A Mathematical Model for Onchocerciasis with Intermittent Treatment

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October 22, 2017

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Funded by ICERM and AIM.

To appear in Mathematical Biosciences and Engineering.

Onchocerciasis (river blindness) facts

- Endemic in parts of sub-Saharan Africa, recently eradicated from Central America.
- Caused by the filarial nematode *Onchocerca vulvulus*, which infects humans through fly bites.
- Listed by WHO as neglected, but targeted by the Carter Center River Blindness Elimination Program.
- **Currently studied with complex simulation models (ONCHOSIM, EpiOncho).**

Onchocerca vulvulus life cycle and treatment

- *O. vulvulus* has a complicated life cycle with four stages:
  1. Larvae undergo their early development in the *Simulium* black fly – about 1 week – then migrate to the fly's mouth.
  2. Larvae complete development in the human host – about 1 year.
  3. Adult worms live in the human host for about 10 years.
  4. Adults produce microfilaria, which migrate to the skin where they are ingested by black flies.
- Ivermectin (Heartgard) kills microfilaria, but does not kill adult worms.
- Treated humans have low infectivity, but still harbor adults.

Why a simple model?

1. Carter Center reports indicate less treatment success than predicted by complex simulations (ONCHOSIM, EpiOncho).
2. Complex models require a large number of parameter values, some of which are difficult to measure.
3. Simple models can be deliberately too optimistic or too pessimistic and find bounds on results.

Key simplifications

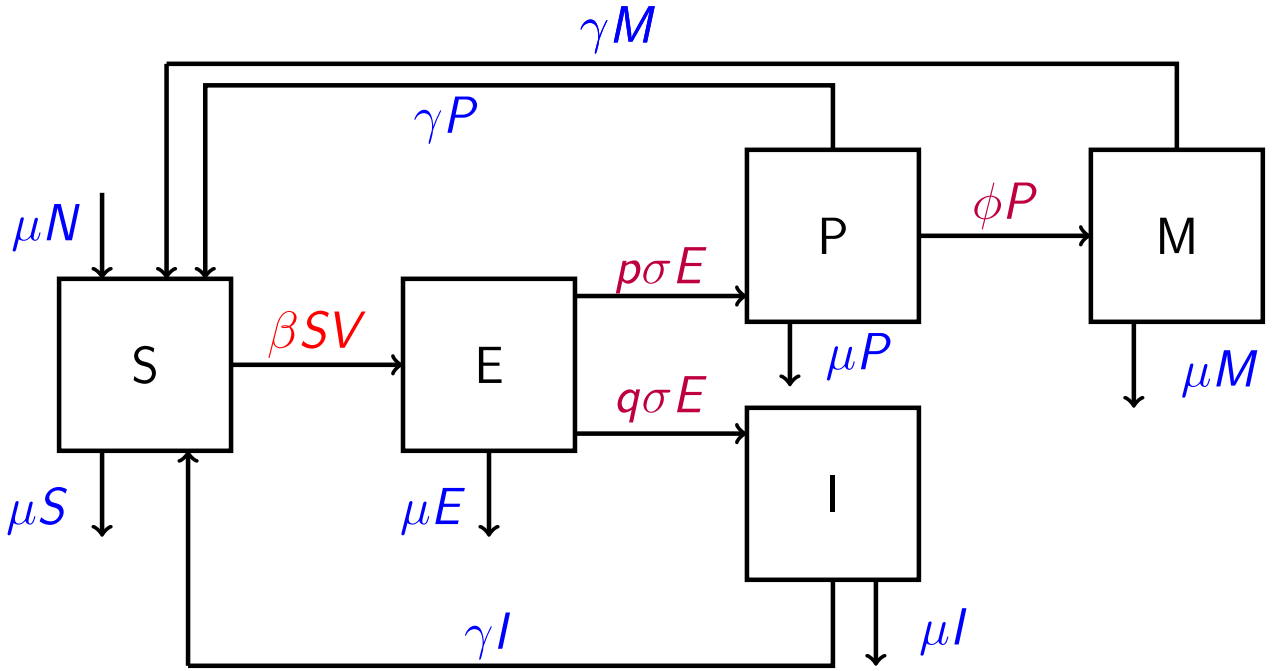
- Ivermectin treatment intially reduces infectivity of humans to flies by nearly 100%, but microfilaria production rebounds to about 65% of normal after a few months.
  - **We assume microfilaria production for treated humans is suppressed by a constant factor ν and take $0.9 \leq \nu \leq 1$.**
- Humans who are not further exposed clear the adult parasites in 10-12 years, but the clock restarts if reinfected by an infective fly.
  - **We neglect the possibility of reinfection.**
- Both assumptions are necessary for a simple epidemiological model.
- Both lead to an optimistic projection of treatment results.

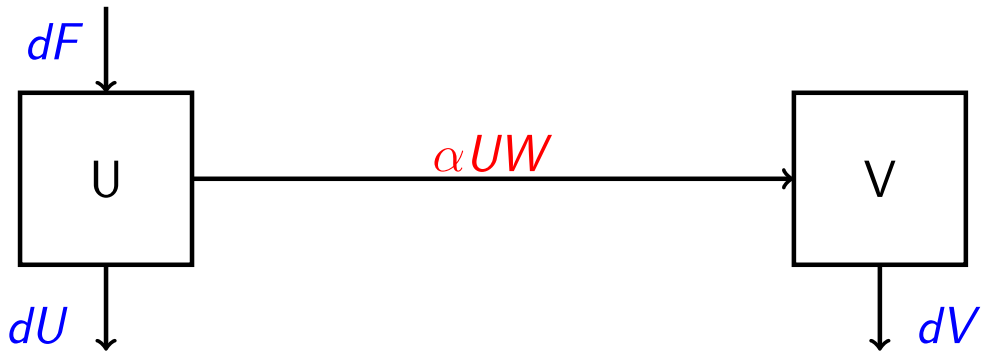
SEIPMS-UV population classes

- **S** usceptible – Humans who are uninfected.
- **E** xposed – Humans who are infected but not infective to flies.
- **I** nfective – Infective humans who are never treated.
- **P** remedicated – Infective humans waiting for first treatment.
- **M** edicated – Infective humans who have been treated.
- **U** ninfected – Flies that have not been infected.
- **V** ector – Infective flies.

- The equations in the model use $H = P + M$ instead of P.
- Constant human population N and fly population F allow $S = N - E - I - H$ and $U = F - V$.

Schematic for continuous model





$W = I + P + (1 - \nu)M = I + H - \nu M$ (effective number of infectives)

Continuous model (dimensionless version)

$$\eta x' = bvs - x$$

$$i' = qx - i$$

$$h' = px - h$$

$$\theta m' = h - (1 + \theta)m$$

$$\delta v' = aw(1 - v) - v$$

$$s + i + h + \eta x = 1$$

$$w = i + h - \nu m$$

- E was scaled with $\eta N \ll N$. Its dimensionless version is x (not e).
- a and b are infectivity parameters.
- δ is a critical time scale parameter.

Key time scale parameters

- The time scales for the life cycle phases are all very different.
  1. Life cycle of human host – 50-60 years (μ^{-1})
  2. Life cycle of adult worm (I, P, M $\rightarrow$ S) – 10 years (γ^{-1})
  3. Incubation period in human host (E $\rightarrow$ I, M) – 1 year (σ^{-1})
  4. Expected wait for medical treatment (P $\rightarrow$ M) – 1/2 year (ϕ^{-1})
  5. Life cycle of black fly host – 1 month (d^{-1})
  6. Microfilaria lifespan after ivermectin treatment – 3 days (0)

- Four dimensionless parameters are ratios of time scales, including

$$\delta = \frac{\gamma + \mu}{d} \approx 0.01 \qquad \frac{\text{fly lifespan}}{\text{infectivity duration}}$$

$$\theta = \frac{\gamma + \mu}{\phi} \approx 0.06 \qquad \frac{\text{treatment wait}}{\text{infectivity duration}}$$

$$\eta = \frac{\gamma + \mu}{\sigma} \approx 0.1 \qquad \frac{\text{incubation period}}{\text{infectivity duration}}$$

Basic reproductive number, part 1 (v to x)

$$\eta x' = bsv - x$$

Maximum average rate for $v \to x$: $\eta^{-1} b$

$$\delta v' = aw(1 - v) - v$$

Expected time for flies: δ

- Expected number for $v \to x$: $(\eta^{-1} b)(\delta) = \delta \eta^{-1} b$

Basic reproductive number, part 2 (v to x to $i + h$)

$$(i + h)' = x - (i + h)$$

Maximum average rate for $x \to i + h$: 1

$$\eta x' = bvs - x$$

Expected time for exposed humans: η

- Expected number for $x \to i + h$: $(1)(\eta) = \eta$

- Expected number for $v \to x$: $\delta\eta^{-1}b$
- Expected number for $v \to x \to i + h$: $(\delta\eta^{-1}b)(\eta) = \delta b$

Basic reproductive number, part 3 (v to x to $i+h$ to v)

$$\delta v' = aw(1-v) - v$$

Maximum average rate for $i+h \to v$: $(\delta^{-1}a)\omega$,

$\omega = 1 - \nu p(1+\theta)^{-1}$ is the expected value of w relative to that of $i+h$.

$$(i+h)' = x - (i+h)$$

Expected time for infected humans: 1

- Expected number for $i+h \to v$: $(\delta^{-1}a\omega)(1) = \delta^{-1}a\omega$
- Expected number for $v \to x \to i+h$: δb

- Basic reproductive number: $R_0 = \omega ab = \left(1 - \frac{\nu p}{1+\theta}\right) ab$

Infectivity parameters

- The endemic disease equilibrium (requires $R_0 > 1$) is

$$i = \frac{1 - R_0^{-1}}{1 + b^{-1} + \eta}, \qquad v = \frac{R_0 i}{b + R_0 i}.$$

- If we know equilibrium fractions $i = I/N$ and $v = V/F$, we can back out the infectivity parameters and basic reproductive number:

$$a = \frac{(\omega i)^{-1}}{v^{-1} - 1}, \quad b = \frac{v^{-1}}{i^{-1} - (1 + \eta)}, \quad R_0 = \frac{1}{(1 - v)[1 - (1 + \eta)i]}.$$

- Using before treatment ($\omega = 1$) data for the most endemic areas, we get worst case values of

$$a = 0.9, \qquad b = 3.0, \qquad R_0 = 2.7.$$

  - It takes about 40 flies to infect one human, but one human infects 110 flies.

Asymptotic approximation

In the asymptotic limit $\delta \to 0$ (very short fly lifespan), the v equation becomes quasi-steady:

$$v = \frac{aw}{1 + aw}$$

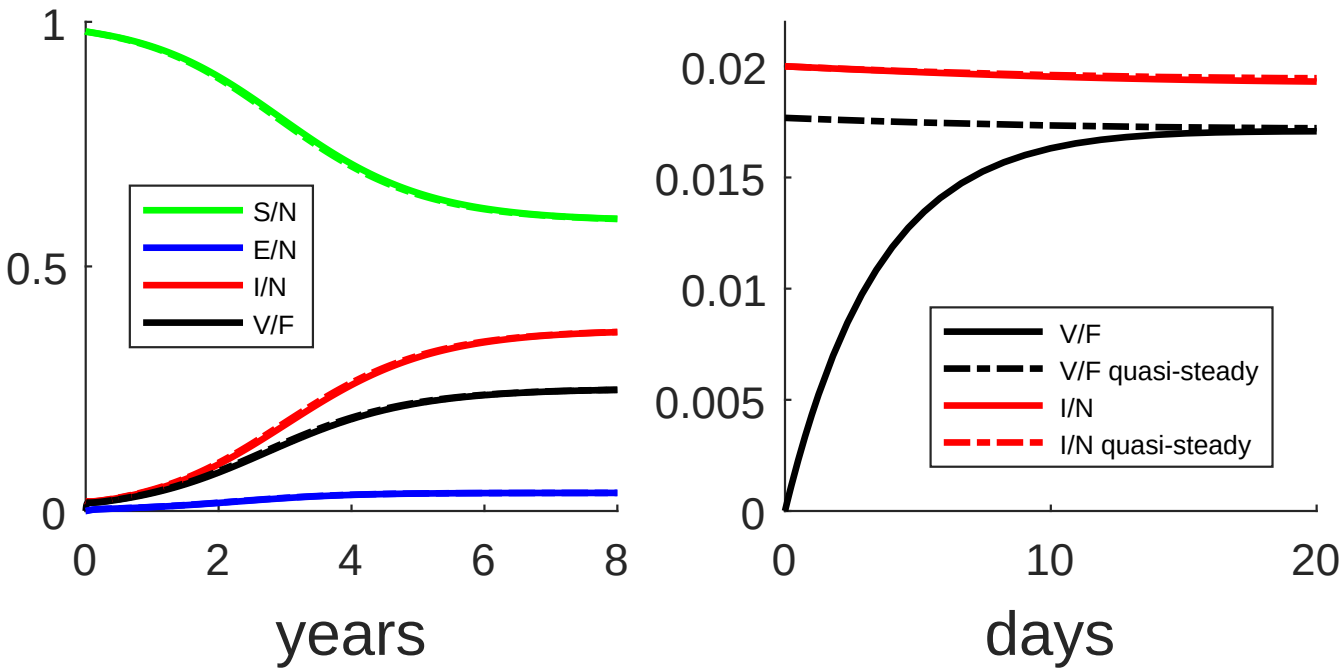
Then the exposure dynamics becomes

$$\eta x' = ab\frac{w}{1 + aw}s - x$$

(w is the effective number of infectives).

- The asymptotic approximation changes the vector-borne SEIPMS-UV model into an infectious SEIPMS model with nonlinear incidence.

Validation of asymptotic approximation



Simulation of the introduction of a small population of human infectives into a previously unexposed population, with solid for $\delta = 0.01$ and dash-dot for $\delta \to 0$.

- The quasi-steady approximation is only a "problem" for the first 20 days.

Pulsed model

The pulsed model follows from two changes:

1. Set $\theta = 0$ because delivery of health care occurs only at fixed intervals;
2. Set $m = h$ at times $n\tau$.

- We get periodic solutions rather than equilibrium solutions.

$$x' = \xi[bsv - x], \qquad x(1) = x(0) = x_0,$$

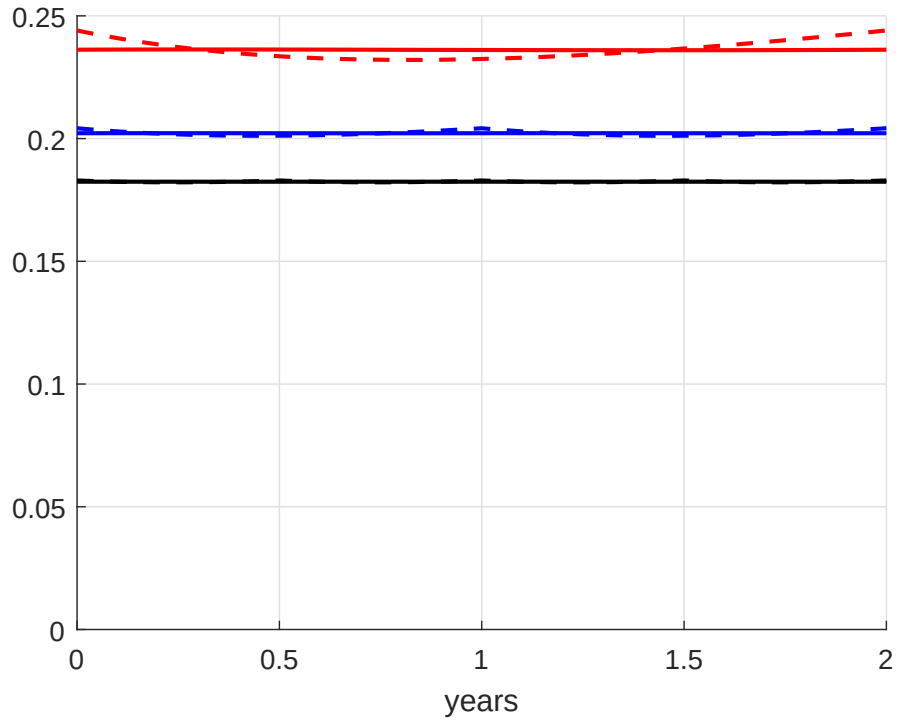
$$y' = \tau(x - y), \qquad y(1) = y(0) = y_0,$$

$$s = 1 - y, \qquad w = y - y_0 \nu p e^{-\tau t}, \qquad v = \frac{w}{a^{-1} + w},$$

- τ is the scaled treatment interval (typically 0.1 or 0.05, corresponding to treatment intervals of 1 year or 6 months).

Periodic solutions

The periodic system can be solved numerically or asymptotically ($\tau \to 0$).



Exposed (dashed) and total infective (solid) classes, with treatment intervals of 2 years, 1 year, and 6 months, top to bottom.

Analytical results

Basic reproductive number:

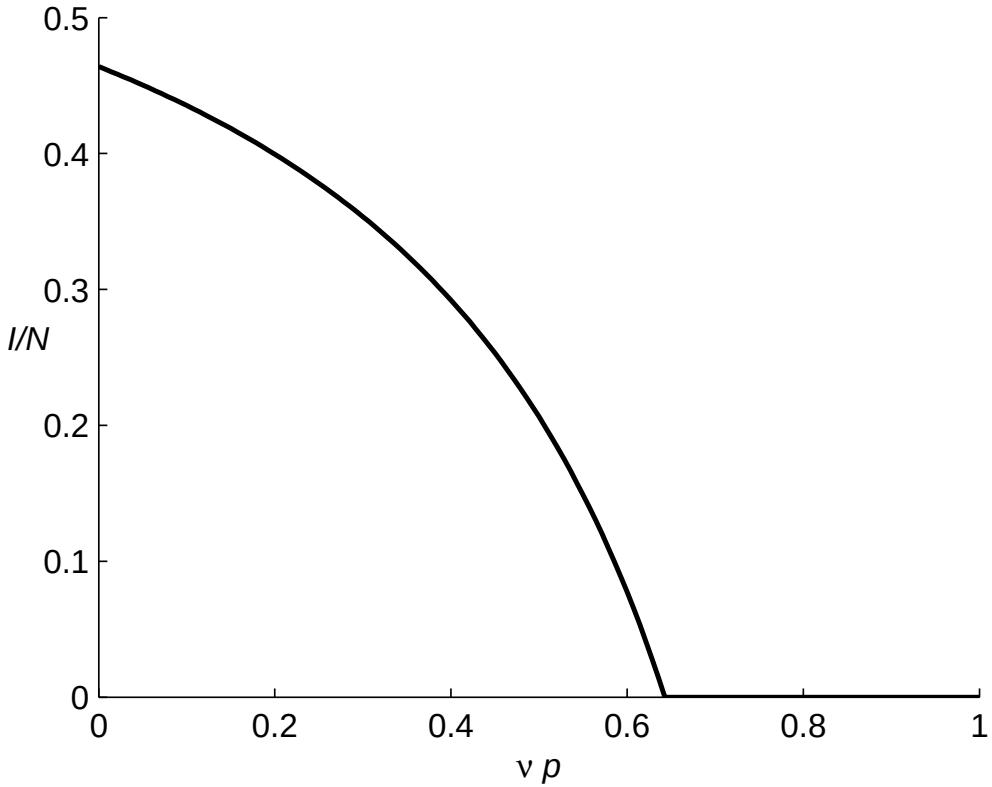
continuous	pulsed
$R_0 = \left(1 - \frac{\nu p}{1+\theta}\right) ab$	$R_0 \sim \left(1 - \frac{\nu p}{1+0.5\tau}\right) ab, \quad \tau \to 0$

- The disease free solutions are stable if $R_0 < 1$.
- The endemic disease equilibrium / periodic solution is stable if $R_0 > 1$.

Prognosis: Effect of νp

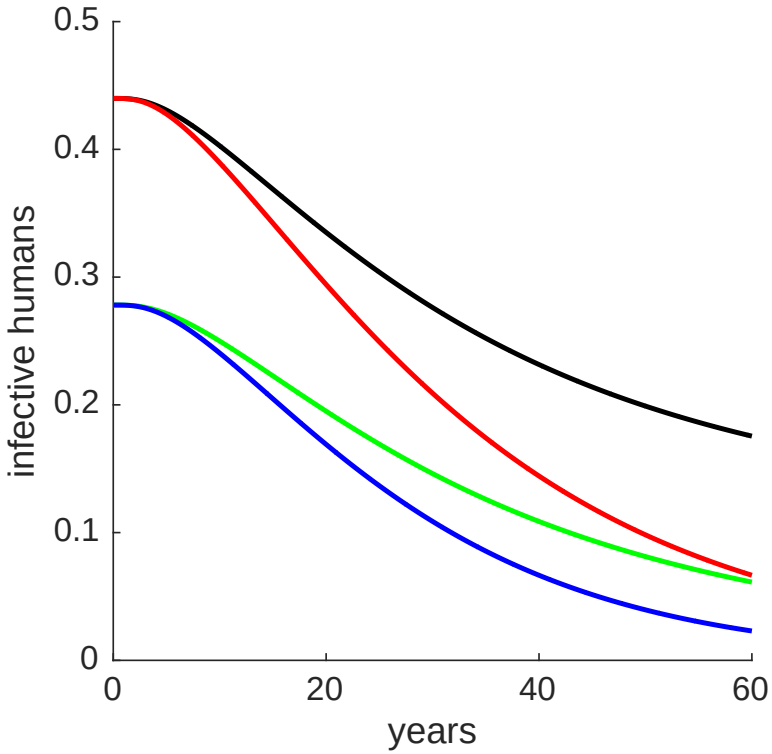
Basic reproductive number: $R_0 = \left(1 - \frac{\nu p}{1+\theta}\right) ab$

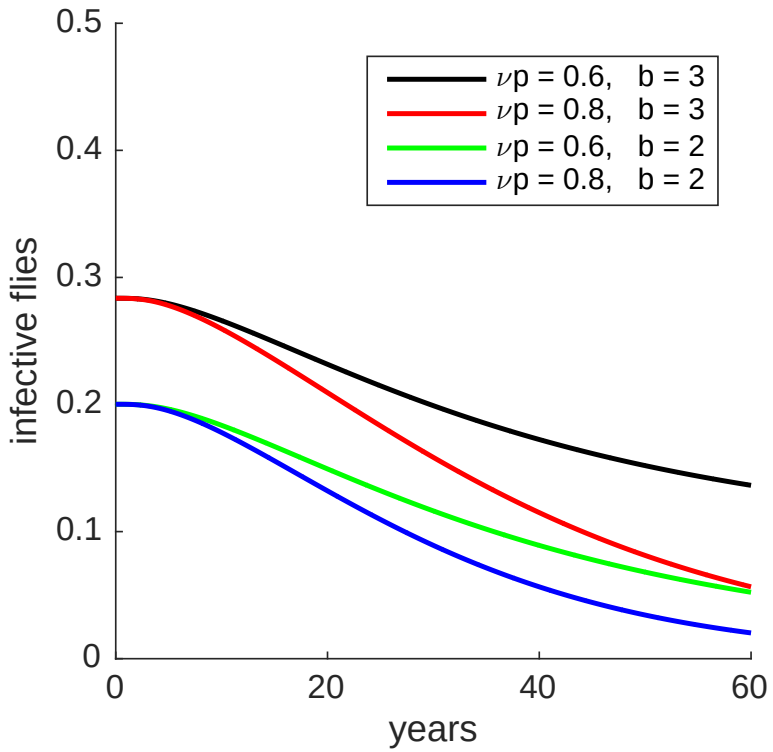
- In practice, $p \approx 0.7$ is typical and $0.35 < \nu < 1$. We take values $a = 0.9$ and $b = 3$ for the worst areas and $\theta = 0$ for instantaneous treatment.



Prognosis: Pace of eradication

Even when the basic reproductive number can be reduced below 1, eradication occurs on the very slow time scale of the adult worm lifespan. R_0 values are **1.16**, **0.64**, **0.77**, **0.43**





Conclusions

1. The current eradication strategy is not going to work in the most endemic areas.
2. The current eradication strategy is too slow even in less endemic areas.
3. Complex simulation models should be supplemented by simplified analytical models when possible.
4. Eradication requires a treatment that targets adult worms rather than microfilaria production.
5. Asymptotic approximation is not just for fluid mechanics!

References

For the onchocerciasis model and analysis, see

- Ledder, Sylvester, Bouchat, Thiel (2018). Continuous and pulsed epidemiological models for onchocerciasis with implications for eradication strategy. To appear in *Math. Biosci. Eng.*

For a presentation of asymptotic analysis and scaling in biological systems, using untreated onchocerciasis as an example, see

- Ledder (2017). Scaling for dynamical systems in biology. To appear in *Bull. Math. Bio.*, but available now at http://link.springer.com/article/10.1007/s11538-017-0339-5. (Or email gledder@unl.edu for this link.)