More IVP's:

Circadian rhythms.

"Circadian" means "occuring naturally on a 24-hour cycle."

One model (see Tyson et al. (1999), on our Canvas page) says: circadian rhythms are regulated by <u>feedback</u> of two proteins, PER (short for "periodic") and TIM (short for "timeless"), on the "per" and "tim" mRNA that yield these proteins.

Variables:
$M$ = per/tim mRNA
$P_1$ = PER/TIM <u>monomers</u> (basic protein building blocks)
$P_2$ = PER/TIM <u>dimers</u> (a dimer is built up from two monomers)

(A more detailed study might have <u>six</u> variables, by not grouping per and tim, or PER and TIM, together. But the above three are enough for us.)

The model says:

$$(CR) \begin{cases} \dfrac{dM}{dt} = \overset{(i)}{\dfrac{a}{1+bP_2^2}} \overset{(ii)}{-\, cM} \\[4mm] \dfrac{dP_1}{dt} = \overset{(iii)}{2M} - \overset{(iv)}{\dfrac{eP_1}{f+P_1+gP_2}} \overset{(v)}{-\, hP_1} \overset{(vi)}{-\, 2kP_1^2} \overset{(vii)}{+\, 2\ell P_2} \\[4mm] \dfrac{dP_2}{dt} = \overset{(viii)}{-\, \dfrac{mP_2}{f+P_1+gP_2}} \overset{(ix)}{-\, nP_2} \overset{(x)}{+\, kP_1^2} \overset{(xi)}{-\, \ell P_2}. \end{cases}$$

$(a, b, c, \ldots, \ell$ are positive parameters.$)$

Analysis of terms:

(i) $P_2$ inhibits production of $M$: (i) tells us that more $P_2$ means slower growth of $M$.

Note the $P_2^2$ here: in other situations, one might have $P_2^h$ where $h$, the "Hill coefficient," reflects certain binding properties of the proteins.

(ii) $M$ is degraded/used up at a rate proportional to the amount of $M$ present.

(iii) $P_1$ is produced at a rate proportional to the amount of $M$ present.

(iv) and (viii) represent phosphorylation: $P_1$ and $P_2$ combine with phosphates and are inactivated. Note that the decay implied by the numerators of (iv) and (viii) is tempered by the denominators.

(v) and (ix) represent <u>proteolysis</u>: $P_1$ and $P_2$ decay (proteins have half-lives).

(vi) and (x) represent the reaction
monomer + monomer → dimer.
[Note that (vi) cancels twice (x).]

(vii) and (xi) represent the reaction
dimer → monomer + monomer.
[Note that (vii) cancels twice (xi).]

COOL FACTS:
(1) Solutions to (CR) are normally circadian, <u>but</u>

(2) A certain <u>mutation</u> per$^L$ of per mRNA changes the "dimerization rate" $k$ in (vi) and (x) above, resulting in $M, P_1, P_2$ having periods > 24 hours!

(3) Equations (CR) can further be reduced, under certain conditions, by combining $P_1$ and $P_2$ into a single protein variable P. See Sage worksheet Circadian.sws (on the Sage Page).