Mathematical Modeling and Analysis as an Interdisciplinary Tool

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Mathematics in Interdisciplinary Problems

Why do we need mathematics?

- Most problems complex, involving
  - interactions
  - thresholds
  - cumulative effects
  - dynamics depending on more than one variable (time, space, etc.)

- Observing systems (understanding data) sets \( \Rightarrow \) involves accounting for effects

- Inverse Problems: Insight into underlying processes (input) from observations (output)
Mathematics in Interdisciplinary Problems (con’t)

Mathematical modeling:

- Formalization of understanding
- Structure and terms represent specific *mechanisms*
- Hypothesis testing tool (does proposed model reproduce observed behavior?)
- Predictive capability

Inverse Problems:

- Estimation of parameters (Calibration of math. model)
- Hypothesis testing tool (mechanisms necessary to generate data?)
- Guide for experimental design (information content of data)
- Decipher specific effects and relative contributions of simultaneous mechanisms (sensitivity analysis)
Mathematics in Interdisciplinary Problems (con’t)

The Iterative Modeling Process

(i) Empirical Observations (experiments and data collection)

(ii) Formalization of properties, relationships and mechanisms which result in a biological or physical model

(iii) Abstraction or Mathematization resulting in a mathematical model

(iv) Formalization of Uncertainty/Variability in model and data resulting in a statistical model

(v) Model Analysis

(vi) Interpretation and Comparison (with the real system)

(vii) Changes in understanding of mechanisms, etc., in the real system.

Formation Stage: (i),(ii),(iii),(iv)

Solution Stage: (v)

Interpretation Stage: (vi), (vii)
Joint work with:

- Dr. Jennifer J. Linderman, Maduresh Sumit, Departments of Chemical & Biomedical Engineering, University of Michigan - Ann Arbor
- Temitope Sanusi, Department of Mathematics, University of Louisiana at Lafayette
Oscillatory systems ubiquitous in regulation of internal physiological processes (gene expression, circadian rhythms)

Lack of clarity on circuit architecture

Previous perturbation/stimulation methods ⇒ multiple plausible mechanisms

- Advances in microfluidics systems allow for periodic stimulation

Temporal stimulus gives rise to unique and pronounced response

- Add and ‘flush out’ stimulus rapidly
- Phase locking: entrainment of oscillatory systems to periodic input
- Phase locking ratio: # of responses: # of stimuli
Overview of Project
Microfluidic setup
Bioengineering: Intracellular Calcium Signaling

**Current Model**

\[
\frac{d[C]}{dt} = k_{f,L}[L][R] - k_{r,L}[C] - k_{grk1,f}[C] + k_{grk1,r}A \cdot C_p
\]

\[
\frac{d[G_{GTP}]}{dt} = -k_4[G_{GTP}] + k_5\frac{[C]}{A} - k_6[PLC]\frac{[G_{GTP}]}{A} + k_3[G]
\]

\[
\frac{d[G_{GDP}]}{dt} = k_4([G_{GTP}] + [PLC^*]) - k_7[G_{GDP}]\left(\frac{[G_{GTP}] + [G_{GDP}] + [PLC^*]}{A}\right)
\]

\[
\frac{d[PLC^*]}{dt} = k_6[PLC]\frac{[G_{GTP}]}{A} - k_4[PLC^*]
\]
\[ \frac{d[IP_3]}{dt} = (k_{ca}[PLC^*] + k_{basal}) \frac{[Ca_{cyt}]^2}{(K_{PLC}^2 + [Ca_{cyt}]^2)} - \left[ k_{3k} \left( \frac{[Ca_{cyt}]^2}{K_{3k}^2 + [Ca_{cyt}]^2} \right) + k_{5p} \right] [IP_3] \]

\[ \frac{d[Ca_{cyt}]}{dt} = \left[ k_1 \left( f_{IP_3} R_a \frac{[Ca_{cyt}]}{K_a + [Ca_{cyt}]} \frac{[IP_3]}{K_p + [IP_3]} \right)^3 + k_2 \right] ([Ca_{ER}] - [Ca_{cyt}]) - V_{serca} \left( \frac{[Ca_{cyt}]^2}{K_{serca}^2 + [Ca_{cyt}]^2} \right) + \epsilon \left( v_0 + \left[ \frac{\phi}{k_{3k} + k_{5p}} (k_{ca}[PLC^*] + k_{basal}) \right] \right) - \epsilon V_{pm} \left( \frac{[Ca_{cyt}]^2}{K_{pm}^2 + [Ca_{cyt}]^2} \right) \]
Current Model (con’t.)

\[
\frac{d[Ca_{ER}]}{dt} = \frac{1}{\beta} \left( V_{serca} \left( \frac{[Ca_{cyt}]^2}{K^2_{serca} + [Ca_{cyt}]^2} \right) \right) \\
- \frac{1}{\beta} \left[ k_1 \left( f_{IP_3R_a} \frac{[Ca_{cyt}]}{K_a + [Ca_{cyt}]} \frac{[IP_3]}{K_p + [IP_3]} \right)^3 + k_2 \right] ([Ca_{ER}] - [Ca_{cyt}])
\]

\[
\frac{df_{IP_3R_a}}{dt} = \frac{1}{\tau_R} \left( 1 - f_{IP_3R_a} \frac{K_i + [Ca_{cyt}]}{K_i} \right)
\]

\[
\frac{dC_p}{dt} = k_{grk1,f} \frac{[C]}{A} - (k_{grk1,r} + k_{grk2,f}) C_p + k_{grk2,r} R_p
\]

\[
\frac{dR_p}{dt} = -(k_{grk2,r} + k_{grk3,r}) R_p + k_{grk2,f} C_p,
\]
Previous results

\[ \text{Ca}^{2+} \text{ signaling} \]
Bioengineering: Intracellular Calcium Signaling

Ca^{2+} signaling: Previous results

**A.** Chay et al.

**B.** Politi et al.

**C.** Revised Politi et al.

**D.** Phase-locking Ratio

**E.** Rest Period (s)

**F.**

**G.** [Ca^{2+}] (nM)

**H.**

**I.**
Resulting questions

- Understanding results → why improvement?
  - What exactly is the role of $k_{basal}$? Is it realistic?
  - Put results on firmer footing (less ad hoc)
- What does pulsatile stimulation really offer? Enhancing information how? Are there ‘better’ stimulation patterns?
- Need for development of methodology for use of phase-locked systems to understand signal pathways
Sensitivity functions can be used to determine:

- action of mechanisms in solution behavior
- relative importance of parameters or mechanisms in solutions and/or data
- information content of data → identifiability
- (correlation between parameters → simultaneous identifiability)
Traditional sensitivity functions (TSFs)

\[ \dot{x}(t) = g(t, x(t), q) \]

- For parameters \( q = (q_1, \ldots, q_k)^T \), traditional sensitivity functions (TSFs) are simply

\[ ts_{q_i}(t) = \frac{\partial x(t)}{\partial q_i} \]

- Sensitivity equations, (or numerically via forward difference)

\[
\frac{\partial}{\partial q} \frac{dx}{dt} = \frac{\partial}{\partial x} g(t, x(t), q) \frac{\partial x}{\partial q} + \frac{\partial}{\partial q} g(t, x(t), q)
\]

- Large in magnitude \( ts_{q_i}(t) \): small changes in parameter \( q_i \) \( \Rightarrow \) large changes in \( x(t) \)

- Regions of high sensitivity \( \rightarrow \) regions of parameter identifiability
Bioengineering: Intracellular Calcium Signaling

TSFs under constant stimulation

\[ [\text{Ca}](t) \text{ (µM)} \] 
\[ t_{s_k}^{\text{basal}} \text{ (µM⋅s)} \]

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Relative sensitivity functions

- Scaling of traditional sensitivity functions to compare sensitivity to parameters
- Given by
  \[ rs_{q_i}(t) = \frac{q_i}{x(t)} \frac{\partial x(t)}{\partial q_i} \]
- Interpretation: Relative change in output \( \frac{\partial x}{x} \) with respect to relative change in parameters \( \frac{\partial q}{q} \)
- Allows for ranking of relative ‘strength’ among parameters
RSFs under constant stimulation

- Most stimulatory to least: \( k_{Ca}, V_{pm}, k_2, k_{basal}, k_1, \tau_R, v_0 \)
- Most inhibitory to least: \( k_{5p}, V_{serca} \)
Some results

- Highly entrained system:
  - Most tsfs of parameters longitudinally identical;
  - Either ‘stimulatory’: (mostly) positive in sensitivity, or
  - ‘inhibitory’: (mostly) negative in sensitivity.

- Balance of stimulatory and inhibitory effects

- Under time-dependent stimulation, differences were:
  - Strongly stimulatory parameter $V_{pm}$ now inhibitory
  - Weak stimulatory parameter $k_{basal}$ now strongly stimulatory

- Increasing devil’s staircase possible with adjusted parameter values, $k_{basal} = 0$
Conclusions/Future Work

- Characterized difference in system under constant versus time-dependent stimulation
  - Better understanding of previous results
  - Insight into role of $k_{basal}$ (perhaps unnecessary)
- Ranked parameters (mechanisms) based on relative importance
- Possible to use PLR to narrow parameter ranges?
  - Data is very noisy, parameter magnitudes uncertain $\rightarrow$ least-squares estimation of parameter not likely fruitful
  - Ranges of values for parameters that strongly affect PLR may possibly be determined.
- Use TSFs, RSFs
  - design experiments to ‘see’ other mechanisms (other stimulation patterns?)
  - characterize subthreshold responses (if biologically important)
Pneumococcal Vaccination

- A leading cause of death in children under 5 worldwide
- Over 90% of children in developed countries affected (ear infection)
- Asymptomatic nasopharyngeal colonization common (30% on average, higher in daycares, etc.)
- Over 90 serotypes (determined by polysaccharide on cell surface)
- Typical vaccine, serotype-specific, effective only in elderly
- Impact of new vaccine, also serotype-specific, unclear
  - Will more invasive serotypes be able to out-compete more common colonizers?
- Publicly funded widespread implementation of new PCV7 vaccine in Australia in 2005
Pneumococcal Vaccination Model

\[
\begin{align*}
\frac{dS}{dt} &= \lambda - \beta S \frac{E + E_V + I + I_V}{N} + \alpha E + \gamma I - \phi S + \rho S_V - \mu S \\
\frac{dE}{dt} &= \beta S \frac{E + E_V + I + I_V}{N} - \alpha E - I \kappa(t) E - \phi E + \rho E_V - \mu E \\
\frac{dS_V}{dt} &= \phi S - \epsilon \beta S_V \frac{E + E_V + I + I_V}{N} + \alpha E_V + \gamma I_V - \rho S_V - \mu S_V \\
\frac{dE_V}{dt} &= \epsilon \beta S_V \frac{E + E_V + I + I_V}{N} - \alpha E_V + \phi E - \rho E_V - \delta \kappa(t) E_V - \mu E_V \\
\frac{dl}{dt} &= l \kappa(t) E - (\gamma + \eta + \mu) l \\
\frac{dl}{dt} &= \delta \kappa(t) E_V - (\gamma + \eta + \mu) l_V.
\end{align*}
\]
Least squares estimation

Assume a standard statistical model

\[ Y_j = g(t_j; q_0) + \varepsilon_j \quad \text{for } j = 1, \ldots, n_d \]

with \( \varepsilon_j \sim \mathcal{N}(0, \sigma^2) \), and assuming existence of \( q_0 \)

Data \( \{y_j\} \) one realization of random variable \( \{Y_j\} \)

Model observed quantity \( g(t) = \mathcal{C}x(t; q) \)

Parameter(s) estimated (\( \hat{q} \)) over feasible parameter space \( \mathcal{Q} \subset \mathbb{R}^{n_q} \), a realization of the estimator

\[ q_{OLS} = \arg \min_{q \in \mathcal{Q}} \sum_{j=1}^{n_d} |Y_j - g(t_j; q)|^2 \]
From monthly case notifications 2002-2004, estimated $\beta, \kappa(t), \delta$;

- Demonstrated that recovery rate $\gamma$ unimportant

- Used now calibrated model to show that only increasing values of $\epsilon$ and $\delta$ could explain new data after PCV7 widely implemented!

![Graph showing cases from Jan 05 thru Jun 07](image)
1. Bioengineering: Intracellular Calcium Signaling
2. Epidemiology: Pneumococcal Vaccination
3. Ecology: Invasive Species
4. Mathematical Research
5. Graduate Studies at UL Lafayette
6. Closing Remarks
Joint work with:

- Lihong Zhao, Department of Mathematics at UL Lafayette
- Jacoby Carter, USGS National Wetlands Research Center
- *Pomacea maculata*, is recently renamed from the island applesnail, *Pomacea insularum*.
- Native to the Amazon basin.
Feeds on aquatic, submerged plants.

Introduced into United States through pet trade.

Documented in Alabama, Florida, Georgia, Hawaii, Louisiana, and Texas.

Once established, they are very difficult to remove.

Overgrazing can greatly alter natural balance of local ecosystem. [Carlsson et al. 2004]

Major pest in rice fields in the Philippines, China, Laos.
Rapid and profuse reproduction.
Unknown predator community.
Potential of population explosion.
Potentially a vector for snail borne diseases.
Little has been quantified re: life cycle

- Eggs in clutches [Colin et al. 2013]
- Clutches contain ≥ 1000 eggs [Colin et al. 2013]
- Non-native range, even more [Colin et al. 2013]
- Eggs begin hatching out, presumably in layers, around 21 days.
- From our preliminary work, approximately 200 days to maximum size.

Growth dynamics, size distribution, sex differences previously not quantified.
Growth Experiments

- Measurements taken roughly weekly, for 13 weeks.
- Snails were individually marked
  - opaque florescent alpha numeric tags: originally attached to outside of the shell, later glued to operculum instead.
  - PIT tags: originally injected, later glued to the shell instead.
  - marking procedures in development: most individuals < 13 weeks
- Recorded: weight, length of operculum, sex (if possible), identification, date.
- Egg masses removed from tank (no birth).
- Fed leafy plants, vegetables from grocery store.
- All snails used in this study were raised from eggs collected from the field (closed population).
Sex Ratio and Weight Differences

- Number of snails sexed: 99 female and 44 male
- Sex ratio is NOT 1:1.
  - 1:1 sex ratio common assumption
- More dynamics observed in weight than operculum size
- The maximal weight observed: 105.1g for female and 77.2g for male

**Table: Basic Statistics for Weight**

<table>
<thead>
<tr>
<th></th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Top</td>
<td>Mean Standard Deviation</td>
<td>Number of Observations</td>
</tr>
<tr>
<td>50 %</td>
<td>68.61397 14.1872</td>
<td>551</td>
</tr>
<tr>
<td>10 %</td>
<td>89.64636 5.6071</td>
<td>110</td>
</tr>
</tbody>
</table>
The weight distribution for females and males are different.
Females and males may have different growth dynamics.
Individual Variation

- Large degree of variation in individual growth rates.
- However, some trends were observed:
  - hypothesize that growth rates differ depending on size (development),
  - consistent with ecological theory: energy shift in initial growth to sexual reproduction.
- Calculated growth rates in weight *ranges*

\[
g(x) = \begin{cases} 
g_1, & \text{if } x_{\text{min}} \leq x \leq x_1 \\
g_2, & \text{if } x_1 < x \leq x_{\text{max}}
\end{cases}
\]

![Graph showing growth rates](image)
Growth rates from direct calculation not statistically supported.

**Table: Basic Statistics for Growth Rates–Female (99 Total)**

<table>
<thead>
<tr>
<th>Stages</th>
<th>(&lt; 23\text{g})</th>
<th>(23.1–40\text{g})</th>
<th>(40.1–53\text{g})</th>
<th>(53.1–71\text{g})</th>
<th>(&gt; 71\text{g})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>0.3531553</td>
<td>0.2316956</td>
<td>0.2332250</td>
<td>0.0626806</td>
<td>0.0935414</td>
</tr>
<tr>
<td>std.</td>
<td>0.1199893</td>
<td>0.1525451</td>
<td>0.2550575</td>
<td>0.6382982</td>
<td>0.1362457</td>
</tr>
<tr>
<td>N</td>
<td>38</td>
<td>45</td>
<td>40</td>
<td>36</td>
<td>29</td>
</tr>
</tbody>
</table>

**Table: Basic Statistics for Growth Rates–Male (44 Total)**

<table>
<thead>
<tr>
<th>Stages</th>
<th>(&lt; 24\text{g})</th>
<th>(24.1–40\text{g})</th>
<th>(40.1–55\text{g})</th>
<th>(&gt; 55\text{g})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>0.302</td>
<td>0.1255556</td>
<td>0.2083333</td>
<td>0.05481481</td>
</tr>
<tr>
<td>std.</td>
<td>0.1031504</td>
<td>0.1399206</td>
<td>0.2375723</td>
<td>0.137795</td>
</tr>
<tr>
<td>N</td>
<td>10</td>
<td>9</td>
<td>24</td>
<td>27</td>
</tr>
</tbody>
</table>
Noticeable differences in female and male populations
Growth appears to change throughout snail’s lifespan
Individual data too incomplete to yield reasonable estimates to characterize growth dynamics
Population-level approach may be better (records complete unless snail was missed on observation date)
Female Population Growth Model

Since birth/death/predation/growth rates depend on size, we propose a size-structured model governing the dynamics of the female snail population density $p(t, x)$:

$$\frac{\partial p(t, x)}{\partial t} + \frac{\partial (g(x)p(t, x))}{\partial x} = -\mu p(t, x),$$

$$p(0, x) = p_0(x).$$

for $t > 0$, and $x_{\text{min}} \leq x \leq x_{\text{max}}$, where $x_{\text{min}}$ and $x_{\text{max}}$ represent the minimum and maximum weight achievable by an applesnail.

- $g(x)$: growth rate
- $\mu$: death (and predation) rate:
- BC: birth rate $(g(x)p(t, x))|_{x_{\text{min}}} = \int_{x_{\text{min}}}^{x_{\text{max}}} \beta_F(t, x)p(t, x)\,dx$
- $\beta_F(t, x)$: rate at which females give birth to female snails (zero for lab)
Male population dynamics model is given by

\[
\frac{\partial q(t,x)}{\partial t} + \frac{\partial (h(x)q(t,x))}{\partial x} = -\mu q(t,x),
\]

\[q(0,x) = q_0(x).\]

- Growth rate: \(h(x)\)
- BC: birth rate \((h(x)q(t,x))|_{x_{\text{min}}} = \int_{x_{\text{min}}}^{x_{\text{max}}} \beta_M(t,x)p(t,x)dx\)
- Uncoupled from females due to (current) rates being independent of population density, and **zero birth rate** in lab.
Model Comparison (RSS-based) Statistic

- Appropriate number of ‘stages’ in the growth functions?
- Model comparison statistic \( \Rightarrow \) inclusion of which end points gives statistically sig. improvement?
- Let \( J_K(Y, \theta) \) be minimized residual over parameter space \( \Theta \).
- Define the restricted parameter space to be \( \Theta_H \).
- Observe that \( J_K(Y, \hat{\theta}_H^K) \geq J_K(Y, \hat{\theta}_K^K) \).
- Statistic \( U \rightarrow \chi^2(r) \) where \( r \) is difference in degrees of freedom btwn \( H_0 \) and \( H_a \).
Model Comparison Statistic (con’t)

Table: RSS Statistic: 1-stage vs multi-stages– Female

<table>
<thead>
<tr>
<th>$H_0$: m</th>
<th>$H_a$: m; ${x_i}$</th>
<th>U</th>
<th>Df</th>
<th>Confidence Rej.</th>
<th>$H_0$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2; ${23}$</td>
<td>0.618175916</td>
<td>1</td>
<td>56%</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2; ${40}$</td>
<td>5.865695809</td>
<td>1</td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3; ${23, 40}$</td>
<td>5.979250924</td>
<td>2</td>
<td>94%</td>
<td></td>
</tr>
</tbody>
</table>

- Multi-stage growth functions have statistically significant improvements than single-stage growth function.
- Single-stage growth function is not suitable for female.
Thus, the 2-stage growth function

\[ g(x) = \begin{cases} 
0.286278628, & x \in [x_{\text{min}}, 40] \\
0.0912533, & x \in (40, x_{\text{max}}^F] 
\end{cases} \]

is the best for females, and the 2-stage growth function

\[ h(x) = \begin{cases} 
0.230553432, & x \in [x_{\text{min}}, 24] \\
0.103575229, & x \in (24, x_{\text{max}}^M] 
\end{cases} \]

is the best for males.
Further analysis and data

- Other growth models tried; piecewise constant the ‘best’ with given data set
- Concurrently, large number (1287) snails hatched out in 1 week → overcrowded tank
- Weighed and measured length; in triplicate for 675;
- Better characterize variability in population
Current/Future work

Mathematically:
- Mathematical framework and results from Mm infection project useful here.
- New knowledge of variability in growth rates effects on previous population results?
- Sample size, number of time points, and at which life stages required to characterize growth rate/function?

Experimentally:
- Currently measuring distribution of the hatch out process (i.e., birth rate)
- Currently measuring small snail weights (hatchling to around 8 g), and survivability
1. Bioengineering: Intracellular Calcium Signaling

2. Epidemiology: Pneumococcal Vaccination

3. Ecology: Invasive Species

4. Mathematical Research

5. Graduate Studies at UL Lafayette

6. Closing Remarks
Time Delays

*in collaboration with H. T. Banks, North Carolina State U.

- Delays widespread in applications
  - Hutchinson (1948) equation (logistic with delay)
    \[
    \frac{dx}{dt} = rx \left( 1 - \frac{x(t - \tau)}{K} \right)
    \]
  - Harmonic oscillator with delay (Nicolas Minorsky 1942, 1945 and 1962) in damping:
    \[
    \frac{d^2x(t)}{dt} + K \frac{dx(t - \tau)}{dt} + bx(t) = g(t)
    \]
    and delayed restoring force:
    \[
    \frac{d^2x(t)}{dt} + K \frac{dx(t)}{dt} + bx(t - \tau) = g(t)
    \]
Often delays are *not* discrete, realistically - hatchling of snails from egg masses, HIV

Recent results in general nonlinear, nonautonomous dynamical systems with delays

- Theoretical and computational framework for inverse problem
- Sensitivity to parameters, initial conditions, and delays in systems with *discrete delay*

In Progress:

- Computational considerations of parameter estimation
- Error framework for obtained parameter estimates
Approximation Schemes

- Partial differential equations arise in several applications, such as with applesnail example:

\[
\frac{\partial p(t, x)}{\partial t} + \frac{\partial (g(x)p(t, x))}{\partial x} = -\mu p(t, x),
\]

- Often, focus on numerical studies; intractable to qualitative analysis

- Live research area: numerical approximation of solution
Variability in rates

- Variability not uncommon!
  - Growth rates of applesnails

- Need to address:
  - numerical schemes with approx. prob. distributions
  - estimation of parameters & associated distributions
1. Bioengineering: Intracellular Calcium Signaling

2. Epidemiology: Pneumococcal Vaccination

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6. Closing Remarks
Graduate studies in mathematics at UL Lafayette

- **Research Areas**
  - Algebra (3)
  - Analysis (2)
  - Applied Mathematics (10)
  - Topology (3)
  - Statistics (4)

- **Stipends:**
  - Master’s: ≥ $15k
  - Ph.D.: ≥ $17k
  - possible summer teaching

- **Application information**
  - Directly to graduate school: gradschool.louisiana.edu
  - Master’s not required for admission to Ph.D.
  - Contact Dr. Arturo Magidin: magidin@louisiana.edu

- **Recent graduates:**
  - ≈ 80% work in field
  - Median time to completion: 5 1/2 yrs
1. Bioengineering: Intracellular Calcium Signaling
2. Epidemiology: Pneumococcal Vaccination
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Thank you!