Investigate immunotherapy for Alzheimer's disease.
Figure 6 of Bitan's paper describes a mechanism for the formation of amyloid, a culprit of Alzheimer's disease.
Source: Gal Bitan, Marina D. Kirkitadze, Aleksey Lomakin, Sabrina S. Vollers, George B. Benedek and David B. Teplow, "Amyloid ß-protein (Aß) assembly: Aß40 and Aß42 oligomerize through distinct pathways" PNAS, Vol. 100, No. 1 (Jan. 7, 2003), pp. 330-335.
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Consider the following mechanism, where monomers eventually form fibrils.

$k_{mn} := 1$ $k_{no} := 1$ $k_{op} := 1$ $k_{pf} := 1$

monomer (M) $\longleftrightarrow$ paranuclei (N) $\longleftrightarrow$ large oligomers (O) $\longleftrightarrow$ protofibrils (P) $\longrightarrow$ fibril (F)

$k_{nm} := 1$ $k_{on} := 1$ $k_{po} := 0.5$

Bitan et al. also consider the following 2 paths leading to protofibrils (P)

$k_{mp} := 0.1$

monomer (M) $\longrightarrow$ protofibrils (P)
paranuclei (N) $\longrightarrow$ protofibrils (P)

$k_{np} := 0.1$

We propose a means of reducing fibril by "mopping" away one of the precursors, say, protofibrils (P), with a monoclonal antibody (A).

$k_{ap} := 1$

A + P $\longleftrightarrow$ AP

$k_{pa} := 1$

Elementary reaction kinetics

$dMdt(M,N,O,P,F,A,AP) := -k_{mn}\cdot M + k_{nm}\cdot N - k_{mp}\cdot M$

$dNdt(M,N,O,P,F,A,AP) := k_{mn}\cdot M - k_{nm}\cdot N - k_{no}\cdot N + k_{on}\cdot O - k_{np}\cdot N$

$dOdt(M,N,O,P,F,A,AP) := k_{no}\cdot N - k_{on}\cdot O - k_{op}\cdot O + k_{po}\cdot P$

$dPdt(M,N,O,P,F,A,AP) := k_{op}\cdot O - k_{po}\cdot P - k_{pf}\cdot P + k_{mp}\cdot M + k_{np}\cdot N - k_{ap}\cdot A\cdot P + k_{pa}\cdot AP$

$dFdt(M,N,O,P,F,A,AP) := k_{pf}\cdot P$

$dAdt(M,N,O,P,F,A,AP) := -k_{ap}\cdot A\cdot P + k_{pa}\cdot AP$

$dAPdt(M,N,O,P,F,A,AP) := k_{ap}\cdot A\cdot P - k_{pa}\cdot AP$

Combine all ODEs into a standard vector form

$$dydt(t,y) := \begin{bmatrix} dMdt(y_0,y_1,y_2,y_3,y_4,y_5,y_6) \\ dNdt(y_0,y_1,y_2,y_3,y_4,y_5,y_6) \\ dOdt(y_0,y_1,y_2,y_3,y_4,y_5,y_6) \\ dPdt(y_0,y_1,y_2,y_3,y_4,y_5,y_6) \\ dFdt(y_0,y_1,y_2,y_3,y_4,y_5,y_6) \\ dAdt(y_0,y_1,y_2,y_3,y_4,y_5,y_6) \\ dAPdt(y_0,y_1,y_2,y_3,y_4,y_5,y_6) \end{bmatrix} \qquad y_{init} := \begin{bmatrix} 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}$$

Solve the ODEs /wo antibody (A)

$ty := \text{rkfixed}(y_{init}, 0, 10, 1000, dydt)$ $t := ty^{<0>}$ $i := 0 .. \text{last}(t)$

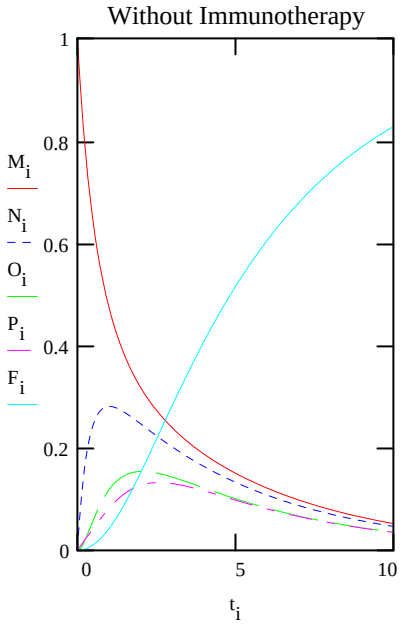
$M := ty^{<1>}$ $N := ty^{<2>}$ $O := ty^{<3>}$ $P := ty^{<4>}$ $F := ty^{<5>}$

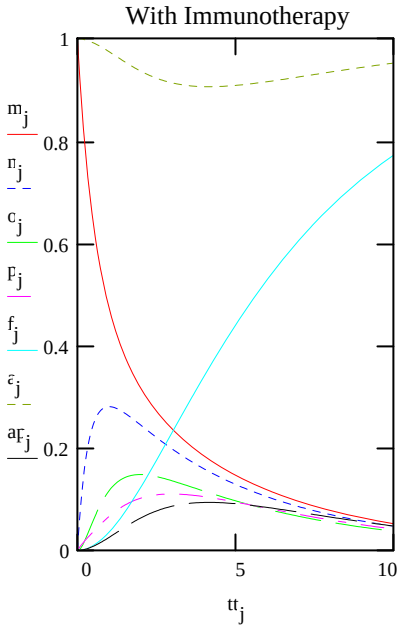
Solve the ODEs /w antibody (A)

$$y_{init} := \begin{bmatrix} 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \end{bmatrix}$$

$ty := \text{rkfixed}(y_{init}, 0, 10, 1000, dydt)$ $tt := ty^{<0>}$ $j := 0 .. \text{last}(tt)$

$m := ty^{<1>}$ $n := ty^{<2>}$ $o := ty^{<3>}$ $p := ty^{<4>}$ $f := ty^{<5>}$ $a := ty^{<6>}$ $ap := ty^{<7>}$





With immunotherapy, (curve F=without antibody A; curve f=with antibody A), the amount of fibril decreased slightly (but remained significant) at clinical endpoint of t=10 compared to that without immunotherapy. Thus, with the given kinetic parameters and antibody dosage, immunotherapy is ***not*** effective.

Design **an antibody that binds stronger and faster to P**, $k_{ap} := 100$ $k_{pa} := 0.1$

$dPdt(M,N,O,P,F,A,AP) := k_{op}\cdot O - k_{po}\cdot P - k_{pf}\cdot P + k_{mp}\cdot M + k_{np}\cdot N - k_{ap}\cdot A\cdot P + k_{pa}\cdot AP$

$dAdt(M,N,O,P,F,A,AP) := -k_{ap}\cdot A\cdot P + k_{pa}\cdot AP$

$dAPdt(M,N,O,P,F,A,AP) := k_{ap}\cdot A\cdot P - k_{pa}\cdot AP$

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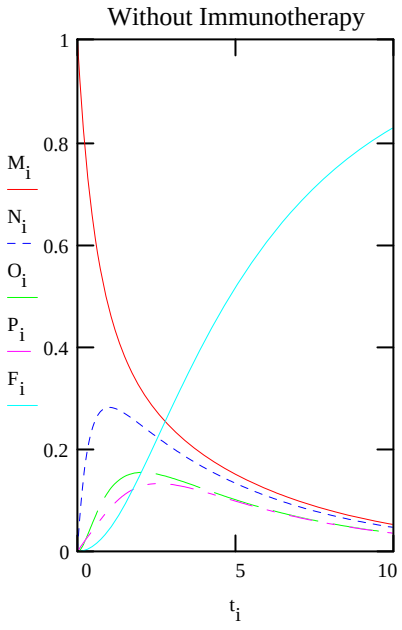
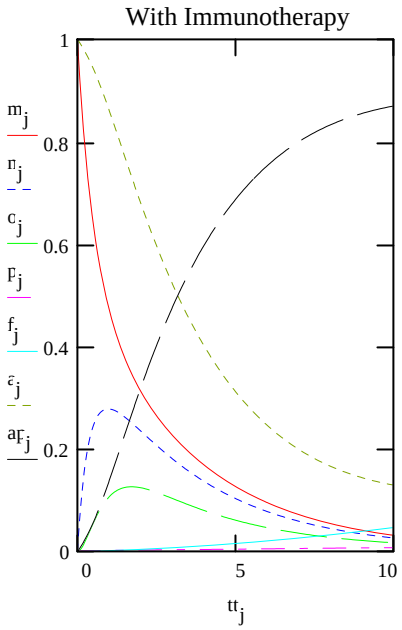
Solve the ODEs /w antibody (A)

$ty := rkfixed(y_{init}, 0, 10, 1000, dydt)$ $tt := ty^{\langle 0 \rangle}$ $j := 0 .. last(tt)$

$m := ty^{\langle 1 \rangle}$ $n := ty^{\langle 2 \rangle}$ $o := ty^{\langle 3 \rangle}$ $p := ty^{\langle 4 \rangle}$ $f := ty^{\langle 5 \rangle}$ $a := ty^{\langle 6 \rangle}$ $ap := ty^{\langle 7 \rangle}$





Fibril (f) formation is greatly suppressed. Hopefully a stronger-binding antibody can delay the onset of Alzheimer's disease long enough.

What if the antibody targeted other species in the amyloid pathway instead: monomer (M), paranuclei (N), or large oligomers (O)? What if we start immunotherapy at t=1, 2, or 3 instead of t=0? (Can early detection be the key?)