Using differential equations to model prion growth

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Goals of this talk

- Give high-level overview of one of my research topics
- Identify connections between my research and typical undergraduate courses
  Intro to ODEs Numerical methods
- Get students excited about research and ODEs!
Equilibria

▶ System of autonomous ODEs:

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▶ Equilibrium point: \( \dot{x} = \dot{y} = 0 \)
For systems of differential equations involving $x(t)$ and $y(t)$

- Shows trajectories for different initial conditions
- Allows for quantitative understanding of evolution of $x$ and $y$ with time

Image source: http://faculty.sfasu.edu/judsontw/ode/html-snapshot/systems01.html
Stiff equations

- Dynamics occur over widely different time scales
- Difficult to solve numerically (choosing time-step)
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- Unlike other pathogens, prions do not contain DNA or RNA
- Prions self-assemble into linear amyloid fibrils
- Leading theory for replication process is **nucleated polymerization**: healthy proteins converted to infectious
Seminal model for nucleated polymerization developed by Masel et al.
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A coupled set of differential equations (dynamical system) describing the time-dependence of populations of prion assemblies of varying lengths

Need for a New Model

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- These findings carry repercussions for our understanding of fibril growth, and a **new mathematical model** is needed.
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Masel Model: Variables

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Masel Model: Monomer/Polymer Creation/Destruction

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- Monomers degrade at a rate proportional to their population with constant of proportionality $d$.

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- Monomers degrade much more easily than polymers; thus $a \ll d$
Monomers attach directly to a polymer of length $i$ at a rate proportional to the product of their populations with constant of proportionality $\beta$. Therefore monomer concentration decreases at a rate $\beta y_i$, concentration of polymers of length $i$ increases at a rate $\beta y_i - 1 (y_i - 1 \rightarrow y_i)$, and decreases at a rate $\beta y_0 (y_i \rightarrow y_i + 1)$.
Mason Model: Monomer Attachment

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Masel Model: Polymer Fragmentation

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- Polymers of length $i \geq n$ fragment into two pieces of size $j$ and $i - j$ at a rate proportional to their population with constant of proportionality $b$
- \( n \): critical size below which polymers are unstable and instantly disintegrate into \( \text{PrP}^C \) monomers
- Polymers of length \( i \geq n \) fragment into two pieces of size \( j \) and \( i - j \) at a rate proportional to their population with constant of proportionality \( b \)
- As chains fragment, more infectious assemblies onto which \( \text{PrP}^C \) monomers can attach are created
Masel Model: Dynamics

\[
\begin{align*}
\dot{x} &= \lambda - dx - \beta xy + 2b \sum_{i=1}^{n-1} \sum_{j=i+1}^{\infty} iy_j \\
\dot{y}_i &= -ay_i + \beta x(y_{i-1} - y_i) - b(i - 1)y_i + 2b \sum_{j=i+1}^{\infty} y_j, \quad i \geq n \\
y_i &= 0, \quad i < n
\end{align*}
\]

J. Kotas (Menlo College)
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- suPrP oligomers are themselves made up of PrP\textsuperscript{C} monomers (assume 3)
- suPrP is highly stable and does not degrade
- PrP\textsuperscript{C} do not form isolated suPrP
- No critical size $n$ below which PrP\textsuperscript{Sc} is unstable
SuPrP Model: Variables

- $x(t)$: concentration of PrP\textsuperscript{C} monomers
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SuPrP Model: Processes

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 ▶ Attach to a polymer of length $i$ proportionally to the product of those populations with constant $3 \beta$
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- **Isolated oligomers suPrP**
  - Attach to a polymer of length \(i\) proportionally to the product of those populations with constant \(p\)
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- **Is**olated oligomers suPrP
  - Attach to a polymer of length $i$ proportionally to the product of those populations with constant $p$

- **P**olymers PrP$^Sc$
  - Depolymerize into isolated suPrP proportionally to their population with constant $k$
SuPrP Model: Illustration of Processes

Modeling prion growth
SuPrP Model: Dynamics

\[
\begin{align*}
\dot{x} &= \lambda - dx - 3\beta xy \\
\dot{y}_1 &= k(y - y_1 + y_2) - py_1 y \\
\dot{y}_i &= -ay_i + k(y_{i+1} - y_i) + py_1 (y_{i-1} - y_i) + 3\beta x(y_{i-1} - y_i), \quad i > 1 \\
\dot{y} &= (y - y_1)(k - a) - py_1 y + 3\beta xy_1
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Dynamical system is infinite-dimensional (no limit on length of polymers)
Case where $\lambda = 0$:

- Recall that $\lambda$ represents formation of monomers by the cell and thus $\lambda = 0$ could occur in an *in vitro* sample where the initial concentration of PrP$^C$ is fixed.
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- Equilibria are the origin and:

\[
\begin{align*}
    x^* &= 0 \\
    y_i^* &= \frac{p^{i-1}}{k^{i-1}} y_1 \quad \text{for } i \geq 2
\end{align*}
\]
Truncated SuPrP Model: Dynamics

Assume $y_i = 0$ for $i > N$, $N$ large
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\dot{y}_N &= -ay_N - ky_N + py_1 y_{N-1} + 3\beta xy_{N-1} \\
\dot{y} &= (y - y_1)(k - a) - py_1(y - y_N) + 3\beta xy_1
\end{align*}
\]
Case where $\lambda = a = 0$:

- $a = 0$ is assumed for simplicity, since degradation of polymers is usually negligible compared to other terms.
- Equilibria are the origin and the one-parameter family given by:

  $x^* = 0$

  $y_i^* = \frac{p_i^{i-1}}{k_i^{i-1}} y_1^i$, for $2 \leq i \leq N$
Simulation: Parameters

\[
\begin{align*}
\lambda &= 0 \text{ Ms}^{-1} \\
d &= 10^{-9} \text{ s}^{-1} \\
a &= 0 \text{ s}^{-1} \\
\beta &= 10^2 \text{ M}^{-1}\text{s}^{-1} \\
k &= 1/3 \times 10^{-1} \text{ s}^{-1} \\
p &= 10^5 \text{ M}^{-1}\text{s}^{-1} \\
x(0) &= 0 \text{ M} \\
y_i(0) &= \text{discretized, truncated Gaussian distribution with } \mu = 28, \sigma = \sqrt{5} \\
&\text{and normalized such that } \sum_i iy_i(0) = 10^{-6} \text{ M} \\
N &= 200
\end{align*}
\]
Initial conditions simulate a sample where PrP\textsuperscript{Sc} polymer of length $\approx 28$ have been isolated at $t = 0$
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Simulation: Parameters

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- Parameters vary over many orders of magnitude \(\Rightarrow\) dynamics occur on widely varying time scales.
- Thus, equations are numerically stiff.
Simulation: Parameters

- Initial conditions simulate a sample where PrP<sup>Sc</sup> polymer of length $\approx 28$ have been isolated at $t = 0$
- Parameters vary over many orders of magnitude $\Rightarrow$ dynamics occur on widely varying time scales
- Thus, equations are numerically stiff
- Matlab’s ODE solver “ode23s” is used
Initial distribution at $t = 0$: blue
Final distribution at $t = 2 \times 10^3$: red
Equilibrium point: green
Simulation: Sensitivity Analysis on $p$

Numerical validation of equilibria found analytically
Simulation: Sensitivity Analysis on $p/k$

$p/k = 3 \times 10^4$

$p/k = 3 \times 10^6$

$p/k = 3 \times 10^8$

Sensitivity analysis on parameters $k$ and $p$.

$p = 10^3$ (first row), $10^5$ (second row), $10^7$ (third row)

Initial time: blue; final time: red
Conclusions

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- Applied mathematicians use math for better decision-making and understanding of complex systems
- Your math skills are useful in a wide variety of applications
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Thank you! :)
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