Course notes: MATH-4335
Mathematical Biology

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Abstract

Instructor's note: These are class notes and do not represent a citable original work. They draw heavily from the referenced sources to which the instructor is indebted.

Chapter 1

2 Species Interactions

1.1 Predator-Prey

matlab >> preprey.m

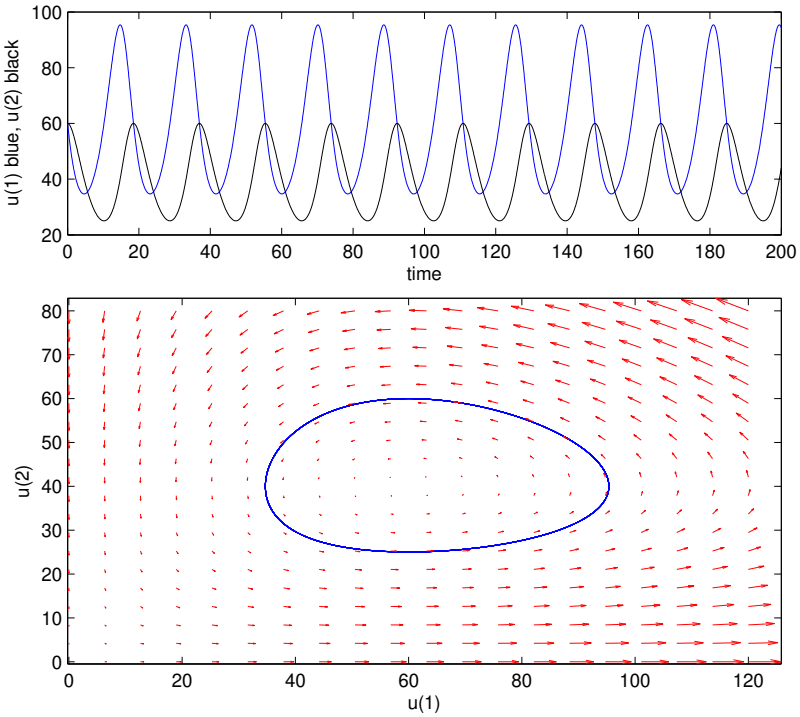
Phase plane: 2D version of plase line.

- Shows only the state of the system (R, W).
- Time is increasing but "in the background."
- Mouse selects an IC $(R(0), W(0)) = (R_0, W_0)$.
- A TRAJECTORY shows the evolution of the system starting from a given IC.
- The VECTOR FIELD of dashes are *tangent* to the trajectories.
- Different ICs $\Rightarrow$ different trajectories.

Change ICs to get different solutions.

Observations:

- More $R \Rightarrow$
  More food for $W \Rightarrow$
  More $W \Rightarrow$
  Less $R \Rightarrow$
  Less food for $W \Rightarrow$
  Less $W \Rightarrow$
  More $R \Rightarrow$ repeat
- No extinction. $(R, W) = (0, 0)$ is bottom left corner.
- No coexistence steady-state. $(R, W) = (R_s, W_s)$ in center of loops.
- Closed loops = ORBITS in phase plane = PERIODIC SOLUTIONS in time.


u(1) blue, u(2) black
time
u(2)
u(1)

1.2 Competing Species

matlab >> competing.m

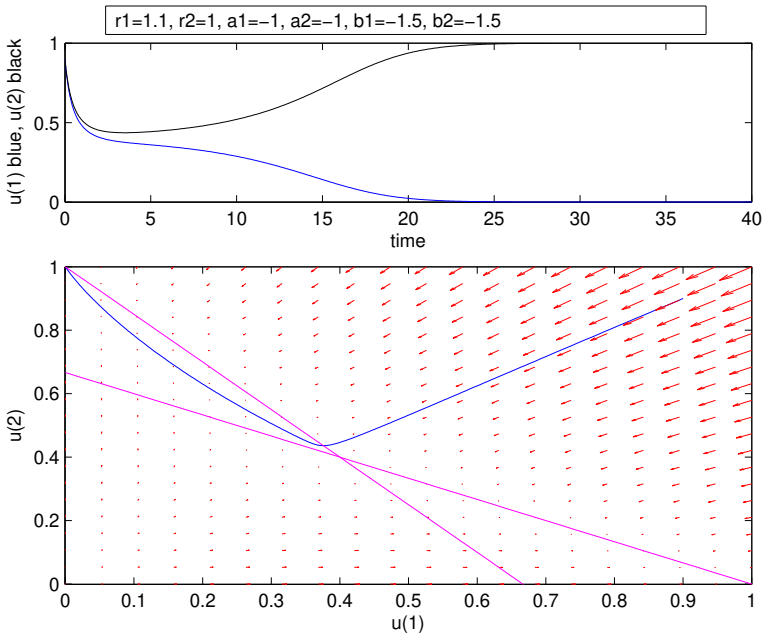
1.2.1 Winners and losers

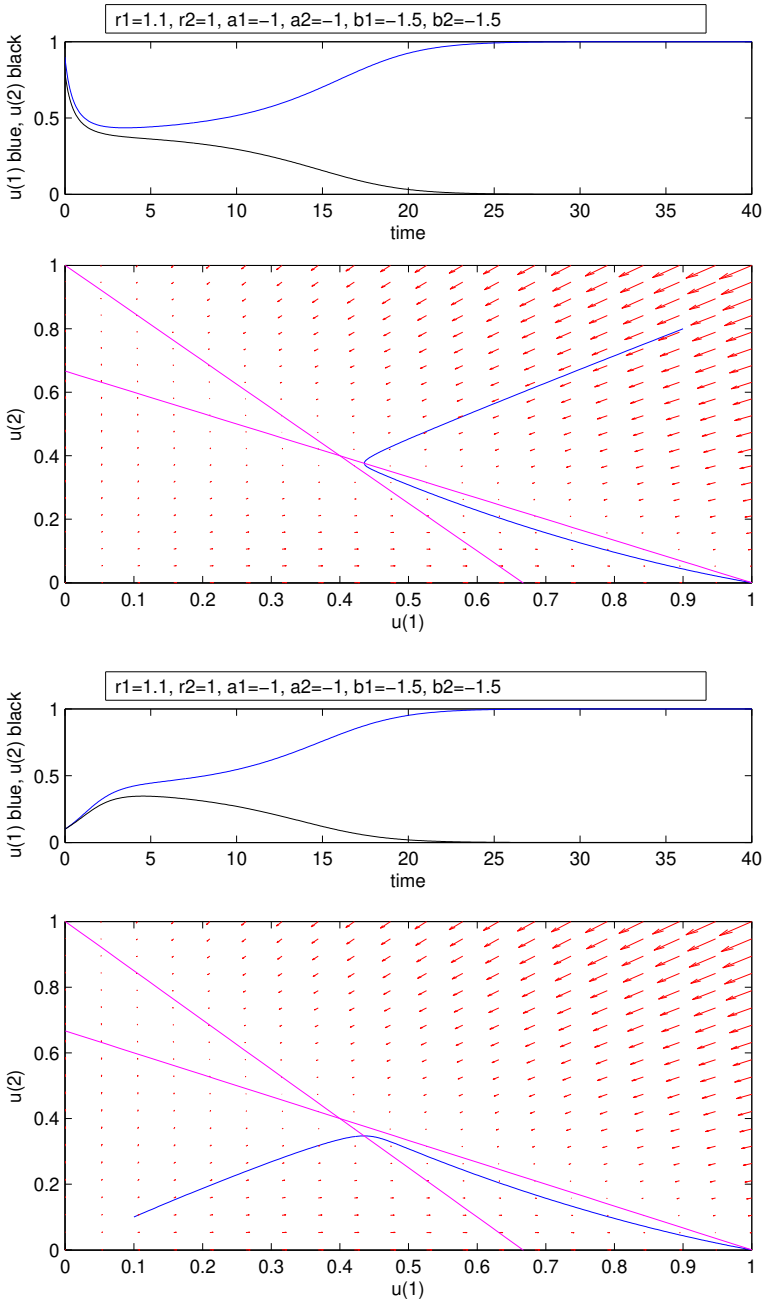
Let x be the *fraction* of the total sheep population. That is, if N_s is the total number of sheep, then $x = S/N_s$. Similarly, $y = C/N_c$ is the fraction of the cow population. Thus, both x and y vary between 0 and 1.
For the default parameter values:

- The extinction steady state is UNSTABLE.
- Utopia/coexistence is UNSTABLE.
- Both $(x, y) = (\#, 0)$ or $(0, \#)$, corresponding to one species being selected over the other, is STABLE.
- Which stable steady state is ultimately exhibited depends on the ICs.

Questions:

- What are the magenta lines? How do they relate to the arrows that are shown?
- How do we know which ICs will go to which steady state?
- Definition of stable or unstable.




r1=1.1, r2=1, a1=−1, a2=−1, b1=−1.5, b2=−1.5
u(1) blue, u(2) black
time
u(2)
u(1)
r1=1.1, r2=1, a1=−1, a2=−1, b1=−1.5, b2=−1.5
u(1) blue, u(2) black
time
u(2)
u(1)

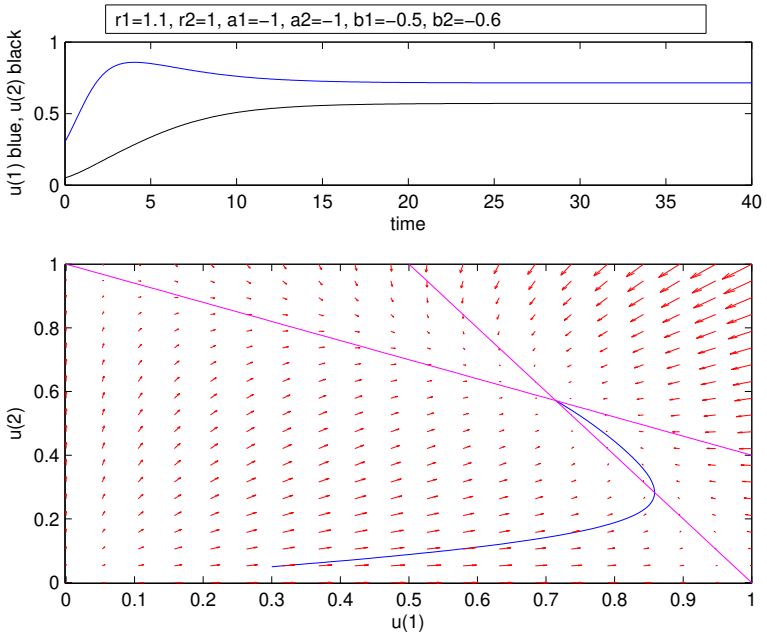
1.2.2 Coexistence

Change the parameters ⇒ changes the steady states and their stability.

- What was stable can become unstable.
- System properties depend upon the parameters.

Decrease the mutual competition coefficients b_j to favor coexistence.

- If $b_1 = b_2 = 0$ the populations/compartments do not interact.
- Each individually satisfies the logistic equation with growth rate a_1 or a_2 and carrying capacity equal to 1 (because we have rescaled to fractions).



Chapter 2

Epidemiology

2.1 The basic questions

Consider a population that is "naive" in that it is completely free of disease. Assume that one infected individual is introduced.

- Does this cause an epidemic?
- If so, with what rate does the number of infected individuals increase?
- What proportion of the population will eventually be infected?

Why is mathematical modeling and analysis important and useful?

- It is often difficult, impossible or unethical to conduct traditional laboratory experiments on infectious diseases in humans.
- Field data is often incomplete, distorted or unavailable.

A crude characterization of disease causing parasites:
Microparasites: parasites that have direct reproduction, usually at very high rates, within the host. Typified by small size and short generation time (length of time within the host). Hosts usually acquire immunity for some period of time.
Macroparasites: parasites that do not reproduce within the host. Often larger and have longer generation times sometimes on the order of the hosts lifetime. Periods of immunity are very short if at all.

In our discussions we will assume that we are dealing with **microparasites** unless otherwise indicated.

2.2 A Short History of Mathematical Epidemiology

- 1760 Bernoulli: Examine effectiveness of current smallpox treatments.
- 1906 Hamer: Discrete-time measles model. Spread of disease depends on the rate of contact between those who are susceptible and those who are infected. Principle of "mass action."

- 1911 Ross: Continuous-time malaria model. Malaria spread by mosquitoes.
- 1927 Kermack and McKendrick: Threshold theory- a minimum population size is required for disease spread.
- 1975 Bailey: "The Mathematical Theory of Infectious Diseases."
- ....
- 1992 Perelson: Multi-drug therapies ("cocktails") for HIV-AIDS.

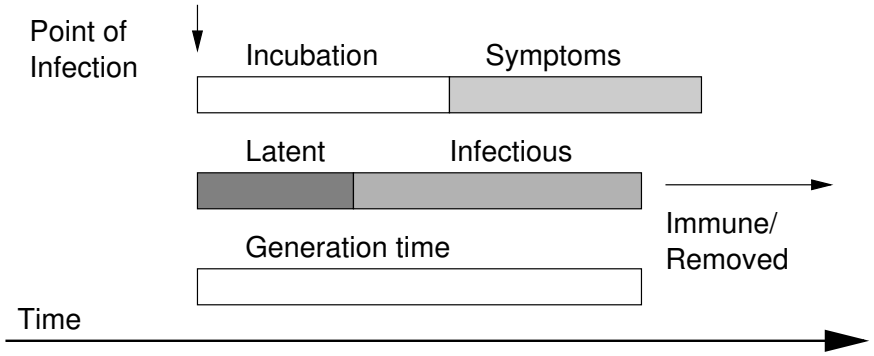
Mathematical models have contributed to the understanding and control of human and wildlife diseases such as: measles, rubella, chickenpox, whooping cough, smallpox, plague, influenza, gonorrhea, chlamydia, syphilis, HIV/AIDS, hepatitis, tuberculosis, malaria, dengue fever, West Nile virus, cholera, SARS, schistosomiasis, Lyme disease, foot and mouth disease (cow, pigs), rabies (skunks, bats, coyotes, raccoons), hantavirus (rodents), chytridiomycosis (amphibians).

2.3 Compartment models

Modeling

- No force balance like Newtons laws or Navier Stokes.
- Often don't know the "forces" involved.
- Often modeling social processes.

The diagram below illustrates the course of a hypothetical microparasite infection.



From Anderson & May

Compartment models: A population of $N(t)$ individuals is divided into distinct classes (compartments) based on their health and immunity. Common classes are $S(t)$, $I(t)$, $R(t)$:

- $S(t)$: *Susceptible* class. Individuals not infected but are capable of becoming infected.
- $I(t)$: *Infected* class. Individuals who are infected and are capable of transmitting the diseases (infectious).
- $R(t)$: *Removed* class. Individuals who were infected but now are recovered and immune (neither susceptible or infectious).

Table 2.1: Data obtained from *Infectious Diseases of Humans*, by R.M. Anderson and R.M. May (Oxford University Press, Oxford, 2002)

Infectious Disease	Incubation period	Latent period	Infectious period
Measles	8-13	6-9	6-7
Mumps	12-16	12-18	4-8
Whooping cough	6-10	21-33	7-10
Chicken Pox	13-17	8-12	10-11
Hepatitus B	30-80	13-17	19-22
Influenza	1-3	1-3	2-3
Smallpox	2-3	1-2	14-21

- Other classes may be introduced depending on the dynamics of the diseases. For example, there may be an *Exposed* class, $E(t)$ where an individual has contracted the disease but is not yet infectious. Individuals may only have temporary immunity before returning to the susceptible class.

The variables S, I and R, as defined above denote the *number* of individuals in that class. It is often more convenient to instead consider *fractions* such as $\tilde{S} = S/N$, where $0 \leq \tilde{S} \leq 1$. This merely involves rescaling of the model variables and possibly different definitions in parameters (to absorb N).

Model Types:

- SI = no recovery. $S \to I$.
  HIV-AIDS
- SIR = recovery with immunity. $S \to I \to R$.
  Viruses such as measles, mumps, chickenpox.
- SIS = recovery but no immunity. $S \to I \to S$.
  Bacterial diseases such as sexually transmitted diseases, plague, meningitis, and protozoan agents such as malaria
- SIRS = temporary immunity. $S \to I \to R \to S$.
  Whooping cough
- SEIR = latent period before infectious and immunity. $S \to E \to I \to R$.

Refinements to these models can include effects due to:

- Disease related factors such as infectious agent, mode of transmission, latent period, infectious period.
- Social factors such as cultural issues, demographics, economics and geographics.
- Vector or reservoir dynamics. Mosquitoes are the **vector** for the transmission of malaria in that they carry the disease from one human to another.

A couple of definitions...

Prevalence: the number of infected individuals at any time, $I(t)$.
Incidence: the number of *new* infected individuals per unit time, $i(t)$.

2.4 Basic Reproductive Number/Ratio: R_0

Definition of R_0:

- "The average number of offspring over the lifetime of an individual."
- "The average number of secondary infections produced when one infected individual is introduced into a host population where everyone is susceptible."
- "Expected number of secondary cases per primary case."

If in a population of susceptible individuals a small number $I(t)$ of infectives individuals is introduced, and if

- $R_0 < 1$, then on average every individual infects less than one other individual. $I(t)$ will decrease and the disease dies out.
- $R_0 > 1$, then more than one new infected individual for every current infected person and $I(t)$ will increase. This is referred to as an **epidemic**, i.e., an outbreak of disease.

In the latter case when $R_0 > 1$ and there is an initial epidemic, then as $t \to \infty$, the number of infected individuals may:

- Decay back to 0.
- Reach a non-zero steady-state referred to as an **endemic** state.
- Become oscillatory, pulsating, chaotic, etc.

From a dynamical systems point of view we will find that R_0 is *sometimes* related to the linear stability of the $I = 0$ state. For example,

$$\frac{dI}{dt} \approx (R_0 - 1)I, \quad \text{or} \quad I_{n+1} \approx R_0 I_n.$$

More specifically, the endemic state is positive ($I > 0$) and stable ($Re[\lambda] < 0$) for $R_0 > 1$. This provides a simple way to determine the definition of R_0. (However, it may be that $\lim_{t\to\infty} I = 0$ but an epidemic with $R_0 > 1$ occurs as a transient. See the first bullet above. Thus, this simple way to define R_0 does not work in all cases).

"Epidemiology, the quest for R_0," B. Ayati.
In general, epidemiologist search for *thresholds* that must be exceeded for a diseases to exhibit an epidemic or remain endemic, for example, the reproduction number greater than 1, or critical values of the population size or vector density.

Table 2.2: Data obtained from *Anderson and May* (see above for citation).

Infection	Location	Time period	R_0
Measles	Cirencester, England	1947-1950	13-14
	England & Wales	1950-68	16-18
	Kansas, USA	1918-21	5-6
	Ontario, Canada	1912-13	11-12
	Ghana	1960-68	14-15
Chicken pox	Maryland, USA	1943	7-8
	Baltimore, USA	1943	10-11
HIV (type I)	England & Wales (male homosexuals)	1981-85	2-5
	Kampala, Uganda (heterosexuals)	1981-87	10-11

Chapter 3

COVID 19

3.1 Some words from an applied mathematician

How math helps us get even better vaccines even faster

`https://www.youtube.com/watch?v=8QMBazAI9mY\&t=1s`

SIAM member Jeffrey R. Sachs, who leads vaccine modeling and simulation efforts at Merck, explains how mathematics plays a critical role in our daily lives, specifically focusing on how math is used in the development, discovery, and manufacturing of vaccines. Learn more about what vaccines are, how they work, and the important research and discovery of applied mathematicians in making vaccines even more effective and accessible.

3.2 COVID aerosol spread: a mixture problem

See separate document for analysis. Generally speaking, our intuition is pretty good and we can back it up with mathematical analysis.

- We prefer to start with a clean room (small Q_0).
- We prefer a weak source of C19 aerosol (small a).
- We prefer a large room (large V).
- We prefer a lot of ventilation (large r).
- The ventilation must be supplying fresh air. Recirculated air effectively just improves the well-mixed assumption.
- As the room gets bigger, add more ventilation (keep r/V as big as possible.)
- Taking into account spatial transport, it is probably best to be far away from the speaker (diffusion).
- If there is a dominant direction to airflow, being upwind is better than downwind (advection).

3.3 What is R_0 and what it isn't

P.L. Delameter et al., "Complexity of the Basic Reproduction Number (R_0)," *Emerging infectious diseases,* (2019) 25. DOI: https://doi.org/10.3201/eid2501.171901

"R_0 is an estimate of the contagiousness that is a function of human behavior and biological characteristics of the pathogen. R_0 is not a measure of the severity of an infectious disease or the rapidity of spread through a population."

Just because R_0 is high does not necessarily mean the disease is severe. Similarly, a disease with low R_0 may be fatal.

C-J Yu et al., "Assessment of basic reproductive number for COVID19 at global level," *Medicine,* (2021) 100:18(e25837). DOI: http://dx.doi.org/10.1097/MD.0000000000025837

"R_0 is affected by lots of biosocial factors and is estimated by various complex mathematical models. Therefore, the R_0 values are usually dependent on model structures and assumptions. It is recommended not to compare values based on different models."

The exact same disease may have a different R_0 in the US than in Europe or Asia due simply to behavior differences.

E. Mahase, "Covid-19: What is the R number?" BMJ (2020) 369:m1891. DOI: 10.1136/bmj.m1891

"The R number could refer to either the basic reproduction number, known as the R nought or zero (R_0), or the effective reproduction number (R_e).

R_0 describes how many people each infected person will infect on average, assuming that there is no pre-existing immunity in the community. It is often estimated using three factors: the duration of contagiousness after a person becomes infected, the likelihood of infection in each contact between a susceptible person and an infectious person or vector, and the frequency of contact.

R_e is the number of people that can be infected by an individual at any specific time, and it changes as the population becomes increasingly immunised, either through individuals gaining immunity after being infected or through vaccination, and also as people die. R_e can also be affected by people's behaviour, such as by social distancing. R_0 and R_e are often confused or just referred to as the R number."

We have to be mindful of the details of definitions.

3.4 What is R_0 for Covid?

M.A. Billah, "Reproductive number of coronavirus: A systematic review and meta-analysis based on global level evidence," *PLoS ONE*, (2020) 15(11): e0242128.
DOI: https://doi.org/10.1371/journal.pone.0242128

"Total of 42 studies included in this review whereas 29 of them were included in the meta-analysis. The estimated summary reproductive number was 2.87 (95% CI, 2.39–3.44). We found evidence of very high heterogeneity (99.5%) of the reproductive number reported in the included studies. Our sub-group analysis was found the significant variations of reproductive number across the country for which it was estimated, method and model that were used to estimate the reproductive number, number of case that was considered to estimate the reproductive number, and the type of reproductive number that was estimated. The highest reproductive number was reported for the Diamond Princess Cruise Ship in Japan(14.8). In the country-level, the higher reproductive number was reported for France (R, 6.32, 95% CI, 5.72–6.99) following Germany (R, 6.07, 95% CI, 5.51–6.69) and Spain (R, 3.56, 95% CI, 1.62–7.82). The higher reproductive number was reported if it was estimated by using the Markov Chain Monte Carlo method (MCMC) method and the Epidemic curve model. We also reported significant heterogeneity of the type of reproductive number-a high-value reported if it was the time-dependent reproductive number."

C-J Yu et al.

"Results: We identified 185 unique articles, yielding 43 articles for analysis. The selected studies covered 5 countries from Asia, 5 countries from Europe, 12 countries from Africa, and 1 from North America, South America, and Australia each. Exponential growth rate model was most favored by researchers. The pooled global R0 was 4.08 (95% CI, 3.09–5.39). The R0 estimates for new and shifting epicenters were comparable or even higher than that for the original epicenter Wuhan, China."

Locatelli et al., "Estimating the basic reproduction number for COVID-19 in Western Europe. *PLoS ONE*, (2021) 16(3): e0248731. DOI: https://doi.org/10.1371/journal.pone.0248731

"Despite the possible unreliability of some official statistics about COVID-19, the spread of the disease appears to be remarkably similar in most European countries, allowing us to estimate an average R0 in Western Europe of 2.2 (95% CI: 1.9–2.6).

The value of R0 for COVID-19 in Western Europe appears to be significantly lower than that in China. The proportion of immune persons in the European population required to stop the outbreak could thus be closer to 50% than to 70%."

3.5 Compartment models for Covid

Mugisha JYT, Ssebuliba J, Nakakawa JN, Kikawa CR, Ssematimba A (2021) Mathematical modeling of COVID-19 transmission dynamics in Uganda: Implications of complacency and early easing of lockdown. PLOS ONE 16(2): e0247456. https://doi.org/10.1371/journal.pone.0247456
Model variables:

- S = susceptible
- E = exposed
- I_a = infectious, not in quarantine, asymptomatic
  Eventually identified and hospitalized

- I_s = infectious, not in quarantine, symptomatic
  Die or are hosptialized
- H = infectious but in quarantine (Hospitalized)
  Die or recover
- R = recovered Recovery is temporary. No one is permanent removed.
- Recruitment of new individuals into the population (susceptible, exposed or recovered only)

Conclusions:

- For Uganda, even if the prevent the import of any new infections it would take 9 months to clear covid.
- The success of lockdowns depends critically on not "releasing too many too soon.
- Contact tracing (and subsequent measures) can reduce but not eliminate a second wave.

Oliveira, J.F., Jorge, D.C.P., Veiga, R.V. et al. Mathematical modeling of COVID-19 in 14.8 million individuals in Bahia, Brazil. Nat Commun 12, 333 (2021). https://doi.org/10.1038/s41467-020-19798-3
Model variables:

- S = susceptible
- E = exposed
- I_a = infectious, not in quarantine, asymptomatic
  Eventually identified and hospitalized
- I_s = infectious, not in quarantine, symptomatic
  Die or are hosptialized
- H = infectious but in quarantine (Hospitalized)
  Die or recover
- R = recovered Recovery is temporary. No one is permanent removed.
- D = Dead

Conclusions:

- Considered a transmission rate that varied in time. Determined relative importance of the transmission rate pre-intervention vs post-intervention.
- The portion of the population needing hospitalization is important.
- Population behavior changes and government interventions are important to decreasing the severity of the epidemic but are still insufficient to curb the epidemic. The effective reproductive number remains greater than 1. indicating a scenario of continuing growth.

Anwar Zeb, Ebraheem Alzahrani, Vedat Suat Erturk, Gul Zaman, "Mathematical Model for Coronavirus Disease 2019 (COVID-19) Containing Isolation Class", BioMed Research International, vol. 2020, Article ID 3452402, 7 pages, 2020. https://doi.org/10.1155/2020/3452402
Model variables:

- S = susceptible
- E = exposed
- I = infectious
- Q = quarantine
- R = recovered

Conclusions:

- "Our findings show that human to human contact is the potential cause of outbreaks of COVID-19. Therefore, isolation of the infected human overall can reduce the risk of future COVID-19 spread."

Ashleigh R. Tuite, David N. Fisman and Amy L. Greer, "Mathematical modelling of COVID-19 transmission and mitigation strategies in the population of Ontario, Canada," CMAJ May 11, 2020 192 (19) E497-E505; DOI: https://doi.org/10.1503/cmaj.200476
Model variables:

- S = Susceptible
- E Exposed
- Q Exposed, quarantined
- A Infectious, pre-symptomatic
- W Infectious, pre-symptomatic, in isolation
- B Infectious - mild
- C Infectious - severe
- Y Infectious - mild, in isolation
- Z Infectious - severe, in isolation
- G Isolated - mild, not previously in quarantine
- H Hospitalized, never in ICU
- H1 Hospitalized, pre-ICU admission
- I Hospitalized, in ICU
- H2 Hospitalized, post-ICU

- R Recovered
- D Dead
- Each class is divided into subclasses by 5 year age groups

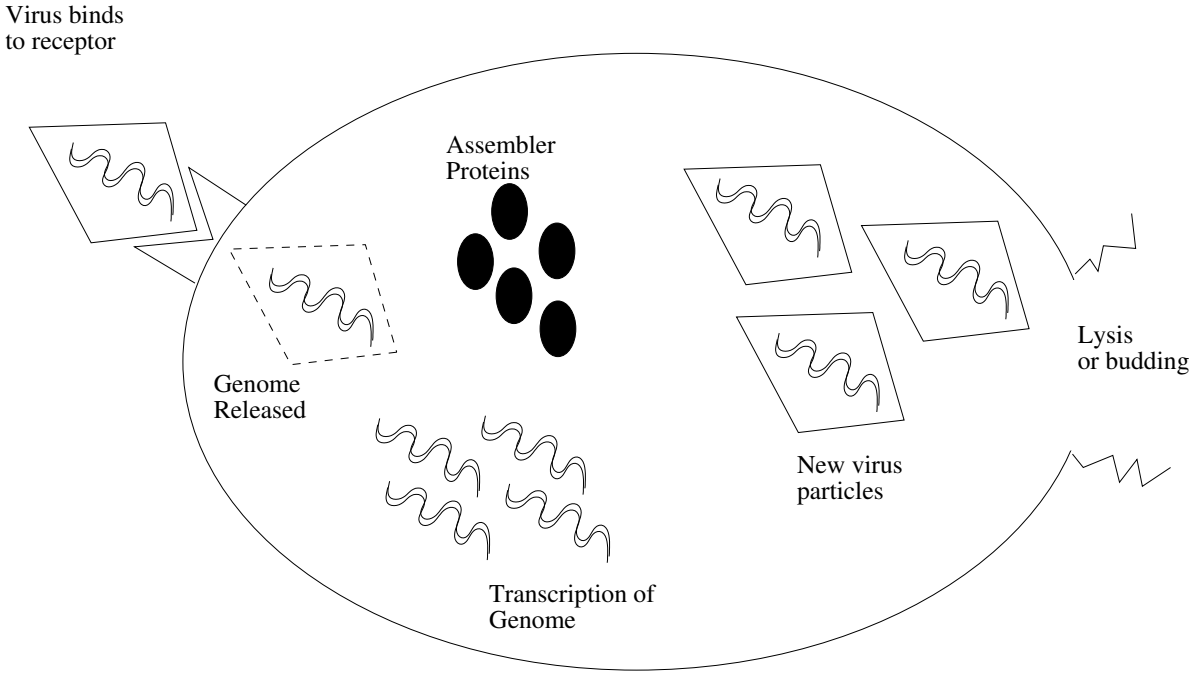
Conclusions:

- 56% of the population of Ontario will be infected, 107k hospitalized, 55.5k ICU
- All interventions will delay and reduce the epidemic peak.
- Physical distancing most important, the longer the better.

Chapter 4

Immunology - HIV/AIDS

4.1 Basic viral dynamics



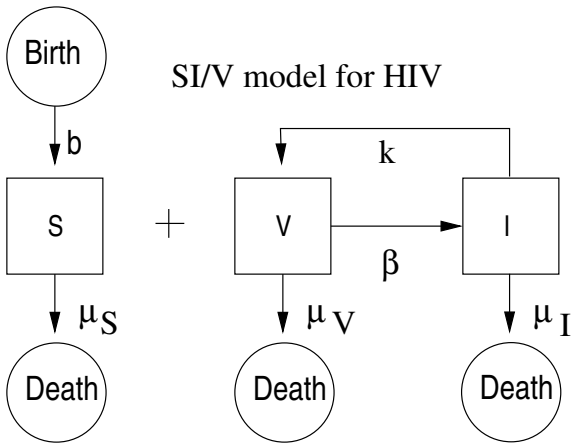
- A virus is a genome (DNA or RNA) enclosed in a protein shell.
- It reproduces using the replication machinery of living cells.
- The virus binds to a receptor site on the cell wall and is absorbed into the cell.
- The protein shell degrades.
- The genome migrates to the nucleus where it is replicated by the cell's own machinery. In addition, proteins that will build new virus particles are generated.
- The new genomes are packaged into new shells that are released either by lysis (cell dies) or by budding (cell lives).

We will track the number of susceptible or infectious cells and the number of virus particles, all within a single host. As example, in HIV, the virus attacks T-cells that fight infections from other diseases.

$$\frac{dS}{dt} = b - \beta SV - \mu_s S, \tag{4.1}$$

$$\frac{dI}{dt} = \beta SV - \mu_i I \tag{4.2}$$

$$\frac{dV}{dt} = kI - \mu_v V. \tag{4.3}$$



- S: *number* of T-cells that are susceptible (targets). I: *number* of infected T-cells. V: *number* of virions.
- All die naturally with a mean time $1/\mu_j$.
- New T-cells are reproduced at a constant rate b (not an exponential birth process).
- Contact between a virion and a susceptible cell leads to infection with transmission rate β. Notice that there is not a $1/N$ factor because the entire virion population is, by definition, "infected."
- When infected cells die they release the virions within with rate k. We do not include a loss of a virion when it enters the cell under the assumption that this is small relative to k.
- These equations are similar in form to an SEI model.
- Effectively a predator (virus) - prey (cells) system.

Steady-states There is a disease-free state $S = b/\mu_s \equiv S_0$, $I = V = 0$ and an endemic state

$$S_s = \frac{S_0}{R_0}, \quad I_s = \frac{\mu_s \mu_v}{\beta k}(R_0 - 1), \quad V_s = \frac{\mu_s}{\beta}(R_0 - 1), \tag{4.4}$$

$$R_0 = \frac{\beta b k}{\mu_s \mu_i \mu_v} \tag{4.5}$$

Linear-stability analysis verifies there is a transcritical bifurcation when $R_0 = 1$. Notice that we have used S_0 to define the disease-free equilibrium number of susceptible cells (not the IC).

4.2 HIV Dynamics

In our previous models we assumed a homogeneous population where everyone was susceptible and infectious to the same degree. In contrast, the dynamics of STDs is affected by the general heterogeneity of the population affected by the disease. Specifically,

1. Only sexually active individuals need to be considered (core group). These individuals can be further divided into highly active or less active groups. Because of the transmission process, population density is not a primary determinant of transmission rate.

2. The carrier phenomena is important. For example, with gonorrhea many carry the disease but are asymptomatic, particularly women.

3. There is little or no immunity following recovery.

The net effect is that these diseases are better adapted to persisting in small and low-density populations.

Core group There are some individuals, referred to as "super-spreaders" who due to being highly active have an $R_0 > 1$. Less active individuals have an $R_0 < 1$. Thus, by targeting the "core group" the disease will die out in the complete population because the disease is non-epidemic in the non-core group.

History & biology of HIV

- 1981: CDC notes increased occurrence of rare diseases associated with weakened immune system in populations of homosexual men in New York, San Francisco and Los Angeles.

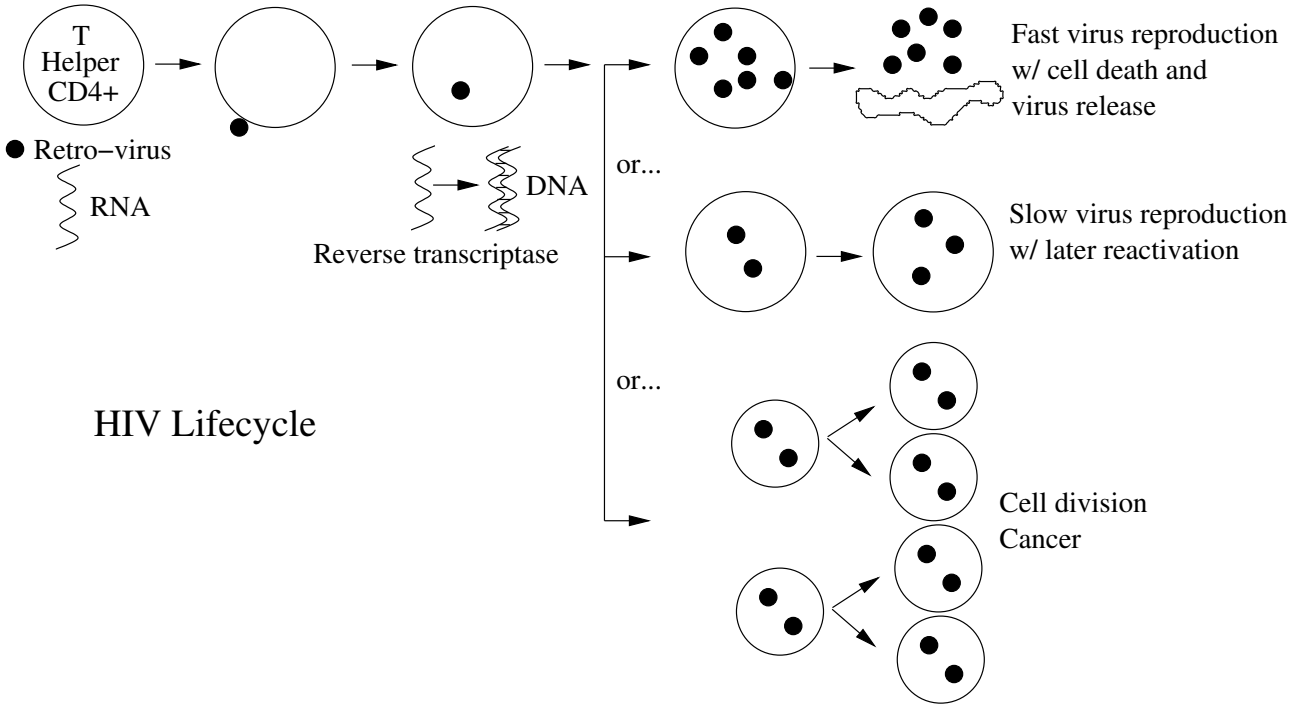
- 1983: Retrovirus identified. A retrovirus carries RNA. When inserted into the host cell the enzyme reverse transcriptase generates DNA from the RNA. This virus DNA is inserted into the host DNA where cell dynamics generated more virus RNA.

Three phases of infection

1. After infection individuals develop very large virus loads and exhibit flu like symptoms. CD4 cell count drops transiently but recover to almost normal levels. Finally, symptoms disappear as virus load decreases.

2. Virus load increases. CD4 cell count falls, rapidly in some but more slowly in others. Average length of time is 10 years.

3. AIDS. The CD4 count is so low that opportunistic diseases cause death.



4.3 Drug Therapies

4.3.1 Reverse-transcription Inhibitor

RT-Inhibitors prevent the infection of new cells so that $\beta = 0$. This decouples the S and (I, V) populations so that we have

$$\frac{dI}{dt} = -\mu_i I \tag{4.6}$$

$$\frac{dV}{dt} = kI - \mu_v V. \tag{4.7}$$

Thus, given an initial population of infected cells $I = I_0 \exp(-\mu_i t)$ and the number of virions is

$$V(t) = \left(V_0 - \frac{kI_0}{\mu_v - \mu_i}\right) e^{-\mu_v t} + \frac{kI_0}{\mu_v - \mu_i} e^{-\mu_i t}. \tag{4.8}$$

The number of infected cells decays exponentially. After an initial "shoulder phase" the number of virions will decay exponentially according to the slower of the two decay terms.

Fast virions, less fast cells In general, individual virions have a shorter lifetime than an individual cell. Thus, $\mu_v > \mu_i$ and after a initial "transient"

$$V(t) \approx e^{-\mu_i t}. \tag{4.9}$$

Good data In 1995 George Shaw and David Ho collect data on the virus load (number of virions) at frequent enough intervals so that a fit to the above results was possible. This combined effort of experimentation and modeling resulted in an estimate of

$$\frac{1}{\mu_i} = 2\text{days}. \tag{4.10}$$

Attack of the mutants The infected cells that produce most of the HIV virus have a life-time, or turn over time, of 2-3 days. Thus, even though the evolution of the disease in an individual takes many years, the dynamics of the disease is occurring on a very short time scale.

A direct implification of this rapid turn-over is that it is possible for the virus to mutate on a very fast time scale. A single drug may be able to kill a large fraction of the current virus population. However, a resistant mutant can quickly reinfect the individual. Within 2 to 4 weeks the virus load in a patient can return to 100%. Thus, the standard therapy is now to use several drugs simultaneously.

As an aside, only 10% of the infected cells actually produce virions. Most infected cells have defected genomes such that they can not generate new virions.

4.3.2 Protease Inhibitor

Protease inhibitors prevent infected cells from producing infectious virus V, but instead, *non-infectious* virus W. Thus, while the existing virus cells can still cause $S \to I$, when I produce virions they are W type.

$$\frac{dS}{dt} = b - \beta SV - \mu_s S, \tag{4.11}$$

$$\frac{dI}{dt} = \beta SV - \mu_i I, \tag{4.12}$$

$$\frac{dV}{dt} = -\mu_v V, \tag{4.13}$$

$$\frac{dW}{dt} = kI - \mu_w W. \tag{4.14}$$

Depending on the relative sizes of decay constants the decay of the total number of virions $(V+W)$ virions can be $\exp(-t)$ or $t\exp(-t)$.

4.3.3 Long-lived infected cells

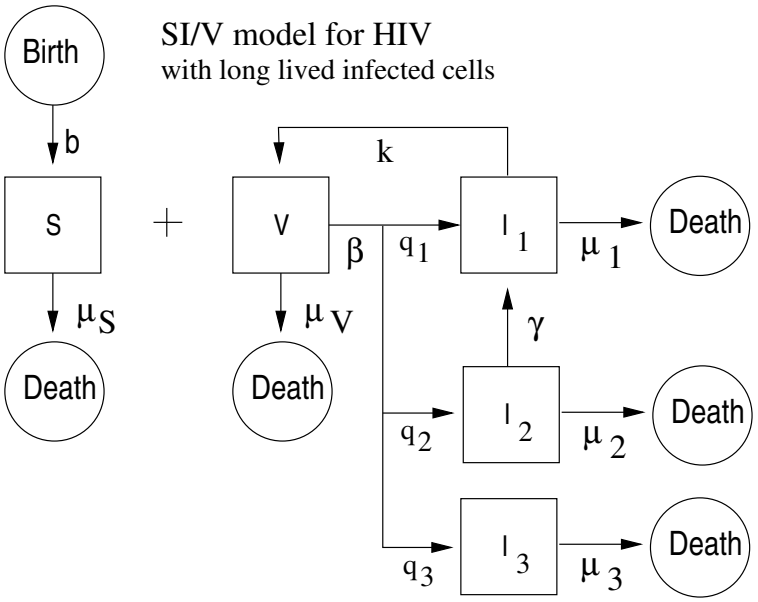
We mentioned earlier only 10% of the infected cells produce almost 99% of the virions. In sum, we have

- I_1: short-lived virus producing cells.

And a number of classes of long-lived cells consisting of

- I_2: latently infected cells, which do not presently produce virions but can become reactivated at later times. We assume this occurs with a mean time $1/\gamma$ and reassign the cell to the I_1 class.

- I_3: cells with a defective virus that can not reproduce.
- Chronic producers but in only small amounts.



- q_i is the probability of, or fraction of, newly infected cells that enter class I_i. $q_1 + q_2 + q_3 = 1$.
- I_2 and I_3 are the long-lived infected cells so $\mu_1 \gg \mu_2,\ \mu_3$.
- $\mu_1 > \mu_2 + \gamma > \mu_3$.

$$\frac{dS}{dt} = b - \beta SV - \mu_s S, \tag{4.15}$$
$$\frac{dI_1}{dt} = q_1 \beta SV - \mu_1 I_1 + \gamma I_2 \tag{4.16}$$
$$\frac{dI_2}{dt} = q_2 \beta SV - \mu_2 I - \gamma I_2 \tag{4.17}$$
$$\frac{dI_3}{dt} = q_3 \beta SV - \mu_3 I \tag{4.18}$$
$$\frac{dV}{dt} = k I_1 - \mu_v V. \tag{4.19}$$

Steady-states Straightforward analysis identifies the steady-states and identifies a relevant R_0. There is a steady-bifurcation from disease-free to the non-zero endemic state.

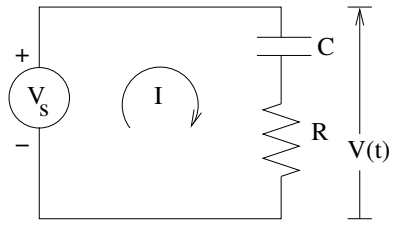
Drug-therapy Of particular interest is the effect of anti-viral therapy.

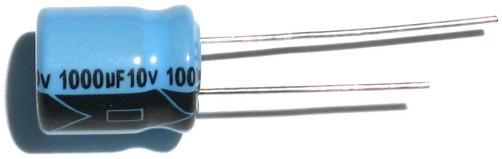
- Consider the case when the virus is prevented from producing new cells, $\beta = 0$. The susceptible cells decouple and we again have a linear set of equations for the number of infected cells.
- The important point is that in solving these equations the decay in the number of virions is governed by three rate constants, μ_v: death rate of virus, μ_1 the death rate of the virus producing cells in class I_1, and $\mu_2 + \gamma$.
- Each constant can be identified with an interval of the decay data/curve for virions. In particular, the long-term exponential tail is again determine by the slowest decay constant, which in this case is $\mu_2 + \gamma$.

Chapter 5

Circuit Theory

5.1 Series circuit





- $q(t)$ = CHARGE as a function of time.
- $I(t) = dq/dt$ = CURRENT = flow of charge as a function of time.
- $V(t)$ = VOLTAGE = "battery" pumps charges to higher energy (up hill).
- R = RESISTOR = impedes the flow of charges.
- C = CAPACITOR = "holding tank" for charges to maintain potential energy difference.

OHM's law: Drop in voltage (energy) across R.

$$V_R(t) = I(t)R$$

Let $g = \frac{1}{R}$ = CONDUCTANCE.

$$V_R(t) = I(t)\frac{1}{g}.$$

FARADAY'S law:

$$V_c(t) = \frac{q(t)}{C}.$$

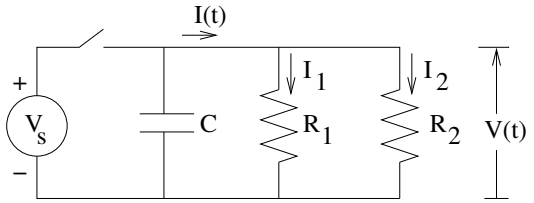
Charges on the "plates" maintain a voltage difference.

$$\frac{dV_c}{dt} = I(t)\frac{1}{C}$$

KIRCHOFF'S law: The voltage supplied, i.e., the energy need to "raise" the charges from ground to $V(t)$, is equal to the sum of the voltage drops over the circuit elements.

$$V(t) = V_R(t) + V_C(t). \tag{5.1}$$

5.2 Parallel circuit



$t < 0$**:**

Switch is closed.

Charge flows from source to circuit.

Charge builds on the capacitor until

$$V_C = \frac{q}{C} = V_S$$

$t = 0$**:**

Switch is open. No longer a supply from the source.

Current drains from C through the R_j.

Voltage drop across each must be the same.

KIRCHOFF'S law: At the *nodes/junctions*

$$\sum \text{input currents} = \sum \text{output currents}$$

$$I(t) = I_1(t) + I_2(t)$$

$$-C\frac{dV}{dt} = g_1 V(t) + g_2 V(t)$$

Negative sign due to current coming out the + side of the capacitor.

$$\frac{dV}{dt} = -\frac{g_1 + g_2}{C} V$$

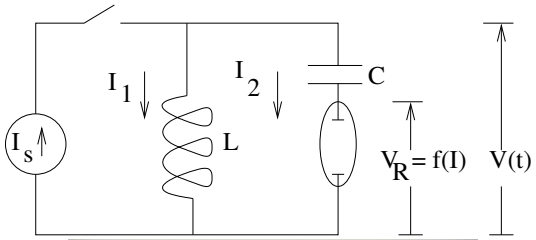
$$\frac{dV}{dt} = -kV, \quad V(0) = V_s (\text{initial voltage on capacitor})$$

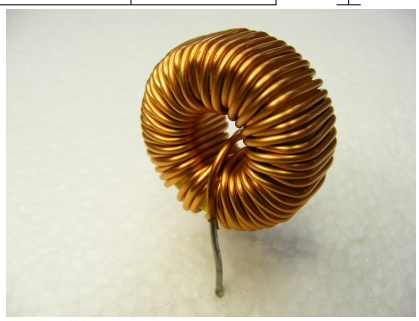
Solving

$$V(t) = V_s e^{-kt}$$

The voltage decays until the capacitor is completely drained.

5.3 Van der Pol oscillator





- L = INDUCTOR. Stores energy in a magnetic field due to time changing $I(t)$. Typically a coil of wire/conductor.

$$V = L\frac{dI}{dt}$$

- Nonlinear circuit element. Old days = tubes. Nowadays = integrated circuit.

$$V_R = f(I) = -R(I - \frac{1}{3}I^3)$$

If $I \ll 1 \Rightarrow V \approx -IR$: Negative resistor.
If $I \gg 1 \Rightarrow V \approx +\frac{R}{3}I^3$: Positive nonlinear resistor.

$t < 0$: Switch closed. Current source charges the capacitor.
$t = 0$: Open the switch.

$t > 0$:

$$\text{KIRCHOFF'S law:} \quad I_1 + I_2 = 0$$

$$\text{INDUCTOR:} \quad V = L\frac{dI_1}{dt}$$

$$\begin{aligned} \text{CAPACITOR:} \quad V - V_R &= \frac{1}{C}q_2(t) && (5.2) \\ \frac{d}{dt}(V - V_R) &= \frac{1}{C}I_2(t) && (5.3) \end{aligned}$$

$$\text{RESISTOR:} \quad V_R = f(I_2)$$

$$\begin{aligned} \frac{d}{dt}\left[L\frac{dI_1}{dt} - f(I_2)\right] &= \frac{1}{C}I_2 \Rightarrow I_1 = -I_2 \\ -LI_2'' - \frac{d}{dt}f(I_2) &= \frac{1}{C}I_2 \\ -LI_2'' - \frac{d}{dt}\left[-R(I_2 - \frac{1}{3}I_2^3)\right] &= \frac{1}{C}I_2 \\ -LI_2'' + R(I_2' - I_2^2 I_2') &= \frac{1}{C}I_2 \\ \Rightarrow & \\ LI_2'' + R(I_2^2 - 1)I_2' + \frac{1}{C}I_2 &= 0 \\ I_2'' + \frac{R}{L}(I_2^2 - 1)I_2' + \frac{1}{LC}I_2 &= 0 \qquad (5.4) \end{aligned}$$

Let $T = 1/\sqrt{LC}t$ so that

$$\frac{d}{dt} = \frac{d}{dT}\frac{dT}{dt} = \frac{d}{dt}\frac{1}{\sqrt{LC}}.$$

$$\begin{aligned} \frac{1}{LC}I_2'' + \frac{R}{L\sqrt{LC}}(I_2^2 - 1)I_2' + \frac{1}{LC}I_2 &= 0 \\ I_2'' + \frac{RLC}{L\sqrt{LC}}(I_2^2 - 1)I_2' + I_2 &= 0 \end{aligned} \tag{5.5}$$

Let $\delta = R\sqrt{\frac{C}{L}}$.

Van der Pol's equation:

$$I_2'' + \delta(I_2^2 - 1)I_2' + I_2 = 0 \tag{5.6}$$

Analogy to mass-springs:

- Inductance $\Rightarrow$ mass.
- Nonlinear damping
- Capacitance $\Rightarrow$ spring.

Recall that $I_2 = q' =$ charge on the capacitor.

$$q''' + \delta(q'^2 - 1)q'' + q' = 0 \tag{5.7}$$

Integrate once.

Raleigh's equation

$$q'' + \delta(\frac{1}{3}q'^3 - q') + q = 0 \tag{5.8}$$

Rewrite as a system: Drop the 1/3 (absorb it into the constants). Let $q = u$, $u' = v$. Find v'.

$$\begin{aligned} u' &= v \\ v' &= -\delta(v^3 - v) - u \end{aligned} \tag{5.9}$$

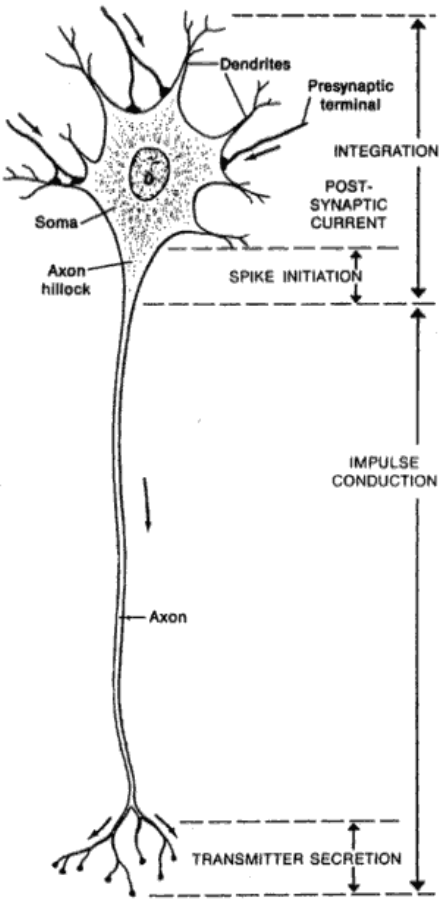
Chapter 6

Neuron Conduction

Figures are from *Mathematical Models in Biology*, by Leah Edelstein-Keshet, (SIAM, 2005).

6.1 Neuron cell structure

- Dendrites: receive inputs from neighboring cells and transmit them to the soma.
- Soma: collects the inputs and sums/integrates them to determine if the cell should fire or not fire.
- Hillock: initiates the electrical pulse.
- Axon: transmits the pulse, called the *action potential*.
- Synapse: Gaps between the cells. Chemical currents carry signals across the synapse.



igure 8.2 Schematic representation of a neuron owing the cell body (soma) which receives stimuli a the dendrites, the axon along which impulses e conducted, and the terminal branches that form connections (synapses) with other neurons. [From Eckert, R., and Randall, D. Animal Physiology, *2d edition. W. H. Freeman and Company. Copyright © 1983, p. 179.]*

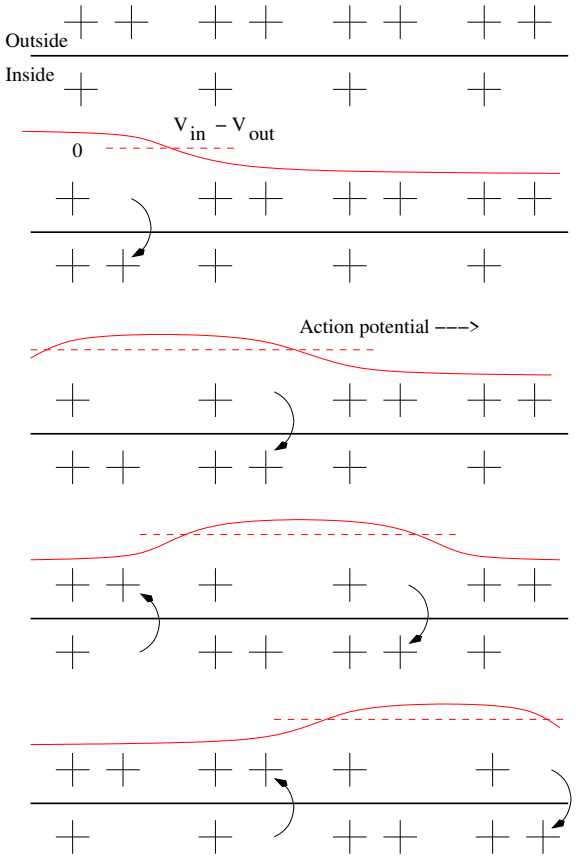
6.2 Pulse transmission

- **NOT** like an electrical cable where electrons flow down the cable.
- There is a voltage difference (action potential) between the inside and outside of the axon membrane that travels down the axon.
- Voltage difference is due to concentration differences in ions, predominantly Na+ and K+, that flow in and out of the cell, i.e., across the axon membrane.
- Ions flow through *pores/channels* that regulate the flow rate.

Action potential

- In its resting state, the inside has a lower net positive charge than the outside.
  $V_{in} - V_{out} < 0$

- Positive (negative) ions would like to flow in (out). Pumps at the pores maintain the concentration gradient of charge.
- The action potential travels down the axon as a net positive charge flows inside the cell so that $V_{in} - V_{out} > 0$. Charge then flows back out returning that area of the axon to the resting potential.



6.3 Action Potential – details

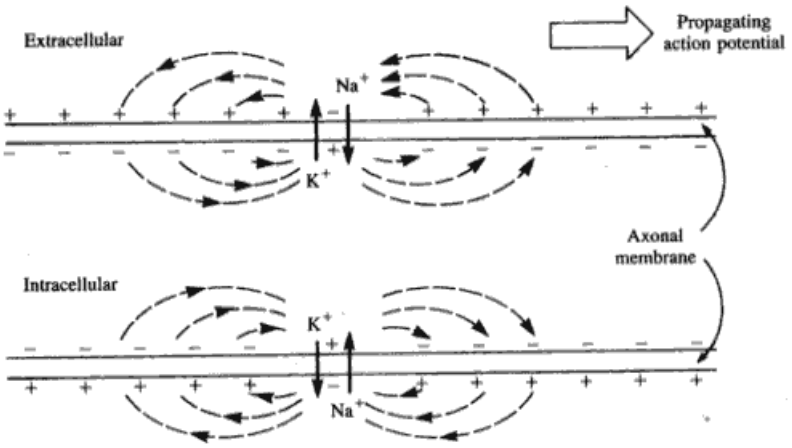


Figure 8.5 When the axon of a neuron receives a sufficiently large stimulus at some point along its length, the conductivities of the membrane for Na^+ *and* K^+ *changes. This permits ions to cross the membrane, creating local currents. Since adjacent portions of the membrane are thereby stimulated, the wave of activity known as the action potential can be propagated.*

- The axon hillock starts "depolarizes" the end of axon (makes the inside net positive). This initiates nearby sodium pores to open so that...
- Na+ pores open so that sodium flows from the outside to the inside so that the inside becomes positive with respect to the outside.
- After a slight delay K+ pores open so that potassium can flow from the inside to the outside, so that the outside returns to being net positive.
- The sodium pores, followed by the potassium pores, then close returning that portion of the axon to the resting state.
- The process repeats.

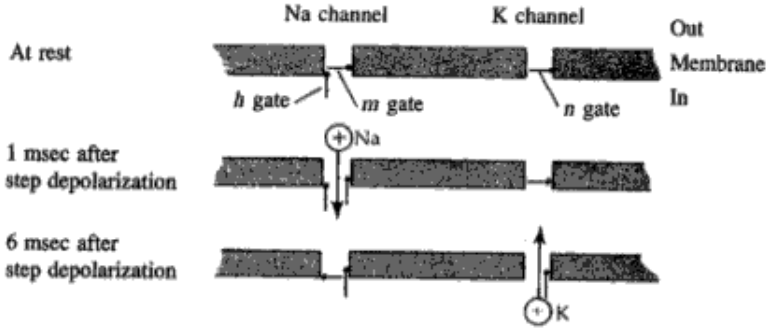


Figure 8.6 Schematic time sequence depicting the membrane of the axon. Shown are separate pores, governed by gates, for the ions Na^+ *and* K^+*. At rest the* m *and* n *gates are closed. When a threshold voltage is applied, the* m *gates open rapidly, followed by changes in the other gates. [From Kuffler, Nicholls, and Martin (1984), p. 149, fig. 12.* From Neuron to Brain, *2nd edition, by permission of Sinauer Associates Inc.]*

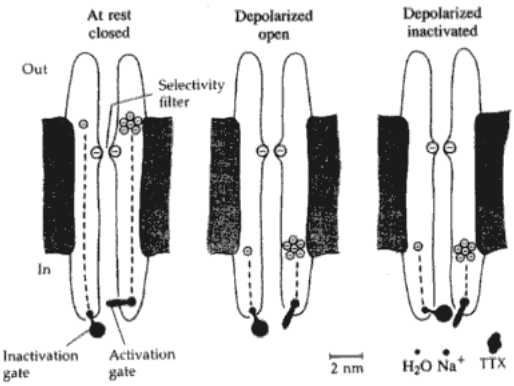


Figure 8.7 Recent biochemical, electron microscope, and electrophysiological information leads to this schematic sketch of a voltage-sensitive sodium channel. Shown are the activation gates and a constriction that permits selectivity to Na^+. *Also shown to scale are molecules of water, sodium, and the blocking agent tetrodotoxin (TTX). [From Kuffler, Nicholls, and Martin (1984), p. 156, fig. 15.* From Neuron to Brain, *2nd edition, by permission of Sinauer Associates Inc.]*

6.4 Voltages, Conductances and Capacitance

- The ion pores can be thought of as variable resistors. When they are closed they have a high resistance. When they are open, they have a low resistance.
- Conversely, in terms of conductances, first the conductance of the sodium channels increases so that Na+ flows in, then the conductance of the potassium channels increases so that K+ flows out.
- The conductances are functions of the applied voltages.
- The axon membrane acts to separate the charges of the inside from the outside and thus has an associated capacitance.

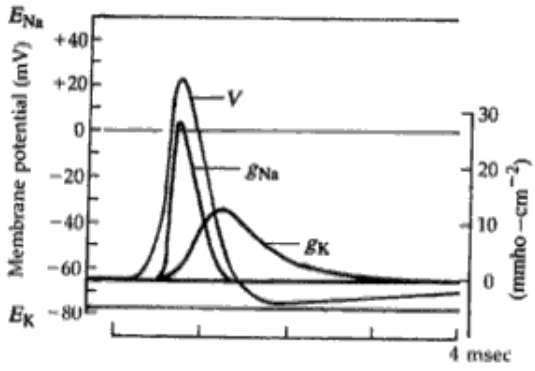


***Figure 8.3** The action potential consists of local changes in voltage across the axon membrane accompanied by changes in the conductivities of the membrane to* Na^+ *and* K^+*(g_{Na}, g_K) in a time sequence shown here.* (Note: *mho, a unit commonly used for conductance, is equivalent to* $1/ohm$.) *This signal is generally propagated along the neuronal axon from soma to terminal branches. [After Hodgkin and Huxley (1952), from Kuffler, Nicholls, and Martin (1984) p. 151, fig. 13A,* From Neuron to Brain, *2nd edition, by permission of Sinauer Associates Inc.]*

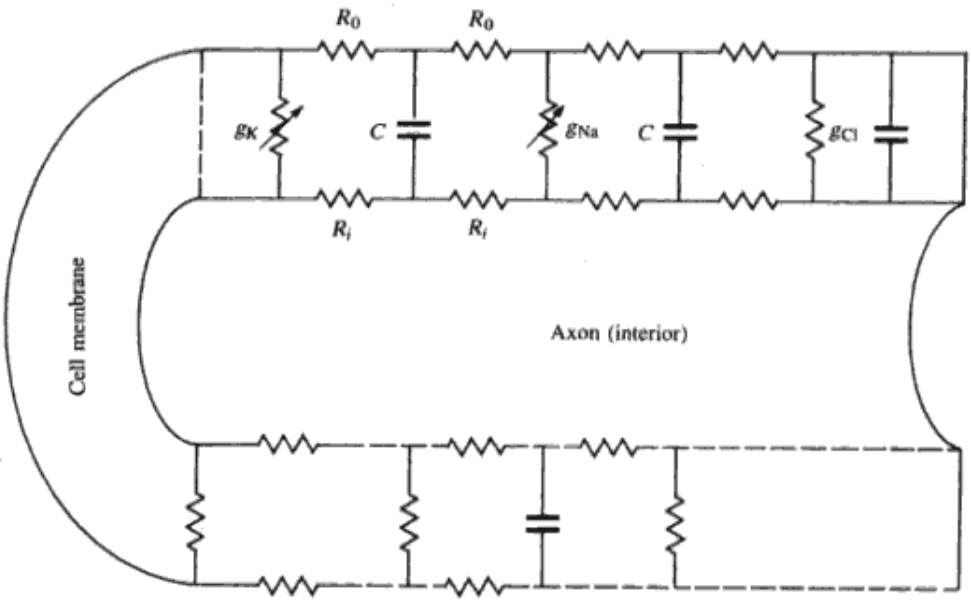


Figure 8.9 A schematic version of the electric wiring diagram roughly equivalent to the axonal membrane. g_K, g_{Na}, *and* g_{Cl} *are the voltage-dependent conductivites to* K^+, Na^+, *and* Cl^-; R_i *and* R_0 *represent the resistance of inside and outside environments;* C *depicts the membrane capacitance. (*Note: g_{Cl} *is assumed to be constant.)*

6.5 Hodgkin-Huxley Equations

- $q(x,t)$ = charge density inside the axon as a function of position and time.
- C = capacitance of the membranes.
- $v(x,t)$ = deviation of the membrane voltage from the resting state as a function of position and time.

$$v(x,t) = \frac{1}{C} q(x,t). \tag{6.1}$$

Assume the axon is *voltage clamped* so that there is no variation in q or v with position. Experimentally, this is accomplished by inserting a thin wire along the length of the axon and applying a constant voltage along the entire length. Ionic currents and action potentials are still generated across the cell membrane but it is the same at all positions. Hence, we can remove the spatial dependence.

$$v(t) = \frac{1}{C} q(t) \tag{6.2}$$

or

$$\frac{dv}{dt} = \frac{1}{C} \frac{dq}{dt} \tag{6.3}$$

The net current dq/dt is due to

- $I_{NA}(t)$ = sodium ion current.

- $I_K(t)$ = potassium ion current.
- $I_L(t)$ = all other ionic currents.

$$\frac{dq}{dt} = -(I_{NA} + I_K + I_L) \tag{6.4}$$

where the negative sign is due to the fact that the ions are positively charged. Each of these currents depends upon the voltage applied across them according to Ohm's law, expressed in terms of conductances.

$$I_{NA} = g_{NA}(v)(v - v_{NA}), \qquad I_K = g_K(v)(v - v_K), \qquad I_l = g_L(v - v_L), \tag{6.5}$$

where the v_{NA}, v_K and v_L are constants and represent that portion of the membranes potential due to each of the different ions. Notice that each of the conductances g_{NA} and g_K are functions of the membrane voltage v, i.e., as the voltage across the membrane changes the conductivity of the different ions changes. Thus,

$$\frac{dv}{dt} = -\frac{1}{C}\left[g_{NA}(v)(v - v_{NA}) + g_K(v)(v - v_K) + g_L(v - v_L)\right]. \tag{6.6}$$

Hodgkin and Huxley did not have the experimental or theoretical ability to derive the functional dependence for $g_{NA}(v)$ and $g_K(v)$ from first principles or some physical laws. Instead, they used trial and error so that the mathematical description *best fit* experimental observations. The net results was that they needed to introduce three more dynamical variables n, m and h such that

$$g_{NA}(v) = \bar{g}_{NA} m^3 h, \qquad g_K(v) = \bar{g}_K n^4 \tag{6.7}$$

where

$$\frac{dm}{dt} = \alpha_m(v)(1 - m) - \beta_m(v)m, \tag{6.8}$$

$$\frac{dn}{dt} = \alpha_n(v)(1 - n) - \beta_n(v)n, \tag{6.9}$$

$$\frac{dh}{dt} = \alpha_h(v)(1 - h) - \beta_h(v)h, \tag{6.10}$$

and where

$$\alpha_m(v) = \frac{0.1(v + 25)}{e^{(v+25)/10} - 1}, \qquad \beta_n(v) = 4e^{v/18}, \tag{6.11}$$

$$\alpha_n(v) = \frac{0.01(v + 10)}{e^{(v+10)/10} - 1}, \qquad \beta_n(v) = 0.125e^{v/80}, \tag{6.12}$$

$$\alpha_h(v) = 0.07e^{v/20}, \qquad \beta_h(v) = \frac{1}{e^{(v+30)/10} + 1}. \tag{6.13}$$

To be sure, that was *a lot* of trial and error. In hindsight, we can interpret the equations for n, m and h as concentrations of various proteins that depend on the voltage v and that control the pore (channel) conductivity. While the detail molecular mechanisms are much better understood at present, deriving the Hodgkin-Huxley equations from physical *laws* still has not been done. In spite of these *philosophical* inadequacies, the Hodgkin-Huxley equations have been extremely successful in understand the neuron action potentials and even predicting results that hadn't yet been observed.

Unfortunately, the results is a coupled system of four nonlinear differential equations. Thus, the phase space is 4D!

6.6 Slow vs. Fast: 4D to 2D

Fitzhugh observed that both n and h vary much more slowly than v and m. Thus, to first approximation, we will consider n and h as constants and study what happens to v and m.

$$\frac{dv}{dt} = -\frac{1}{C}\left[g_{NA}(v)(v - v_{NA}) + g_K(v)(v - v_K) + g_L(v - v_L)\right]. \tag{6.14}$$

$$\frac{dm}{dt} = \alpha_m(v)(1 - m) - \beta_m(v)m. \tag{6.15}$$

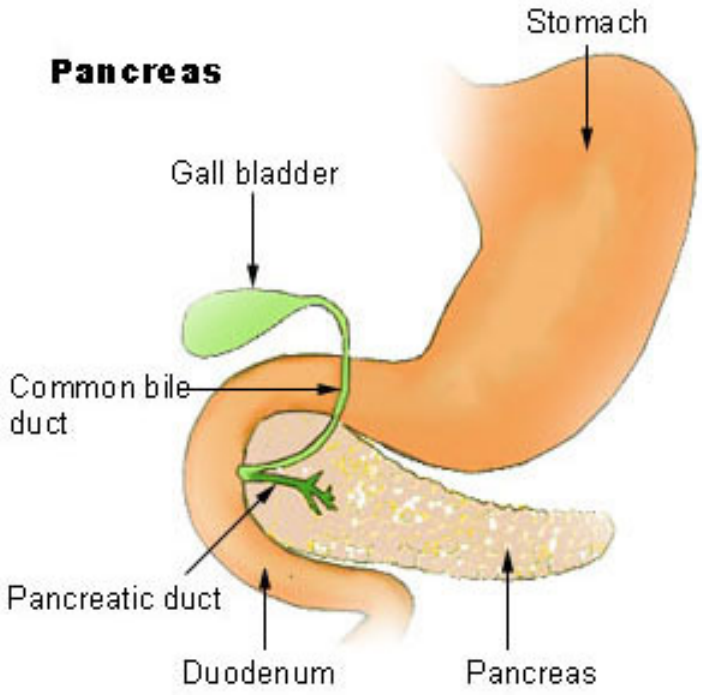
Chapter 7

Pancreatic β-cells

Figures are from "Mathematica Physiology," by J. Keener and J. Sneyd (Springer-Verlag, 1998)

Pancrease

- The exocrine portion of the pancrease secretes digestive enzymes that are carried through a duct to the duodenum.
- The endocrine portion of the pancrease is made up of the islets of Langerhans, which are groups of cells that releases hormones.
  - Alpha cells produce glucagon.
  - Beta cells produce insulin and amylin.
  - Delta cells produce somatostatin.
  - PP cells produce pancreatic polypeptide.
  - Epsilon cells produce ghrelin.
- In response to an increase concentration of glucose in the blood, the $\beta - cells$ release insulin which causes muscles and the liver to absorb the glucose. If glucose levels drop, then there is a decrease in the amount of insulin released, which causes the other body tissues to burn their stored glucose. Diabetes represents the ill-functioning of this feedback system.



Bursting

- The β-cells of the pancrease exhibit oscillations in the ionic concentrations across the cell membrane.
- The temporal evolution of the *beta*-cell oscillations are more complicated than the simple relaxation oscillations of the neuron.
- Generically, bursting is when there are time periods of very rapid oscillations separated by time periods of very slow change.

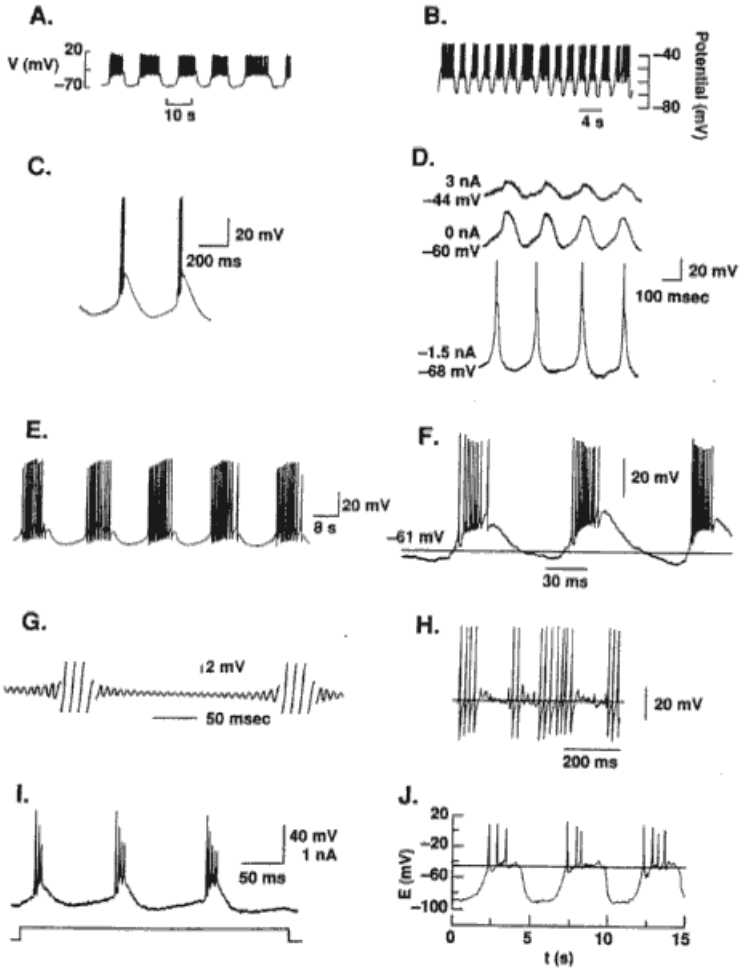


Figure 6.1 Electrical bursting in a range of different cell types. A: Pancreatic β-cell. B: Dopamine-containing neurons in the rat midbrain. C: Cat thalamocortical relay neuron. D: Guinea pig inferior olivary neuron. E: *Aplysia* R15 neuron. F: Cat thalamic reticular neuron. G: *Sepia* giant axon. H: Rat thalamic reticular neuron. I: Mouse neocortical pyramidal neuron. J: Rat pituitarygonadotropin-releasing cell. (Wang and Rinzel, 1995, Fig. 2.)

From "Mathematical Physiology," J. Keener and J. Sneyd (Springer, 1998)

Potassium and calcium channels

- We will consider one of the first models for bursting in the β-cells formulated by Chay and Keizer (1983). It ignores many cellular processes, while trying to identify those important to bursting.
- It relies on the inclusion of a slowly changing intracellular calcium concentration. However, since the time the model was proposed, the role of calcium in generating the bursting has been under debate.

Calcium activated potassium channel Calcium controls the conductance of one set of potassium passing pores through the cell membrane.

$$g_{K,Ca} = \bar{g}_{K,Ca} \frac{c}{K_d + c}$$

where c is the intracellular calcium concentration. Thus, for low c the conductance is low, while for high c the conductance saturates to a constant.

Voltage controlled potassium channel Similar to the Hodgkin-Huxley model for the neuron, the voltage difference across the cell membrane affects the conductance of this set of potassium channels.

$$g_K = \bar{g}_k n^4$$

Again similar to the Hodgkin-Huxley model, n represents the concentration of proteins that control the conductance of the channel. The concentration of n depends on the voltage according to

$$\frac{dn}{dt} = \alpha_n(v)(1-n) - \beta_n(v)n.$$

Voltage control calcium channel Similar to the Hodgkin-Huxley model but for calcium instead of sodium, the voltage controls the conductance of calcium across the cell membrane.

$$g_{Ca} = \bar{g}_{Ca} m^3 h$$

m and h represent contentrations of various proteins

$$\begin{aligned} \frac{dm}{dt} &= \alpha_m(v)(1-m) - \beta_m(v)m, \\ \frac{dh}{dt} &= \alpha_h(v)(1-h) - \beta_h(v)h. \end{aligned}$$

It should be noted that the definitions for the functions $\alpha(v)$ and $\beta(v)$ for m, n and h are slightly different that in the Hodgkin-Huxley model. Specifically, the voltage is shifted by a constant amount v^* such that $v \to v + v^*$.

Voltage equation The membrane provides capacitance by separating charges from the inside to the outside of the cell. The total current through the cell membrane is the sum of the potassium, calcium and other miscellaneous ionic currents.

$$C\frac{dv}{dt} = (g_{K,Ca} + g_K)(v - v_K) + 2g_{Ca}(v - v_{Ca}) + g_L(v - v_L).$$

At this stage, the model is very similar to the Hodgkin-Huxley equations in that we have ODEs for the membrane voltage v and the channel controlling variables m, n and h.

Intracellular calcium We also need an equation for the intracellular calcium, which controls one of the potassium channels.

$$\frac{dc}{dt} = \epsilon \left[\bar{g}_{Ca} m^3 h (v - v_{Ca}) - k_C c \right]$$

The calcium concentration depends on two effects.

1. The first term term represents how the calcium ion concentration responds to voltage differences across the cell membrane, which may drive positive calcium ions either into or out of the cell.

2. The second term given by $dc/dt \sim -k_c c$ models the response due to the presence of glucose in the cell. If the amount of glucose increases, k_c increases, causing an increased removal rate of calcium. If the amount of glucose decreases, k_c decreases, causing a decrease in the removal rate of calcium from the cell.

The constant ϵ is small ($\epsilon \ll 1$) indicating the the calcium concentration changes slowly.

Reduced model Similar the the Hodgkin-Huxley model the variables m and h change so slowly that they can be consider as constants. Thus, the resulting model for bursting of the pancreatic *beta*-cells is given by

$$\begin{aligned} \frac{dv}{dt} &= f_1(v, n, c), \\ \frac{dn}{dt} &= f_2(v, n, c), \\ \frac{dc}{dt} &= \epsilon g(v, c; k_c), \qquad \epsilon \ll 1. \end{aligned}$$

7.1 Slowly changing calcium

- With $\epsilon \ll 1$ then
$$\frac{dc}{dt} \approx 0.$$
- This implies that $c \approx constant$. The constant is found from the third equation by solving
$$g(v, c; k_c) = 0$$
for c.
- The result is that $c = c(v; k_c)$.
- Thus, we can study the first two equations in the phase plane
$$\begin{aligned} \frac{dv}{dt} &= f_1(v, n, c(v; k_c)), \\ \frac{dn}{dt} &= f_2(v, n, c(v; k_c)) \end{aligned}$$

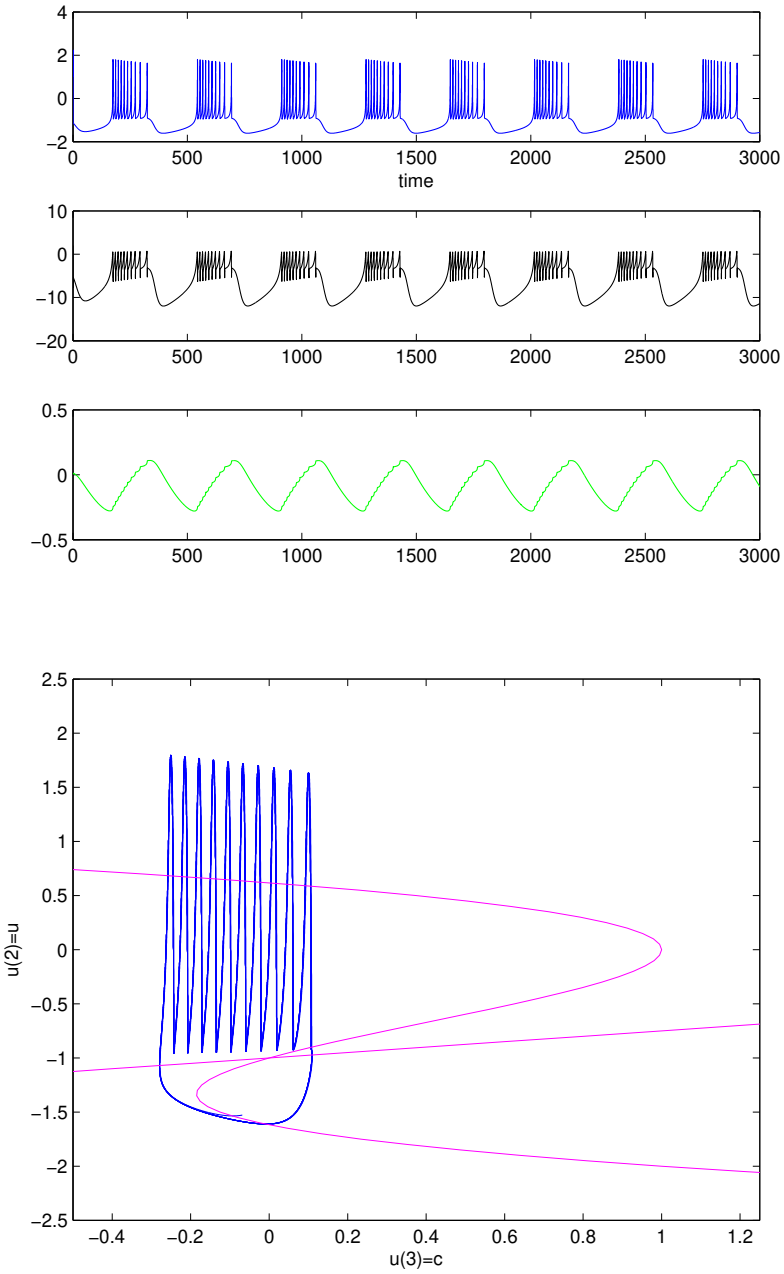


Figure 7.1: Top: u (blue), v (black) and c (green) for $\epsilon = 0.005$ and $\beta = 4.0$. Bottom: (u, c) phase plane superimposed on the (u, c) bifurcation curve and the $c' = 0$ nullcline.

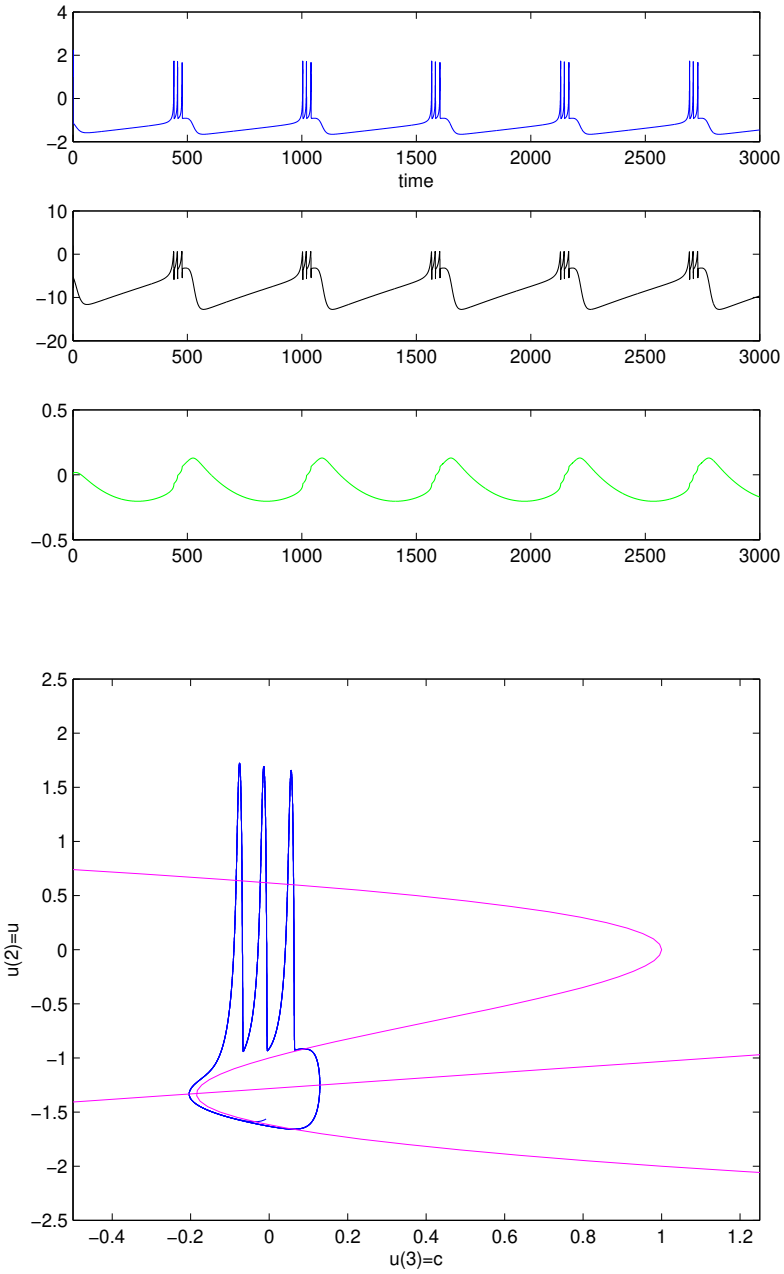


Figure 7.2: Top: u (blue), v (black) and c (green) for $\epsilon = 0.005$ and $\beta = 5.13$. Bottom: (u, c) phase plane superimposed on the (u, c) bifurcation curve and the $c' = 0$ nullcline.

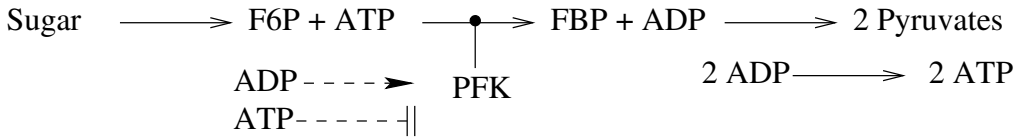
Chapter 8

Biochemical oscillations

Presentation based on material in the following:
(1) C.P. Fall, E.S. Marland, J.M. Wagner and J.J. Tyson, *Computational Cell Biology* (Springer-Verlag, New York, 2002)
(2) S.P. Ellner and J. Guckenheimer, *Dynamical Models in Biology* (Princeton Univ. Press, Princeton, NJ, 2006)

8.1 Glycolysis

Glycolysis refers to the process of converting sugar to alcohol. Instead of a steady production, the process can exhibit oscillations whereby conversion is high, then low, then high, etc. The figure below roughly describes glycolysis in anaerobic yeast. First, sugar supplies the molecule fructose-6-phosphate (F6P). Next, the enzyme phosphofructokinace (PFK) is the catylist for the conversion of F6P to fructose-1,6-biphosphate (FBP). In the process ATP donates the phosphate-group and is converted to ADP. Finally, FBP is used in the production of Pyruvate. During this last stage of the process 2 ADP and converted to ATP. Given that the goal of glycolysis is to generate energy, which in living cells is supplied by ATP, the intermediate step is sometimes referred to as the investment stage (uses one ATP), while the latter step is the payoff stage (generation of 2 ATP).



Not only is there a net production of ATP, but both ATP and ADP regulate the process. A surplus of ATP relative to ADP in the cell tends to deactivate the PFK reducing production. However, if ATP is in short supply such that there is a surplus of ADP, PFK is activated and the process is increased. This describes a *negative feedback* situation where excess production is controlled by the product slowing the process. Most of the time the system continually adjust to changes always seeking a new steady state. However, sometimes the process becomes unstable and oscillations are exhibited.

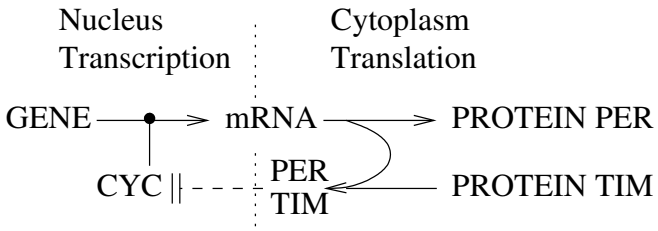
8.2 Circadian Rythms

Circadian rythms referred to many biological processes that are synchronized to the daily 24-hour light-dark cycle. The circadian oscillations exist all the way down to cellular processes and persist even in the absense of an external periodic light source (e.g., the sun). One example is the generation of the protein PER, which provides negative feedback to control its production.

The generation of proteins has two main steps. The transcription step occurs inside the nucleus, followed by the translation step that occurs outside the nucleus in the cytoplasm. As protein is transported back inside the nucleus in inhibits futher production, thus providing negative feedback.

- Gene expression has two main steps:
  (1) Transcription of DNA produces messenger RNA (mRNA).
  (2) Translation produces produces proteins with amino acids.
- Proteins regulate DNA transcription by selectively blocking or enhancing the expression of genes.
- DNA $\Rightarrow$ Proteins $\Rightarrow$ DNA $\Rightarrow \ldots$: Feedback loops.

One example is the protein PER, which exists in Drosophila melanogaster (a fly), whose production exibits and 24 hour oscillation. Generation of the messenger RNA is controlled by transcription factors CLK and and CYC. Once PER is generated, some binds with another protein called TIM, which reenter the nucleus and disrupt the transcription activity of CLK and CYC. We shall see that not only is the negative feedback important in the generation of oscillations, but also the delay time that it takes for the PER-TIM combination to affect transcription.



8.3 The Goodwin Oscillator

One of the first models to attempt to describe biochemical oscillations is the Goodwin Oscillator. It consists of three equations for X_1, the concentration of mRNA, X_2, the concentration of protein, and X_3, the end product of the protein that provides negative feedback on the generation of the mRNA.

$$\frac{dX_1}{dt} = \frac{v_0}{1 + \left(\frac{X_3}{K}\right)^p} - k_1 X_1, \tag{8.1}$$

$$\frac{dX_2}{dt} = v_1 X_1 - k_2 X_2, \tag{8.2}$$

$$\frac{dX_3}{dt} = v_2 X_2 - k_3 X_3. \tag{8.3}$$

The k_j represents the rates of degradation of each molecule and is assumed to occur exponentially, i.e., govern by a Poison process. The v_j are the rates of transcription, translation, and catalysis, the latter being the generation of product by the protein. The generation rate of mRNA is reduced by increased levels of the product X_3, where K is a binding constant (makes the units work out) and p is the cooperativity. p refers to the degree of cooperativity of the feedback process. Chemically, cooperative kinetics refers to when the catalyzing enzyme has a higher rate of action if there is more than one substrate bound to it. A larger p means that there are $p = 2$, 3,... binding sites for substrate and that if there are more substrates attached, the enzyme-substrate complex generates product faster. However, we see here that in the negative feedback process a larger p will increase the regulation of mRNA generation.

Before analysizing, we non-dimensionlize with the change of variables

$$x_1 = \frac{v_1 v_2}{k_2 k_3 K} X_1, \quad x_2 = \frac{v_2}{k_3} K X_2, \quad x_3 = \frac{1}{K} X_3, \quad t_{new} = \alpha t, \quad \alpha = \frac{v_0 v_1 v_2}{k_2 k_3 K} \tag{8.4}$$

The simpler Goodwin oscillator is

$$\frac{dx_1}{dt} = \frac{1}{1 + x_3^p} - b_1 x_1, \tag{8.5}$$

$$\frac{dx_2}{dt} = b_2(x_1 - x_2), \tag{8.6}$$

$$\frac{dx_3}{dt} = b_3(x_2 - x_3). \tag{8.7}$$

where $b_j = k_j/\alpha$.

8.4 The Repressilator

Detailed modeling of intercellular processes remains extremely challenging.

- While we know what the constituent species (mostly, maybe) are in these reactions, we do not always have a firm understanding of the reaction rates or even the correct mass-action rate laws.
- To gain insight into these reactions, take an engineering approach: M.B. Elowitz and S. Leibler, "A synthetic oscillatory network for transcription regulators," Nature 403:335-338, 2000.
- Build from the ground up a network of reactions that operate as feedback loops. The reaction network generates a protein that fluoresces green on a time scale of hours, which is slower than the life cycle of the cells involved. Thus, the state of the system is being transcribed from generation to generation.
- Inserted the requisite gene encoding in Escherichia coli.
- Three repressor proteins:
  (1) *lacI*: inhibits the gene that codes for (2) *TetR*(mRNA (2)).
  (2) *TetR*: inhibits the gene that codes for (3) *cI*(mRNA (3)).
  (3) *cI*: inhibits the gene that codes for (1) *lacI*(mRNA (1)).

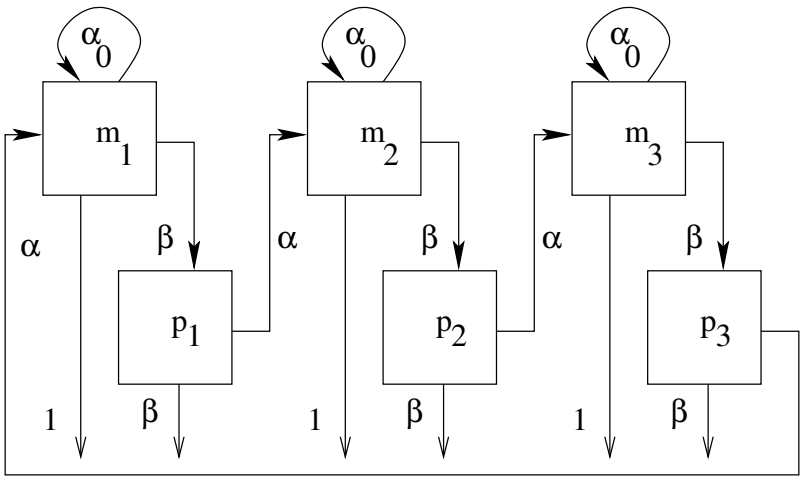


Figure 8.1: Block diagram illustrating the Repressilator model.

- Modeling assumptions:

  - m_i, $i = 1, 2, 3$ are the mRNA corresponding to *lacI*, *TetR* and *cI*, respectively.
  - p_i, $i = 1, 2, 3$ are the repressor proteins corresponding to *lacI*, *TetR* and *cI*, respectively.
  - m_i and p_i have constant probabilties of decay of 1 and β, respectively. Thus, they have mean lifetimes before decay of $1/1$ and $1/\beta$, respectively.
  - The synthesis rate of mRNA has two parts:
    α_0: one that is independent of the repressor protein (α_0).
    $(\alpha/(1 + p_j^n))$: one that is regulated by the repressor protein.
    n: "cooperativity" coefficient, which indicates how strongly the repressor protein acts on the mRNA. Will set $n = 2$.
  - The synthesis rate of the repressor protein p_i is proportional to the concentration of associated mRNA m_i.
  - All rate constants are assumed to be the same for each species.

$$\begin{aligned} \dot{m_i} &= -m_i + \frac{\alpha}{1 + p_j^n} + \alpha_0, \\ \dot{p_i} &= -\beta(p_i - m_i). \end{aligned}$$

$$i = 1 \Rightarrow j = 3, \quad , i = 2 \Rightarrow j = 1, \quad i = 3 \Rightarrow j = 2.$$

Conclusions: Given the modeling assumptions (e.g., equal rates among species)

- Not all chemical reactions settle to equilibrium.
- Oscillations in this model occur if there is a strong repressor dependent generation rate of mRNA. The text refers to this as "tight binding" of the repressor proteins.
- Such networks suggest possible basis for biological clocks and circadian rhythms.

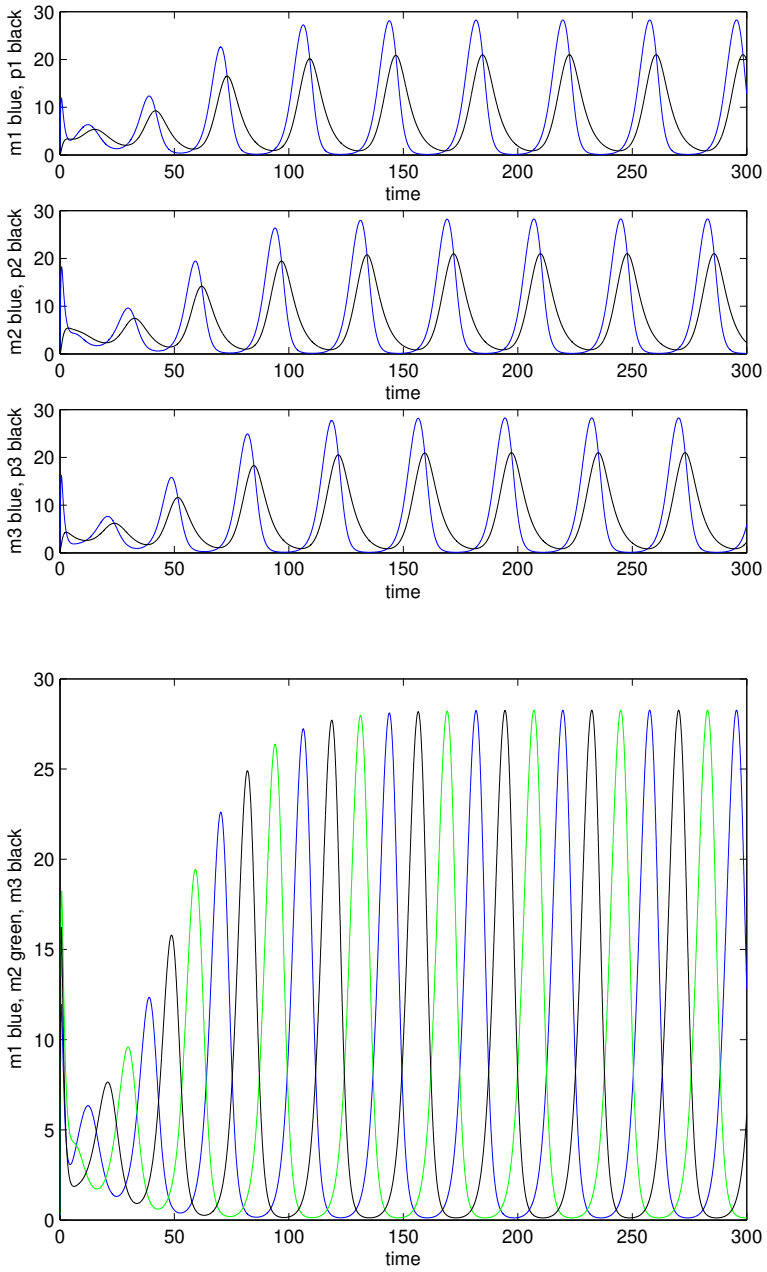


Figure 8.2: Reproduction of Ellner & Guckenheimer Fig. 4.2 with $(\alpha_0, \alpha, \beta, n) = (0, 50, 0.2, 2)$. Thus, there is no repressor independent mRNA generation but the repressor dependent generation is very strong.

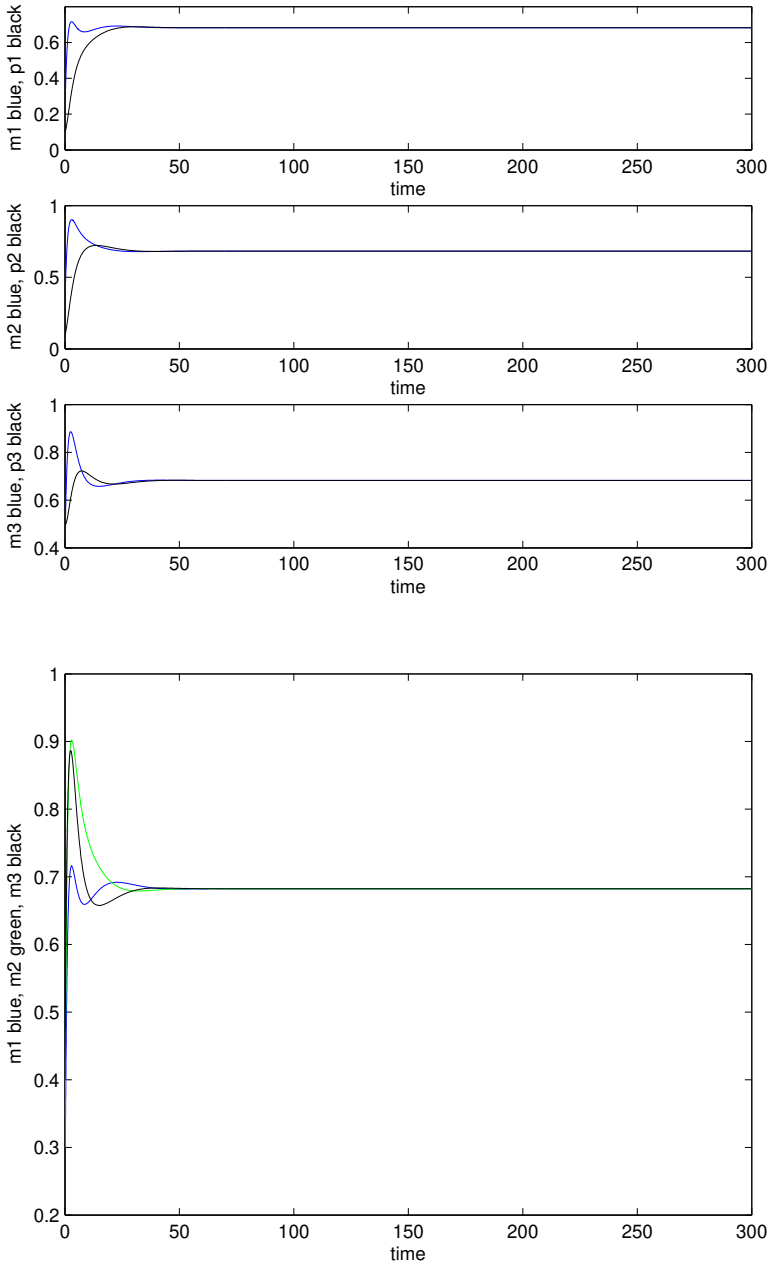


Figure 8.3: Reproduction of Ellner & Guckenheimer Fig. 4.3 with $(\alpha_0, \alpha, \beta, n) = (0, 1, 0.2, 2)$. Thus, there is no repressor independent mRNA generation but the repressor dependent generation is very relatively weak. There are no long term oscillations.

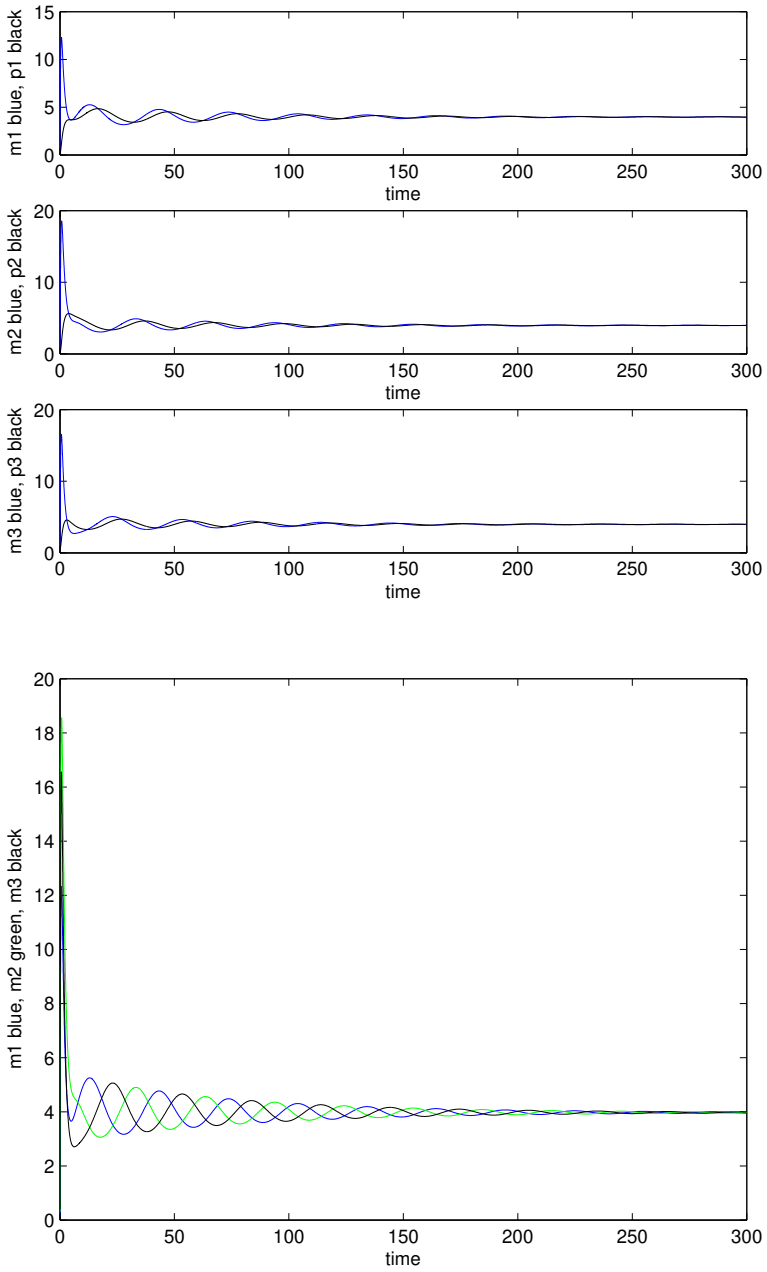
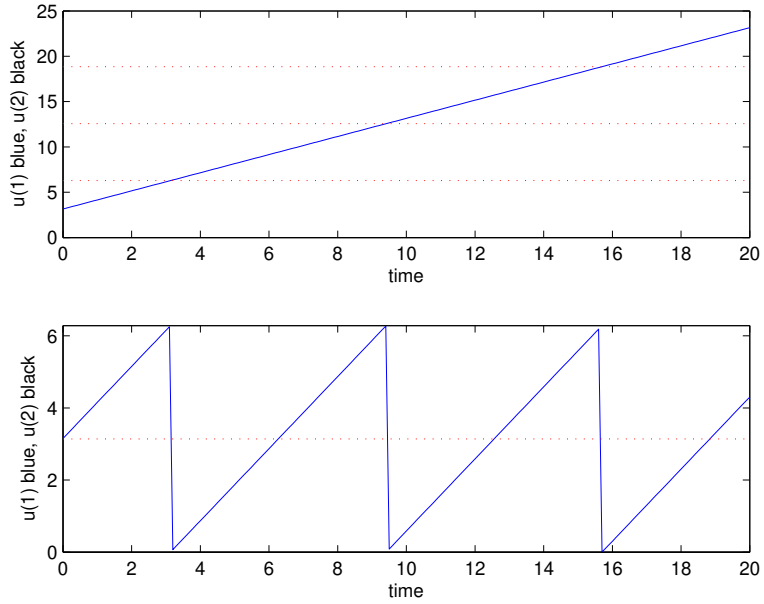


Figure 8.4: Reproduction of Ellner & Guckenheimer Fig. 4.4 with $(\alpha_0, \alpha, \beta, n) = (0, 1, 0.2, 2)$. Thus, there is both repressor independent and dependent mRNA generation. The system asymptotes to an equilibrium but slower than in Fig. 4.3.

Chapter 9

Phase oscillators



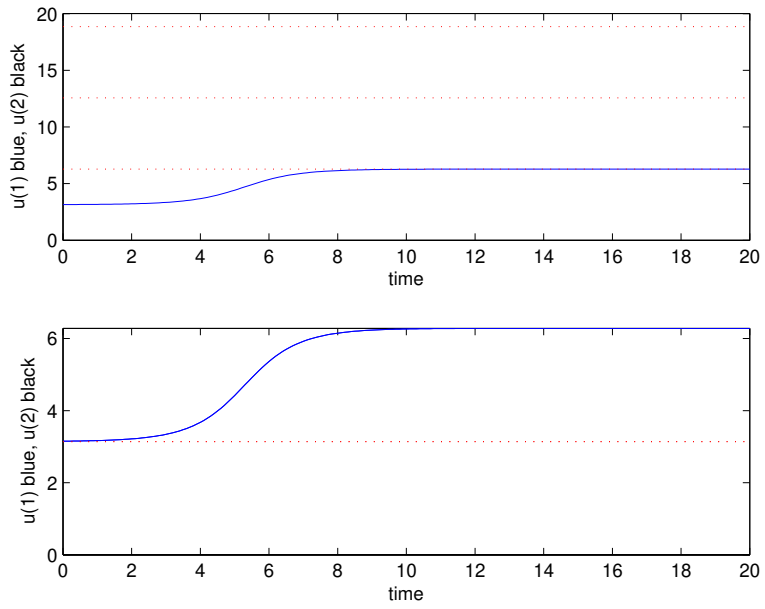


Figure 9.1: Nonuniform oscillator: $\omega = 0$, $a = 1$

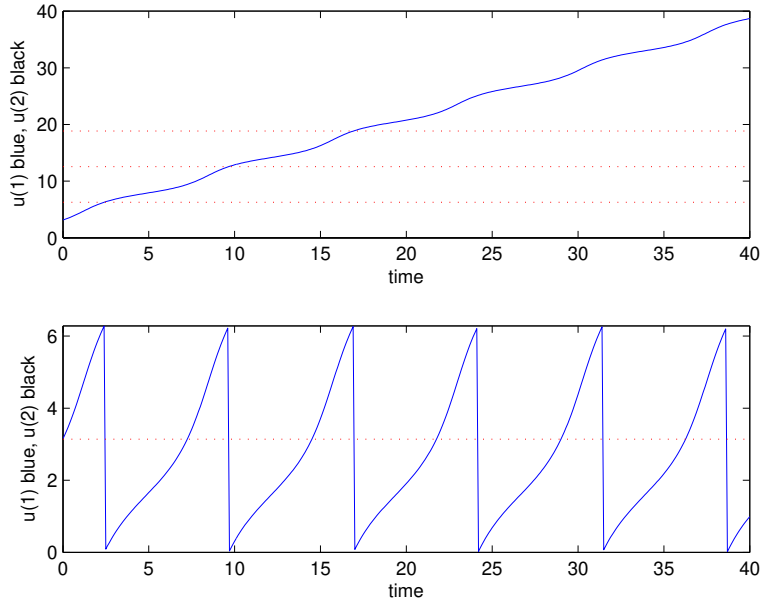


Figure 9.2: Nonuniform oscillator: $\omega = 1$, $a = 0.5$

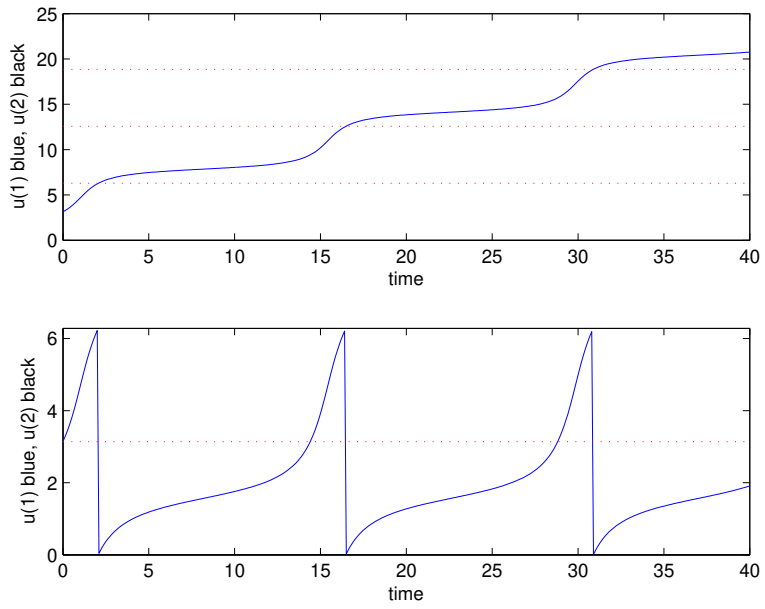


Figure 9.3: Nonuniform oscillator: $\omega = 1$, $a = 0.9$

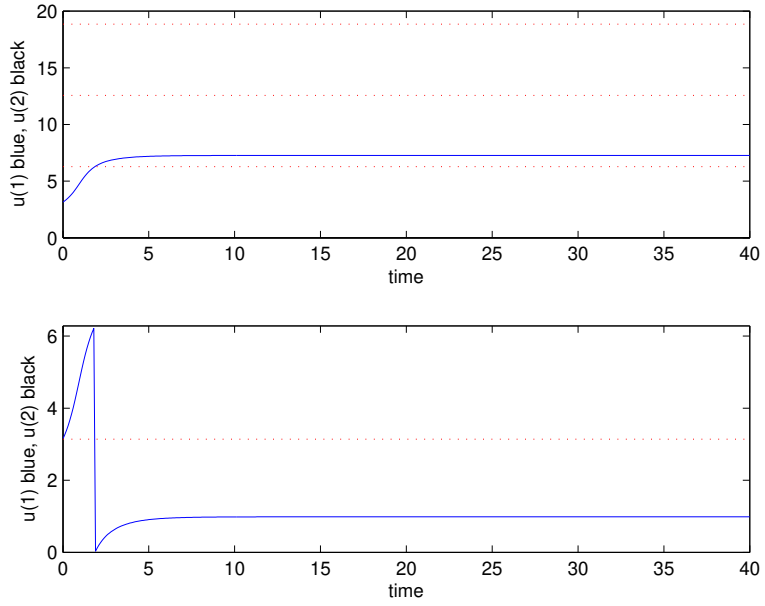


Figure 9.4: Nonuniform oscillator: $\omega = 1$, $a = 1.2$

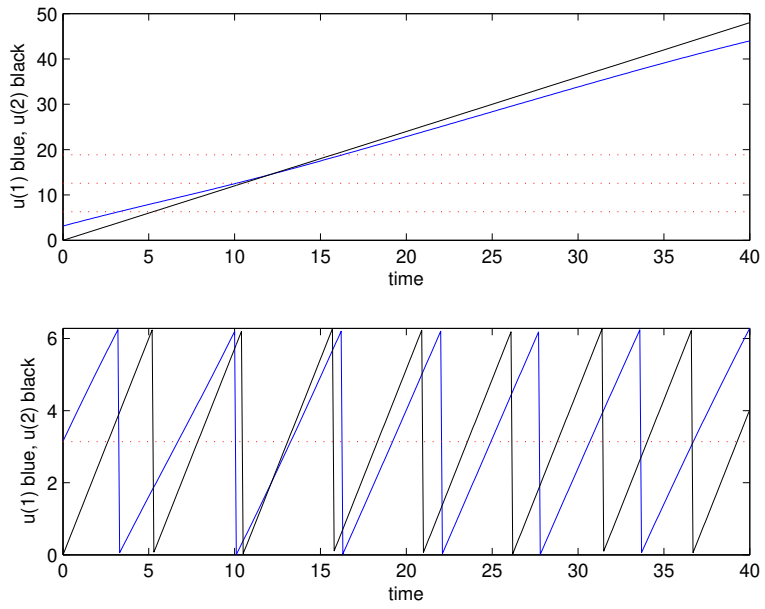


Figure 9.5: Firefly and a flashlight. No phase locking: $\Omega = 1.2$, $\omega = 1$, $A = 0.1$

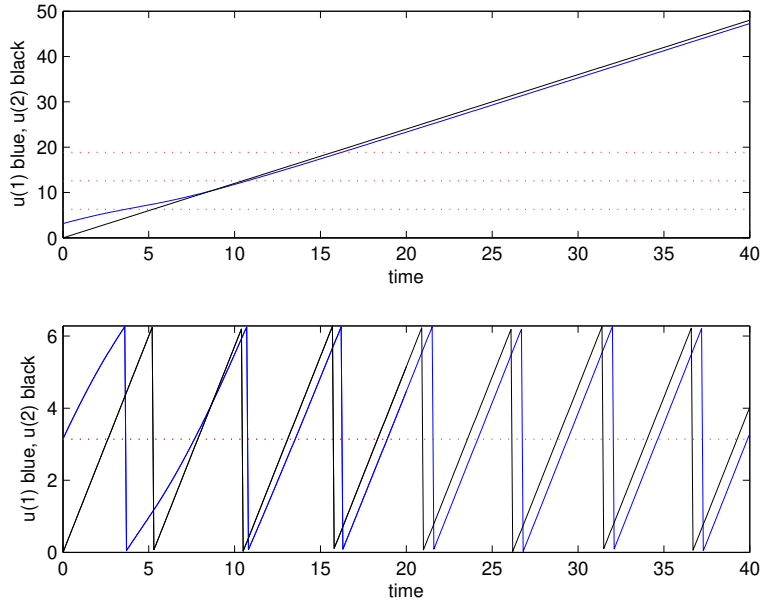


Figure 9.6: Firefly and a flashlight. Phase locking: $\Omega = 1.2$, $\omega = 1$, $A = 0.3$

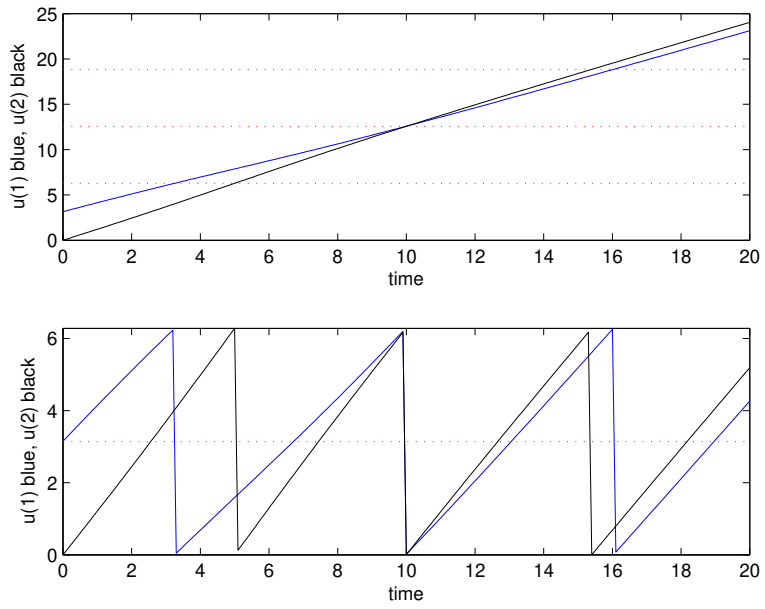


Figure 9.7: Two fireflies. No phase locking: $\Omega = 1.2$, $\omega = 1$, $A = 0.1$

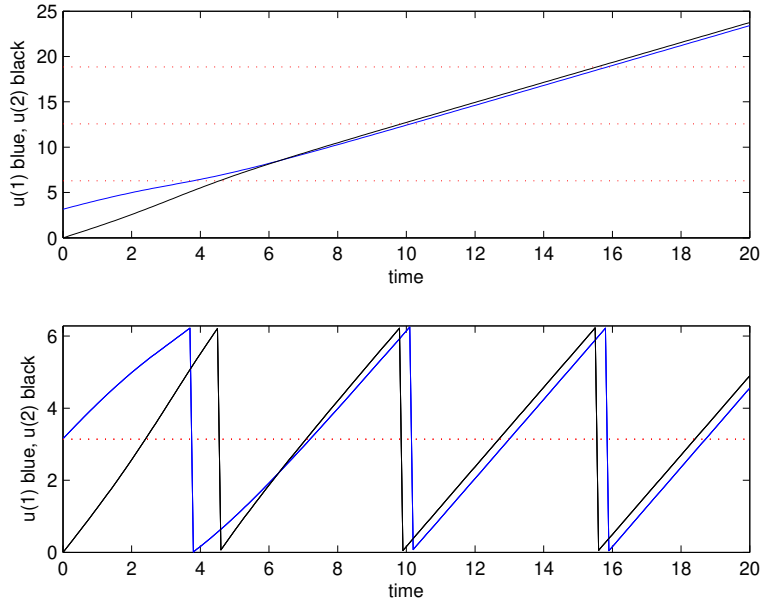


Figure 9.8: Two fireflies. Phase locking: $\Omega = 1.2$, $\omega = 1$, $A = 0.3$

Chapter 10

Tumor Growth

Presentation based on discussion in *Essential Mathematical Biology*, by N. Britton (Springer-Verlag, London, 2003).

10.1 Introduction

Cancerous cells must undergo many changes/mutations to circumvent the bodies natural protections against uncontrolled growth. Some characteristics/abilities are:

- Suppression of normal cell control of birth and death processes.
- Suppression of controls that act on maturation and differentiation.
- Avoidance of immune response to cells with non-self characteristics.
- Stimulation of production of own nutrient supply.
- Avoidance of protections against movement within the body.

These cancer-cell characteristics are the result of:

- Random genetic mutations.
- Chemical or radiation that cause DNA breaks and translocations.
- Viruses that may introduce foreign DNA.

Sequences of small changes build upon each other leading first to only a mild disorder or differentiation sometimes becoming so different and uncontrolled that a tumor developes. Cells that are part of multiplying cell populations have the highest propensity for developing cancers.

- Carcinomas: cancer of epithelial cells, e.g., skin, gut lining. Constitute 90% of cancers.
- Leukemias and Lymphomas: Cancer of blood and lymph system, respectively.

Cell regulatory processes regulate the rate of production of new cells or how many times a particular cell can go through mitosis (cell division). Mutations interrupt the control processes, maturation and differentiation processes, or the death process, such that the cell population growth becomes uncontrolled.

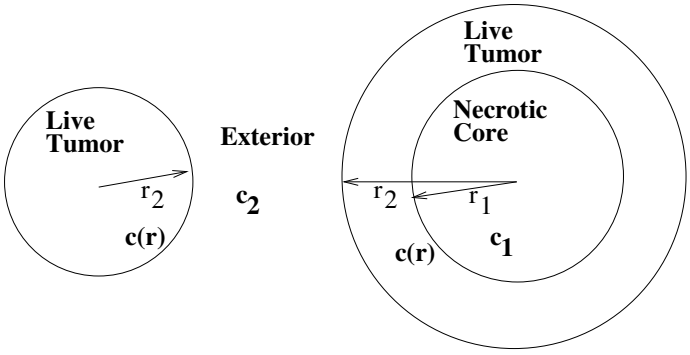
Cells will not multiply without the presence of growth factor proteins that attach to specific locations on the cell. Tumor cells can generate their own growth factors or have their receptor sites damaged such that the cell grows even without growth factor.

10.2 Avascular or Prevascular tumors

This is typically the initial phase of tumor growth were there are no blood vessels inside the tom our. Thus, all nutrients must diffuse from the exterior to the interior of the tumor. This diffusion limited growth prevents the tumor from getting more than a couple millimeters in size. Even at that small size the cells in the center of the tumor are nutrient deprived and die forming a *necrotic core*.

Assume a spherical tumor with

- $r = r_1$ is the radius of the necrotic core, which grows with time.
- $r = r_2$ be the outer radius of the tumor that is fixed.
- $c(t, r)$ is the concentration of nutrient as a function of the radius.
- c_2 is the concentration of nutrient on the outside of the tumor. This determines a *boundary condition* $c(r = r_2) = c_2$.
- c_1 is concentration at or below which cells die.
- The diffusion constant is D, which accounts for the "physics" of how nutrient diffuses through the cells into the interior of the tumor.
- k represents a loss of nutrient related to oxygen uptake by living cells and burning of nutrient.



The partial-differential equation for concentration of nutrient in a spherically symmetric tumor (c depends only on the radius r) is:

$$\frac{\partial c}{\partial t} = -k + D\nabla^2 c \tag{10.1}$$

$$\frac{\partial c}{\partial t} = -k + D\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial c}{\partial r}\right) \tag{10.2}$$

Suppose that the tumor has reached a steady-state size (equilibrium) such that $\partial c/\partial t = 0$. We then have an ODE *boundary value problem*:

$$0 = -k + D\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial c}{\partial r}\right) \tag{10.3}$$

10.2.1 Maximal tumor size without necrotic core

There is no diffusion at the center of the necrotic core and so the nutrient concentration must not change with radius. (If there was still a gradient of nutrient then it would diffusion inward supplying that nutrient.) $\partial c/\partial r(0) = 0$. Thus, our PDE has the boundary conditions

$$\frac{\partial c}{\partial r}(0) = 0, \quad c(r_2) = c_2.$$

- **VERIFY** (sub c into the ODE above) that the following is a solution for the concentration of nutrient as a function of radius.

$$c(r) = -\frac{1}{6}\frac{k}{D}(r_2^2 - r^2) + c_2 \tag{10.4}$$

- **VERIFY** (check that c satisfies condition) that $\partial c/\partial r(0) = 0$.
- Living cells require a nutrient concentration of at least $c = c_1$. **DETERMINE** the maximum value of $r_2 \equiv r_c$ such that the concentration of nutrient at the center is greater than c_1, i.e., $c(0) \geq c_1$.
- **EXPLAIN** the effect of the size of the diffusion on the size of the tumor. For example, if D increases, what happens and why, both mathematically and physically?

10.2.2 Existence of a necrotic core

If the tumor grows bigger than r_c, i.e., $r_2 > r_c$, then we expect the formation of a necrotic core with $r_1 > 0$. In the necrotic core the cells are dead and so do not use any oxygen ($k = 0$). **INTEGRATE** the resulting steady-state diffusion equation twice and with the assumption that the concentration cannot be unbounded show that $c = \hat{c}$ is constant in the necrotic core.

$$0 = D\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial c}{\partial r}\right) \tag{10.5}$$

Because we are assuming a necrotic core and because cells require a concentration of at least c_1, $\hat{c} \leq c_1$ in the core.

10.2.3 Size of the necrotic core

We now determine size $r = r_1$ of the necrotic core. We again have the steady-state diffusion equation.

$$0 = -k + D\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial c}{\partial r}\right) \tag{10.6}$$

On the outside surface of the tumor we know the concentration of nutrient

$$c(r_2) = c_2.$$

The inner radius of the living tumor cells, which is the same as the size of the necrotic core, $r = r_1$. Suppose that the concentration at r_1 is c_1, the minimum level of nutrients to keep cells alive.

$$c(r = r_1) = c_1.$$

Finally, we assume there is no flux of nutrient into the necrotic core. That is, the concentration must be a constant and not change with the radius.

$$\frac{\partial c}{\partial r}(r_1) = 0$$

- **VERIFY** (sub c into ODE) that the following is a solution for the concentration of nutrient as a function of radius.

$$c(r) = \frac{1}{6}\frac{k}{D}r^2 + \frac{A}{r} + B. \tag{10.7}$$

- **DETERMINE AN EQUATION** for the radius of the necrotic core r_1 by using the three boundary conditions to solve for A, B and r_1. (It is algebraically tedious to find an explicit result $r_1 = ...$) You should obtain an implicit equation for r_1 as a function of c_1, c_2, k, D and r_2.

- **EXTRA and OPTIONAL:** In the limit $r_2 \to \infty$, one can show that to prevent unbounded concentrations we require that $r_1/r_2 \to 1$. That is, as the radius of the tumor becomes large, so must the radius of the necrotic core. More precisely, we can find that

$$(r_2 - r_1)^2 = 2\frac{D}{k}(c_2 - c_1). \tag{10.8}$$

  Thus, the tumor can become large but so will the necrotic core.

- Using the last result above, **EXPLAIN** the effect of the size of the diffusion and the concentrations on the tumor size and core size. For example, if D increases, what happens and why, both mathematically and physically? What if $(c_2 - c_1)$ changes (answer both mathematically and physically)?

10.3 Other Effects

- The tumor grows such that the radii are functions of time, $r_1(t)$ & $r_2(t)$. Need to consider the time-dependent partial-differential equation.

- The concentration of growth promoters and inhibitors also effects tumor size.

- The concentration tumor angiogenesis factor induces vascularization (blood vessels) into the tumor. Thus, nutrients are supplied not only by diffusion from the outside but by, effectively, internal sources.

- The immune system attempts to remove the tumor and can accounted for with additional "predator" dynamics, where the tumor is the "prey."

10.4 Phenomenological Model

In the early part of a tumor's growth it's size can be modeled with a logistic equation:

$$\frac{dN}{dt} = rN\left(1 - \frac{N}{K}\right). \tag{10.9}$$

N is related to the number of tumor cells, mass, volume, or some other measure of size. The linear growth constant r accounts for all effects that cause the tumor to grow, e.g., supply of nutrients, growth factor, etc. The carry capacity K accounts for all factors that limit tumor growth such that for long times $N \to K$.

The Generalized logistic equation or Richards-Bertanffy equation is

$$\frac{dN}{dt} = rN\left[1 - \left(\frac{N}{K}\right)^{\gamma}\right], \tag{10.10}$$

where $\gamma \neq 1$. The Gompertz equation is

$$\frac{dN}{dt} = r\ln\left(\frac{K}{N}\right)N = [r\ln K]\,N\left(1 - \frac{\ln N}{\ln K}\right). \tag{10.11}$$

In each case steady states are $N = 0$ and $N = K$ but saturation occurs at different rates. In each case, the solution follows a "sigmoidal" curve growing exponentially from $N = 0$ and then exponentially asymptoting to $N = K$.

Which model to use depends on the application. More specifically, it depends on the growth characteristics and data for the physical process. As it happens, the Gompertz model is an excellent fit to avascular tumor growth. However, it is not clear why or how to derive the phenomenological parameters r and K related to physical parameters and processes, or why the functional form of the growth should be as given above.

- Let $u = \ln(N/K)$, take a derivative with respect to t and find a differential equation for u, solve it, then **DETERMINE** $N(t)$. Use the initial condition $N(0) = N_0$.

Chapter 11

Muscles

Figures are from *Mathematical Physiology*, by J. Keener and J. Sneyd (Springer-Verlag, 1998)

11.1 Muscle physiology

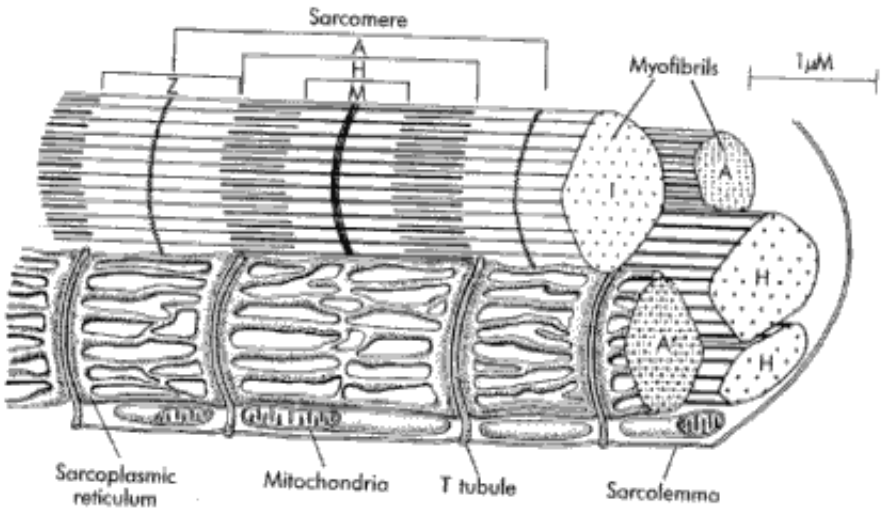


Figure 18.1 Schematic diagram of a skeletal muscle cell. (Berne and Levy, 1993, p. 283, Fig. 17-2.)

- There are three types of muscle cells, skeletal muscles, cardiac muscles and smooth muscles.
- We will focus on skeletal muscles, which have a banded appearance and are referred to as *striated muscle*.
- A single muscle cell is an elongated cylinder with multiple nuclei.
- The functional part of each cell are cylindrical structures called *myofibrils*, which are surrounded by the *sarcoplasmic reticulum*.
- Each contracting segment of the myofibril is called a *sarcomere*.

- The sarcomere ($\approx 2\mu m$) are made up of interlacing (parallel) protein filaments referred to as *thin* and *thick* filaments.

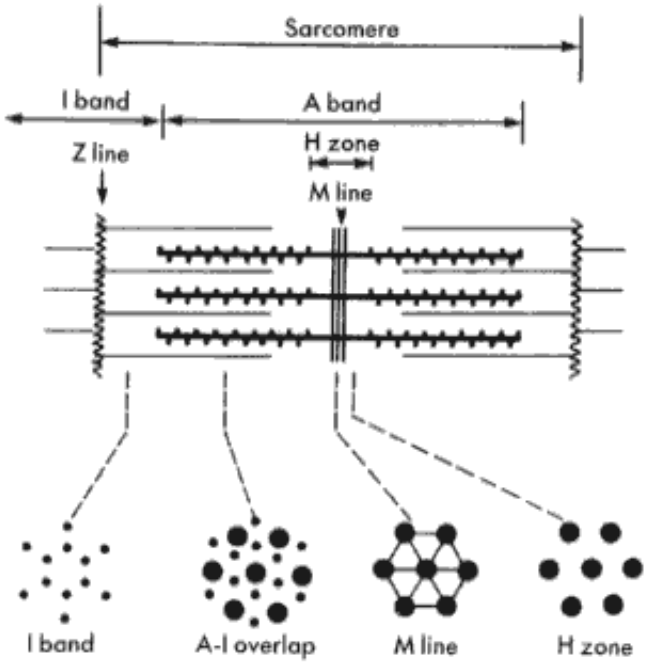


Figure 18.2 Longitudinal section (top panel) and cross-section (lower panels) of a sarcomere showing its organization into bands. (Berne and Levy, 1993, p. 283, Fig. 17-3.)

- Viewed from the end: six thin filaments surround one thick filament in a hexagon.
- View from side: the thin filaments overlap with the thick filaments.
- The thin filaments are anchor to the ends of the sarcomere at the *Z line* and extend to the center.
- The thick filaments are anchored in the center at the *M line* and extend out towards the ends.
- The region at the ends where there are only thin filaments is called the *I band*.
- The region in the center containing only thick filaments and the M line is the *H zone*.
- The region covering the H zone and the regions to either side where the thin and thick filaments overlap is called the A band.
- When the muscle contracts the overlap of the thin and thick filaments increases such that both the I band and the zone decrease.

11.2 Contraction via action potential

- Adjacent neurons transmit an action potential to the muscle cell.

- The action potential spreads into the interior of the cell via the network *T-tubules*.
- The T-tubules are roughly aligned with the junction of the A band and I band.
- The action potential opens Ca^{2+} channels in the cell membrane so that Ca^{2+} enters the cell. As the action potential reaches the myofibril it causes a further release of Ca^{2+} from the sarcoplasmic reticulum.
- The high concentration of calcium causes a change in the molecular structure of the filaments so that the thick filament binds and pulls on the thin filaments.

11.3 Crossbridge Theory

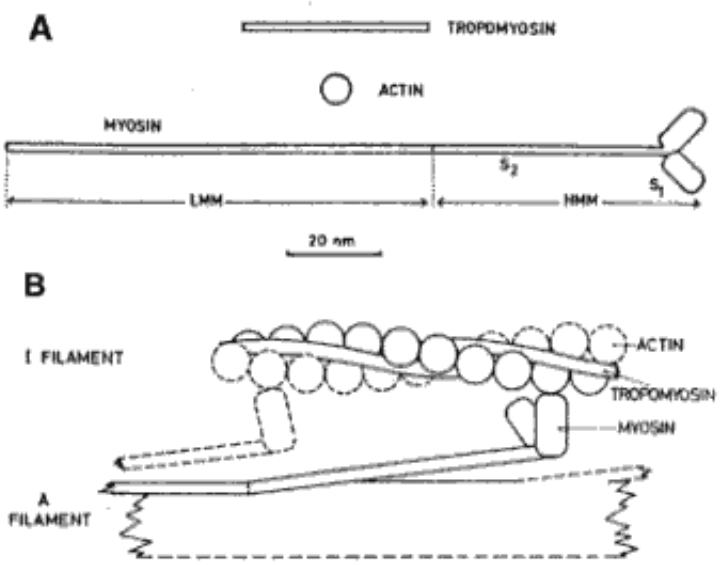


Figure 18.3 A: Scale drawing of actin, myosin, and tropomyosin proteins. B: Scale drawing of the thick and thin filaments (labeled the A and I filaments here), showing the probable way in which the actin, myosin, and tropomyosin proteins fit together. Troponin, which is bound to tropomyosin, is not included in the diagram. (White and Thorson, 1975, Fig. 9, parts A and B (i).)

Thick filaments

- The thick filaments contain the protein *myosin* that has at its free end a globular head.
- The heads of the thick filaments, when bound to the thin filaments, form the *cross bridges*.
- When the cross bridges are form a mechanical change in the molecular structure of the myosin causes the thick filament to pull against the thin filament in a ratchet fashion.
- The myosin heads obtain the energy for the shape change by burning *ATP*.

Thin filaments

- The thin filament has for a backbone the rod-shaped protein *tropomyosin*.
- Attached the the backbone are the spherical proteins *actin*. They are joined such that the composite structure is a double helix.
- The troponin has a binding cite for calcium and a portion that block the cross bridge binding sites on the actin. When calcium is bound to the troponin, a structural change in the troponin exposes the binding site on the actin allowing a cross bridge to form.

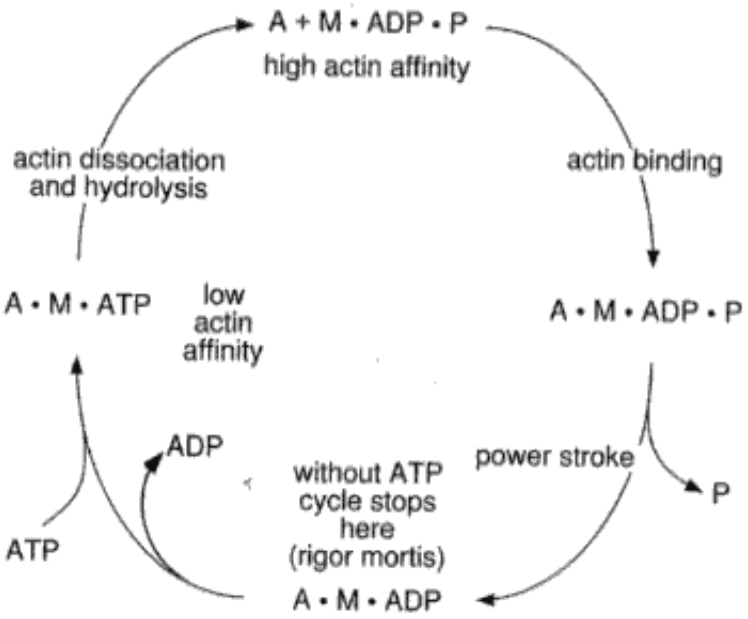


Figure 18.4 Major reaction steps in the crossbridge cycle. M denotes myosin, and A denotes actin.

Contraction

- Before crossbridge:
  - An ADP-P complex (dephosphorylated ATP) is bound to the myosin head.
  - Calcium concentration is low.
- Calcium concentration increases
  - Calcium binds to the troponin-tropomyosin complex.
  - The crossbridge binding site on the actin is exposed.
- Crossbridge formation
  - A weak bond forms between the actin and the myosin head.

  - The ADP-P complex on the myosin head releases the phosphate becoming simply an ADP molecule.
  - The release of the P causes the bond to now be strong.
  - The myosin molecule is no longer in an energy preferred structural state. Its new preferred shape is such that it exerts a pulling force on the actin

- Power stroke
  - The thin and thick filaments are pulled along each other so that the myosin is in its new energetically preferred state.

- Recovery
  - The ADP is released from the myosin head.
  - A new ATP is bound to the myosin head.
  - The binding of a new ATP causes the myosin-actin bond to break.
  - The binding of a new ATP causes the myosin to return to its original unbound structural configuration.
  - The ATP dephosphorylates to ATP-P and the myosin is ready to start a new power stroke.

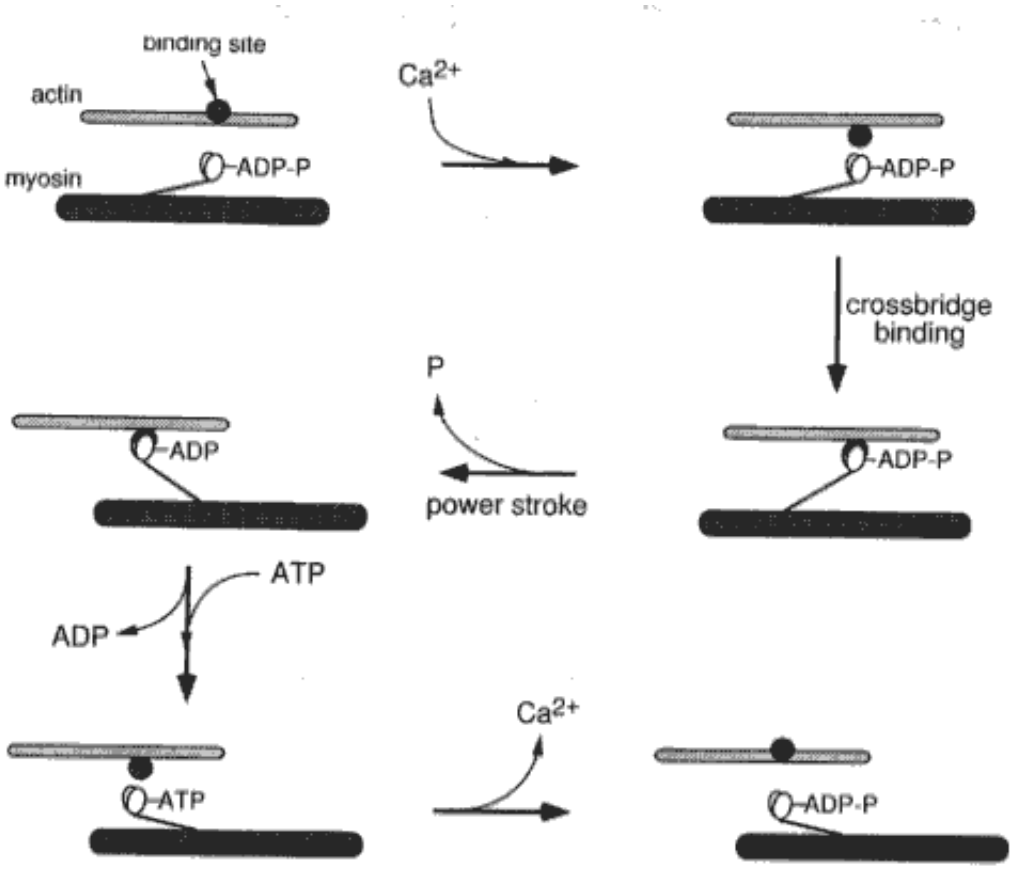


Figure 18.5 Position of crossbridge components during the major steps in the crossbridge cycle. M denotes myosin, A denotes actin, and P denotes inorganic phosphate.

11.4 Tetanus

- Isometric tension: the tension in the muscle when it is held at a fixed length and repeatedly stimulated.
- Tetanus: the state of the muscle when it is saturated with calcium such that the muscle is continually trying to contract. If the muscle is held at a fixed length, then under tetanus it exerts isometric tension.
- While the muscle can not change length, the power stroke for individual myosin proteins still occurs as they burn energy.
- For muscles held at a long length, there is little overlap of the thin and thick filaments and so the muscle can support only a small tension force.
- At short lengths the thin filaments from opposing Z lines overlap decreasing the effective overlap of the thin and thick filaments.
- Maximal tension is supported for mid-range muscle lengths.

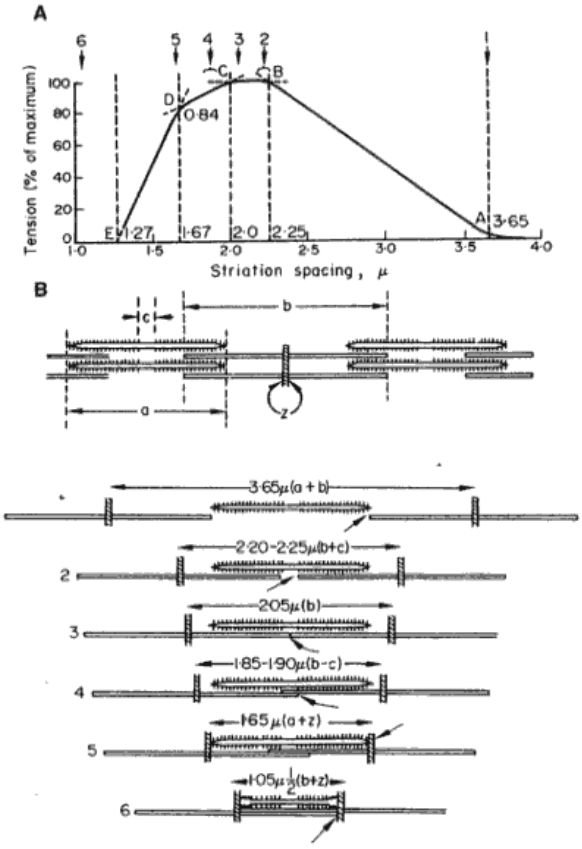


Figure 18.6 A: Isometric tension as a function of the length of the sarcomere. B: schematic diagrams of the arrangement of the thick and thin filaments for the six different places indicated in panel A. (Gordon et al., 1966, reproduced in White and Thorson, 1975, Fig. 14.)

11.5 Huxley crossbridge model

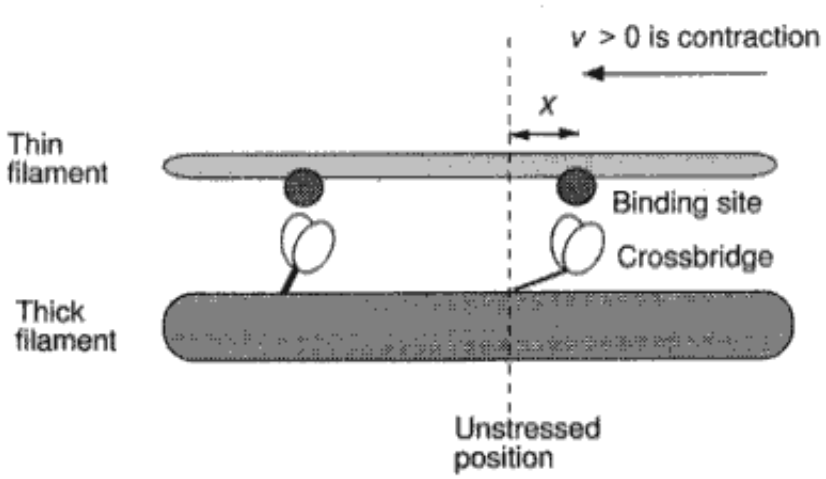


Figure 18.11 Schematic diagram of the Huxley crossbridge model.