Using Scaling and Asymptotics to Simplify Dynamical Systems

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Overview

Many models in biology are unnecessarily complicated.

- Occam's Razor:
  "Entities must not be multiplied beyond necessity."

How do we avoid unnecessary complication?

- Quantitative Simplification:
  Omit terms that have no qualitative effect and a quantitative effect smaller than the uncertainty in parameter values.
- Empirical Simplification:
  Use the Akaike Information Criterion (AIC) to determine when better accuracy is not enough to justify additional complexity.
- **Analytical Simplification:**
  Use asymptotic approximation after nondimensionalizing with suitable scales.

HIV Model (Stafford et al, J Theo Bio, 2000)

$$\frac{dS}{dT} = R - DS - BVS \ , \tag{1}$$

$$\frac{dI}{dT} = BVS - DI - MI \ , \tag{2}$$

$$\frac{dV}{dT} = PI - CV \ . \tag{3}$$

- R: constant rate of healthy cell production.
- DS and DI: rates of natural cell death.
- MI: rate of virus-induced cell death.
- BVS: rate of infection.
- PI: rate of virion production.
- CV: clearance rate for virions.
- No latency.

Brute Force Analysis

- Disease-Free Equilibrium (DF)

$$I = V = 0, \quad S = \frac{R}{D}, \quad J = \begin{pmatrix} -D & 0 & -BR/D \\ 0 & -(D+M) & BR/D \\ 0 & P & -C \end{pmatrix}$$

- Endemic Disease Equilibrium (ED)

$$S = \frac{C(D+M)}{BP}, \quad V = \frac{BPR - DC(D+M)}{BC(D+M)}, \quad I = \frac{BPR - DC(D+M)}{BP(D+M)}$$

$$J = \begin{pmatrix} -\frac{BPR}{C(D+M)} & 0 & -\frac{C(D+M)}{P} \\ \frac{BPR}{C(D+M)} - D & -(D+M) & \frac{C(D+M)}{P} \\ 0 & P & -C \end{pmatrix}$$

So What?

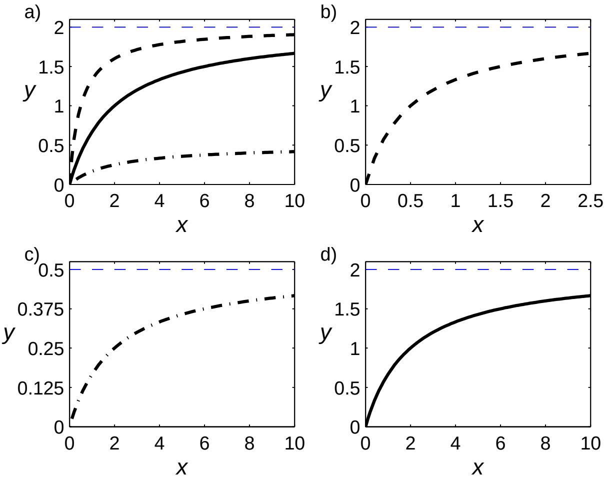
$$S = \frac{C(D+M)}{BP}, \quad V = \frac{BPR - DC(D+M)}{BC(D+M)}, \quad I = \frac{BPR - DC(D+M)}{BP(D+M)}$$

$$J = \begin{pmatrix} -\frac{BPR}{C(D+M)} & 0 & -\frac{C(D+M)}{P} \\ \frac{BPR}{C(D+M)} - D & -(D+M) & \frac{C(D+M)}{P} \\ 0 & P & -C \end{pmatrix}$$

- All 6 parameters appear in the equilibrium formulas.
- Stability calculations require 3×3 eigenvalues or Routh-Hurwitz conditions.
- Calculations of determinant etc are messy.
- Relationship between existence requirements of ED and stability requirements of DF are unclear.

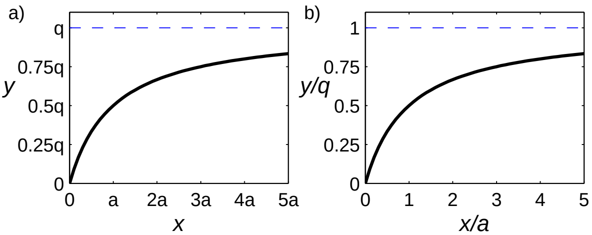
- We can do MUCH better!

Families of Functions



The model $y(x) = \dfrac{qx}{a+x}$, with (q, a) values of $(2, 0.5)$ (dashed), $(2, 2)$ (solid), $(0.5, 2)$ (dash-dot).

A Dimensionless Version



The model $y(x) = \dfrac{qx}{a+x}$, using two different labeling schemes.

The quantities $\dfrac{y}{q}$ and $\dfrac{x}{a}$ are dimensionless counterparts to y and x.

- Moreover, the quantities q and a are **representative** of the meaningful values of y and x.
- The references for nondimensionalization should be **scales** (representative values).

Scaling for the HIV model

$$\frac{dS}{dT} = R - DS - BVS \ , \tag{1}$$

$$\frac{dI}{dT} = BVS - DI - MI \ , \tag{2}$$

$$\frac{dV}{dT} = PI - CV \ . \tag{3}$$

- The normal population of healthy cells is $\frac{R}{D}$.
- The mean residence time for healthy cells is $\frac{1}{D}$.
- A tight upper bound on infected cells is $\frac{R}{M+D}$.
- A tight upper bound on virion population is $\frac{P}{C}\frac{R}{M+D}$.

Use

$$S = \frac{R}{D}\,s, \quad \frac{d}{dT} = D\frac{d}{dt}, \quad I = \frac{R}{M+D}\,i, \quad V = \frac{P}{C}\,\frac{R}{M+D}\,v.$$

Choosing the Dimensionless Parameters

$$\frac{ds}{dt} = 1 - s - \frac{BPR}{DC(M+D)}\, vs, \quad \frac{di}{dt} = \frac{BPR}{D^2 C}\, vs - \frac{M+D}{D}\, i, \quad \frac{dv}{dt} = \frac{C}{D}(i - v)$$

- Dimensional analysis contributes nothing to the choice of parameters (or the scales, for that matter)!
- Prefer parameters that factor out of equations.
- Prefer parameters with meaningful biological comparisons.
- Make parameters small rather than large.

$$\frac{D}{M+D}\,\frac{di}{dt} = \frac{BPR}{DC(M+D)}\, vs - i, \quad \frac{D}{M+D}\,\frac{M+D}{C}\,\frac{dv}{dt} = i - v$$

- $D/(M+D)$ is (healthy cell turnover)/(infected cell death).
- $(M+D)/C$ is (infected cell death)/(virion clearance).

So What?

$$s' = 1 - s - bvs, \qquad \epsilon i' = bvs - i, \qquad \theta\epsilon v' = i - v$$

$$s = \frac{1}{b}, \quad i = v = 1 - \frac{1}{b}$$

$$J = \begin{pmatrix} -b & 0 & -1 \\ \epsilon^{-1}(b-1) & -\epsilon^{-1} & \epsilon^{-1} \\ 0 & \theta^{-1}\epsilon^{-1} & -\theta^{-1}\epsilon^{-1} \end{pmatrix}$$

instead of

$$S = \frac{C(D+M)}{BP}, \quad V = \frac{BPR - DC(D+M)}{BC(D+M)}, \quad I = \frac{BPR - DC(D+M)}{BP(D+M)}$$

$$J = \begin{pmatrix} -\frac{BPR}{C(D+M)} & 0 & -\frac{C(D+M)}{P} \\ \frac{BPR}{C(D+M)} - D & -(D+M) & \frac{C(D+M)}{P} \\ 0 & P & -C \end{pmatrix}$$

- 3 parameters instead of 6; equilibria have only 1 parameter.

Asymptotic Reduction

Nondimensionalization always yields algebraic simplification. With careful choice of scales, it can yield much more.

$$s' = 1 - s - bvs, \qquad \epsilon i' = bvs - i, \qquad \theta\epsilon v' = i - v$$

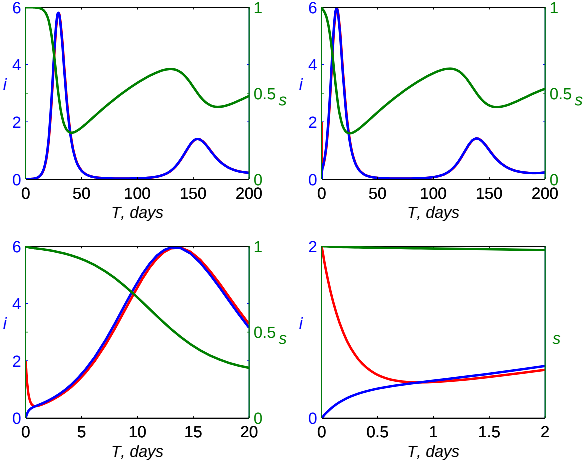
Estimated parameter values are $\epsilon = 0.025$, $\theta = 0.1$. The approximation $\theta\epsilon \to 0$ reduces the v equation to $v \sim i$. This reduces the system to two components:

$$s' = 1 - s - bis, \qquad \epsilon i' = i(bs - 1)$$

The analysis of this model is much simpler. Nullcline analysis is also possible.

Numerical Validation – plots are for 3D model

First plot has $v(0) = 0.01$; others have $v(0) = 2$



- The error is significant for only the first few hours.
- The initial infection level only affects the incubation process.

Scaling with Competing Processes

How do we scale

$$\frac{dX}{dT} = RX\left(1 - \frac{X}{K}\right) - \frac{SX}{X+H}?$$

Forget dimensional analysis. We need biological insight!

- If we think environmental capacity is the primary limitation, we expect X comparable to K, so we choose K.

$$x' = x\left(1 - x - \frac{sx}{1+\epsilon x}\right), \qquad \epsilon = \frac{K}{H} < 1, \quad s = \frac{S}{RH} = O(1)$$

- If we think consumption is the primary limitation, we expect X comparable to H, so we choose H.

$$x' = x\left(1 - \epsilon x - \frac{sx}{1+x}\right), \quad \epsilon = \frac{H}{K} = O(1), \ \ s = \frac{S}{RH} = O_s(1)$$

References

Everything in this talk so far (and much more!) can be found in

G. Ledder, *Mathematics for the Life Sciences: Calculus, Modeling, Probability, and Dynamical Systems*, Springer, August 2013.

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(With apologies for shameless self-promotion)

An Extreme Example: the Spruce Budworm Model

(Ludwig et al, *J Anim Ecol*, 1978;
Brauer and Castillo-Chavez, *Math. Models in Pop. Bio....*;
Ledder, Math Biosci Eng, 2007)

Dimensionless variables:

- B: consumer (insect) population
- E: resource health ($\approx$ leaves/area)
- S: resource density ($\approx$ surface area)
- λ: fixed predator (bird) population

$$\epsilon_1 B' = B\left[1 - \frac{B}{S}\left(\frac{\delta^2 + E^2}{E^2}\right)\right] - \frac{\lambda B^2}{\nu^2 S^2 + B^2}$$

$$\epsilon_2 E' = E(1 - E) - \frac{\gamma B}{S}\left(\frac{E^2}{\delta^2 + E^2}\right)$$

$$S' = S\left(1 - \frac{S}{E}\right)$$

The Spruce Budworm Model

$$\epsilon_1 B' = B\left[1 - \frac{B}{S}\left(\frac{\delta^2 + E^2}{E^2}\right)\right] - \frac{\lambda B^2}{\nu^2 S^2 + B^2}$$

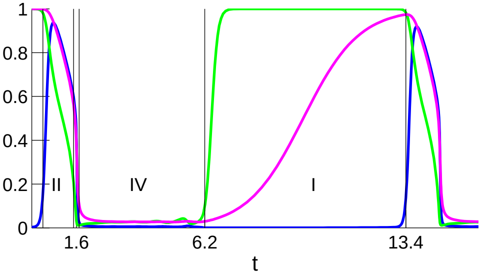
$$\epsilon_2 E' = E(1 - E) - \frac{\gamma B}{S}\left(\frac{E^2}{\delta^2 + E^2}\right)$$

$$S' = S\left(1 - \frac{S}{E}\right)$$

- $\epsilon_1 \approx 0.09, \quad \epsilon_2 \approx 0.07$: relatively fast insect and leaf dynamics
- $\delta \approx 0.02$: very low leaf count decreases insect capacity
- $\lambda \approx 0.004$: predation only matters when $B \ll 1$
- $\nu \approx 0.003$: predation saturates quickly (efficient predators)

- high S, E $\rightarrow$ high B $\rightarrow$ low E $\rightarrow$ low S $\rightarrow$ low B $\rightarrow$ high predation $\rightarrow$ very low B $\rightarrow$ E recovers $\rightarrow$ S recovers $\rightarrow$ B recovers

The “Standard” Scenario



blue-B green-E magenta-S

0–0.4	phase I	infestation
0.4–1.5	phase II	defoliation (high predation, not limiting)
1.5–1.7	phase III	crash
1.7–6.2	phase IV	dormant (predation and resource limiting)
6.2–13.4	phase I	proliferation (predation limiting)