n\kappa+\lambda-n\alpha\lambda+f\,\mathrm{nd}\,\nu}{n}$$

$$\frac{2(-1+f)^2 n\kappa+\lambda-n\alpha\lambda+\nu}{n}$$

(***** no longer neutral ****)

```
atildehsub
```

$$-\frac{1}{n[t]}(-1+h[t])\,h[t]\left(\delta-(1+\alpha)\,\delta\,n[t]+\left(\alpha\delta-\epsilon+2\epsilon f[t]-\epsilon f[t]^2\right)n[t]^2\right)$$

```
(* assume fast n, f relaxation *)
```

```
dhdt = Simplify[atildehsub /. f[t] → f /. n[t] → n]
```

$$-\frac{1}{n}\left((-1+n)(-1+n\alpha)\,\delta-(-1+f)^2 n^2\epsilon\right)(-1+h[t])\,h[t]$$

```
(* as before,
btilde is the Ito-transformed B in the F-P equation for heteroplasmy *)
```

```
btildehsub = Simplify[
  (btildeh /. M1[t] → (1 - f) h[t] n /. M2[t] → f h[t] n /. W1[t] → (1 - f) (1 - h[t]) n /.
     W2[t] → f (1 - h[t]) n)]
```

$$-\frac{1}{n}(-1+h[t])\,h[t]\left(\lambda+n\left((-1+f)^2\epsilon+2(-1+f)^2\kappa-\alpha\lambda\right)+f\,\mathrm{nd}\,\nu+\mathrm{ndf}\,\nu f-f\,\mathrm{ndf}\,\nu f+(\delta-n\alpha\delta)\,h[t]\right)$$

```
(* rates of change of untransformed and transformed heteroplasmy *)
```

```
dvhdt =
 FullSimplify[(2 atildehsub v[t] + btildehsub) /. νf → 0 /. n[t] → n /. f[t] → f]
dvphdt = FullSimplify[dvhdt / (h0 (1 - h0)) /. n[t] → n /. f[t] → f]
```

$$\frac{1}{n}(-1+h[t])\,h[t]\,\Big(-(-1+f)^2\,n\,(\epsilon+2\,\kappa)-\lambda+n\,\alpha\,\lambda-f\,nd\,\nu+(-1+n\,\alpha)\,\delta\,h[t]+2\,\big(-(-1+n)\,(-1+n\,\alpha)\,\delta+(-1+f)^2\,n^2\,\epsilon\big)\,v[t]\Big)$$

$$\Big((-1+h[t])\,h[t]\,\big((-1+f)^2\,n\,(\epsilon+2\,\kappa)+\lambda-n\,\alpha\,\lambda+f\,nd\,\nu+(\delta-n\,\alpha\,\delta)\,h[t]-2\,\big(-(-1+n)\,(-1+n\,\alpha)\,\delta+(-1+f)^2\,n^2\,\epsilon\big)\,v[t]\big)\Big)\Big/\big((-1+h0)\,h0\,n\big)$$

```
(* solution for mean heteroplasmy,
using some substitutions to speed up the algebra *)
```

```
ehsoln = FullSimplify[DSolve[{D[h[t], t] == dhdt, h[0] == h0}, h[t], t]][[1]] /.
```
$$e^{-\frac{(-1+n)\,t\,(-1+n\,\alpha)\,\delta}{n}+(-1+f)^2\,n\,t\,\epsilon}\rightarrow \mathrm{Exp}[(-\gamma1/n+\gamma2/n)\,t]$$

Solve::ifun : Inverse functions are being used by Solve, so some solutions may not be found; use Reduce for complete solution information. ≫

$$\left\{h[t]\rightarrow\frac{1}{1+e^{t\left(-\frac{\gamma1}{n}+\frac{\gamma2}{n}\right)}\left(-1+\frac{1}{h0}\right)}\right\}$$

```
(* resubstitute *)
```

```
γparams = {γ1 → (-1 + n) (-1 + n α) δ, γ2 -> (-1 + f)^2 n^2 ϵ}
```

$$\{\gamma1\rightarrow(-1+n)\,(-1+n\,\alpha)\,\delta,\ \gamma2\rightarrow(-1+f)^2\,n^2\,\epsilon\}$$

```
(* same for variance behaviour *)
```

```
dvhdtsub =
 FullSimplify[dvhdt /. ehsoln] /. (-1 + n) (-1 + n α) δ → γ1 /. (-1 + f)^2 n^2 ϵ → γ2
```

$$\left(\left(-1+\frac{1}{1+e^{\frac{t(-\gamma1+\gamma2)}{n}}\left(-1+\frac{1}{h0}\right)}\right)h0\left(\frac{h0\,(1-n\,\alpha)\,\delta}{e^{\frac{t(-\gamma1+\gamma2)}{n}}\,(-1+h0)-h0}-(-1+f)^2\,n\,(\epsilon+2\,\kappa)-\lambda+n\,\alpha\,\lambda-f\,nd\,\nu+2\,(-\gamma1+\gamma2)\,v[t]\right)\right)\Big/\left(\left(-e^{\frac{t(-\gamma1+\gamma2)}{n}}\,(-1+h0)+h0\right)n\right)$$

```
(* to inform comparison with transformed mouse data *)
```

```
mousesubs = {ϵ → 0, κ → 0, nd → 1, h0 → 1 / 2};
```

```
meanhmouse =
 h[t] /. FullSimplify[DSolve[{D[h[t], t] == dhdt, h[0] == h0}, h[t], t][[1]]] /.
   mousesubs /. (-1 + n) t (-1 + n α) δ / n → β t
varhmouse = FullSimplify[
  v[t] /. FullSimplify[DSolve[{D[v[t], t] == (dvhdt /. mousesubs /. h[t] → meanh),
        v[0] == 0}, v[t], t]][[1]] /. mousesubs /. (-1 + n) t (-1 + n α) δ / n → β t]
```

Solve::ifun : Inverse functions are being used by Solve, so some solutions may not be found; use Reduce for complete solution information. ≫

$$\frac{1}{1+e^{-t\,\beta}}$$

$$-\left(\left(\left(-1+e^{-2\,(-1+\text{meanh})\,\text{meanh}\,t\,\beta}\right)\,\left((-1+n\,\alpha)\,(\text{meanh}\,\delta+\lambda)-f\,\nu\right)\right)\Big/\left(2\,(-1+n)\,(-1+n\,\alpha)\,\delta\right)\right)$$

(*** simplify by setting h0 = 1/2 ***)

```
vsoln1 = Simplify[DSolve[{D[v[t], t] == dvhdtsub, v[0] == 0}, v[t], t]] /.
   t (-γ1 + γ2) / n → b t /. h0 → 1 / 2
```

$$\Bigg\{\Bigg\{v[t]\to\frac{1}{4\,e\,\left(-\frac{1}{2}-\frac{e^{b\,t}}{2}\right)\,(\gamma1-\gamma2)}\Bigg(-\frac{1}{2}\,e^{1+b\,t}\,\left((-1+n\,\alpha)\,\delta-2\,\left(\lambda+n\,\left((-1+f)^2\,\epsilon+2\,(-1+f)^2\,\kappa-\alpha\,\lambda\right)+f\,\text{nd}\,\nu\right)\right)+$$
$$\frac{1}{2}\,e^{\frac{1}{\frac{1}{2}+\frac{e^{b\,t}}{2}}}\,\left(2\,(-1+n\,\alpha)\,\delta-2\,\left(\lambda+n\,\left((-1+f)^2\,\epsilon+2\,(-1+f)^2\,\kappa-\alpha\,\lambda\right)+f\,\text{nd}\,\nu\right)\right)+$$
$$\frac{1}{2}\,e^{\frac{1}{\frac{1}{2}+\frac{e^{b\,t}}{2}}+b\,t}\,\left(2\,(-1+n\,\alpha)\,\delta-2\,\left(\lambda+n\,\left((-1+f)^2\,\epsilon+2\,(-1+f)^2\,\kappa-\alpha\,\lambda\right)+f\,\text{nd}\,\nu\right)\right)-$$
$$\frac{1}{2}\,e\,\left(3\,(-1+n\,\alpha)\,\delta-2\,\left(\lambda+n\,\left((-1+f)^2\,\epsilon+2\,(-1+f)^2\,\kappa-\alpha\,\lambda\right)+f\,\text{nd}\,\nu\right)\right)\Bigg)\Bigg\}\Bigg\}$$

```
vsolns = FullSimplify[v[t] /. vsoln1[[1]]]
```

$$-\frac{1}{4\,e\,\left(1+e^{b\,t}\right)\,(\gamma1-\gamma2)}\Bigg(2\,e^{\frac{2}{1+e^{b\,t}}}\,\left((-1+n\,\alpha)\,\delta-(-1+f)^2\,n\,(\epsilon+2\,\kappa)-\lambda+n\,\alpha\,\lambda-f\,\text{nd}\,\nu\right)+$$
$$2\,e^{\frac{2}{1+e^{b\,t}}+b\,t}\,\left((-1+n\,\alpha)\,\delta-(-1+f)^2\,n\,(\epsilon+2\,\kappa)-\lambda+n\,\alpha\,\lambda-f\,\text{nd}\,\nu\right)+$$
$$e^{1+b\,t}\,\left(\delta-n\,\alpha\,\delta+2\,\left((-1+f)^2\,n\,(\epsilon+2\,\kappa)+\lambda-n\,\alpha\,\lambda+f\,\text{nd}\,\nu\right)\right)+$$
$$e\,\left((3-3\,n\,\alpha)\,\delta+2\,\left((-1+f)^2\,n\,(\epsilon+2\,\kappa)+\lambda-n\,\alpha\,\lambda+f\,\text{nd}\,\nu\right)\right)\Bigg)$$

```
Simplify[Simplify[vsolns /. ((-1 + f)^2 n (ϵ + 2 κ) + λ - n α λ + f nd ν) → ρ /.
      (- (-1 + f)^2 n (ϵ + 2 κ) - λ + n α λ - f nd ν) → -ρ] /. (-1 + n α) δ → φ /. (δ - n α δ) → -φ]
```

$$\left(2\,e^{\frac{2}{1+e^{b\,t}}}\,(\rho-\varphi)+2\,e^{\frac{2}{1+e^{b\,t}}+b\,t}\,(\rho-\varphi)+e^{1+b\,t}\,(-2\,\rho+\varphi)+e\,(-2\,\rho+3\,\varphi)\right)\Big/\left(4\,e\,\left(1+e^{b\,t}\right)\,(\gamma1-\gamma2)\right)$$

```
vsolns /. (-1 + n α) δ - (-1 + f)^2 n (ϵ + 2 κ) - λ + n α λ - f nd ν → ρ1 /.
  ((-1 + f)^2 n (ϵ + 2 κ) + λ - n α λ + f nd ν) → ρ2
```

$$
-\left(\left(2\,e^{\frac{2}{1+e^{b\,t}}}\,\rho 1+2\,e^{\frac{2}{1+e^{b\,t}}+b\,t}\,\rho 1+e^{1+b\,t}\,(\delta-n\,\alpha\,\delta+2\,\rho 2)+e\,((3-3\,n\,\alpha)\,\delta+2\,\rho 2)\right)\Big/\left(4\,e\,\left(1+e^{b\,t}\right)(\gamma 1-\gamma 2)\right)\right)
$$

(*** general h0 ****)

```
vsoln2 =
 Simplify[DSolve[{D[v[t], t] == dvhdtsub, v[0] == 0}, v[t], t]] /. t (-γ1 + γ2)/n → b t
```

$$
\Big\{\Big\{v[t]\to\frac{1}{4\left(e^{b\,t}(-1+h0)-h0\right)(\gamma 1-\gamma 2)}\,e^{-2\,h0}\Big(e^{2\,h0+b\,t}(-1+h0)\left((-1+n\,\alpha)\,\delta-2\left(\lambda+n\left((-1+f)^2\,\epsilon+2\,(-1+f)^2\,\kappa-\alpha\,\lambda\right)+f\,nd\,\nu\right)\right)-
e^{2\,h0}\,h0\left(3\,(-1+n\,\alpha)\,\delta-2\left(\lambda+n\left((-1+f)^2\,\epsilon+2\,(-1+f)^2\,\kappa-\alpha\,\lambda\right)+f\,nd\,\nu\right)\right)-
e^{\frac{2\,h0}{-e^{b\,t}(-1+h0)+h0}+b\,t}(-1+h0)\Big((1+2\,h0)(-1+n\,\alpha)\,\delta-
2\left(\lambda+n\left((-1+f)^2\,\epsilon+2\,(-1+f)^2\,\kappa-\alpha\,\lambda\right)+f\,nd\,\nu\right)\Big)+e^{\frac{2\,h0}{-e^{b\,t}(-1+h0)+h0}}\,h0
\left((1+2\,h0)(-1+n\,\alpha)\,\delta-2\left(\lambda+n\left((-1+f)^2\,\epsilon+2\,(-1+f)^2\,\kappa-\alpha\,\lambda\right)+f\,nd\,\nu\right)\right)\Big)\Big\}\Big\}
$$

```
vsolns2 = FullSimplify[v[t] /. vsoln2[[1]]]
```

$$
\frac{1}{4\left(e^{b\,t}(-1+h0)-h0\right)(\gamma 1-\gamma 2)}
e^{-2\,h0}\Big(e^{2\,h0+b\,t}(-1+h0)\left((-1+n\,\alpha)\,\delta-2\left((-1+f)^2\,n\,(\epsilon+2\,\kappa)+\lambda-n\,\alpha\,\lambda+f\,nd\,\nu\right)\right)-
e^{2\,h0}\,h0\left(3\,(-1+n\,\alpha)\,\delta-2\left((-1+f)^2\,n\,(\epsilon+2\,\kappa)+\lambda-n\,\alpha\,\lambda+f\,nd\,\nu\right)\right)-e^{\frac{2\,h0}{-e^{b\,t}(-1+h0)+h0}+b\,t}
(-1+h0)\left((1+2\,h0)(-1+n\,\alpha)\,\delta-2\left((-1+f)^2\,n\,(\epsilon+2\,\kappa)+\lambda-n\,\alpha\,\lambda+f\,nd\,\nu\right)\right)+
e^{\frac{2\,h0}{-e^{b\,t}(-1+h0)+h0}}\,h0\left((1+2\,h0)(-1+n\,\alpha)\,\delta-2\left((-1+f)^2\,n\,(\epsilon+2\,\kappa)+\lambda-n\,\alpha\,\lambda+f\,nd\,\nu\right)\right)\Big)
$$

```
vsolns2 /. (-1 + f)^2 n (ϵ + 2 κ) + λ - n α λ + f nd ν → ρ /. (-1 + n α) δ → φ
```

$$
\Big(e^{-2\,h0}\Big(e^{2\,h0+b\,t}(-1+h0)(-2\,\rho+\varphi)-e^{2\,h0}\,h0\,(-2\,\rho+3\,\varphi)-
e^{\frac{2\,h0}{-e^{b\,t}(-1+h0)+h0}+b\,t}(-1+h0)(-2\,\rho+(1+2\,h0)\,\varphi)+e^{\frac{2\,h0}{-e^{b\,t}(-1+h0)+h0}}\,h0\,(-2\,\rho+(1+2\,h0)\,\varphi)\Big)\Big)\Big/
\left(4\left(e^{b\,t}(-1+h0)-h0\right)(\gamma 1-\gamma 2)\right)
$$