# 1 Introduction

*Modeling is a central concept in mathematical biology since there are not fundamental 'laws' to rely on. Therefore it is important to have an idea of a model in mind. By definition, models are approximations of reality. Good models are capable of providing insight into biological hypotheses and built to be refined and adjusted.*

All models are wrong, but some are useful.

Attributed to George E. P. Box

Models should be as simple as possible, but no simpler.

Adaptation of Albert Einstein

## 1.1 What is a model?

Models are the translation of a real world problem into a statement or question in mathematical language. Models connect the lab scientist, clinician or practitioner to the mathematician/quantitative scientist. Bridging this gap requires an understanding of both languages, as well as an appreciation of the gap between them.

Like translations, there can be good and bad translations – those that are accurate, those that capture the spirit of the primary language and those that open up insights. So what makes a good model? This depends a lot of the context. Some qualities that make good models include accuracy (how true to the science is the model), flexibility (if you change the experiment slightly, do you need a brand new model?), simplicity (is the model tractable?), practicality (does it include things that are not measurable?).

## 1.2 Projectile Motion

There are many relationships that are really models. For example, $D = rt$ models the how the distance travels depends on the rate and time. The ideal gas law relates pressure, volume and temperature, $PV = nRT$. Einstein derived a model describing the relationship between energy and mass, $e = Mc^2$. All of these are models that provide insight into different processes. There are distinctions between these models. It is hard to imagine how $D = rt$ could not be an accurate model (although there is an underlying assumption that the rate is constant) while the ideal gas law becomes less and less accurate when the gas is close to a phase transition, say near the condensation point. The last relationship depends on assumptions underlying much of modern physics. So models can come in a range of subjective interpretation.

We will detail one model that is familiar to any student in calculus – projectile motion. We assume that an object is fired directly upwards from a certain height above ground. The object goes up, stops moving, reverses direction and returns down. A description of the height of the object as a function of time is $y(t) = -\frac{1}{2}gt^2 + v_0t + y_0$. Gravitational acceleration is denoted $g$, the initial velocity and positions are $v_0$ and $y_0$. There is a choice in frame of reference where we are assuming that gravity only acts in one direction (the object is dropped or thrown vertically with no horizontal displacement) and that gravity causes acceleration in the 'negative' direction. If the object starts with a positive height, $y_0$ and is released the height will decrease.

This is often presented as 'projectile motion' and as though it is always true. We could think of this function as the model – we can make predictions about the time it takes to return to $y = 0$ or what is the maximum height the object reaches. However, viewing this relationship that way obscures a broader modeling method – How do we adjust this for multiple objects? How In calculus you might have seen this as a question about motion under constant acceleration. Acceleration is the rate of change of velocity, $v(t)$ and Newton argued that acceleration due to gravity is constant so that,

$$\frac{dv}{dt} = -g.$$

Since $g$ is a constant, we can integrate both sides,

$$v(t) = -gt + c_0.$$

Now we know how the velocity changes over time and velocity is the rate of change of position,

$$\frac{dy}{dt} = -gt + c_0.$$

Since $g$ and $c_0$ are constant, we can integrate both sides,

$$y(t) = -\frac{1}{2}gt^2 + c_0 t + c_1. \tag{1.1}$$

You can almost see the correspondence between $y = -\frac{1}{2}gt^2 + v_0 t + y_0$ and $y(t) = -\frac{1}{2}gt^2 + c_0 t + c_1$, but we have not yet determined the integration constants. We have to provide some information to do this. If we denote the initial position – the position at time 0 as $y(0) = y_0$, and plug this into 1.1, we find that $c_1 = y_0$.

So what is $c_0$? One way to determine it is if we define the initial velocity, $v(0) = v_0$. Then the velocity (the derivative of the position, $y(t)$) is,

$$dy(t) = -gt + c_0. \tag{1.2}$$

Evaluating this at $t = 0$, we find that $c_0 = v_0$.

So the 'model' $y = -\frac{1}{2}gt^2 + v_0 t + y_0$ is really the solution to the model,

$$\frac{d^2y}{dt^2} = -g. \tag{1.3}$$

This is a differential equation, and if we prescribe information $y(0) = y_0$ and $\frac{dy}{dt}(0) = v_0$, we can solve this completely.

But where did the model come from? Part of the point of this book is to learn how to invent these sorts of models, so we won't go into too much detail here. However, this is a nice example that has roots to Newton and the time that calculus was created. One of Newton's most valuable contribution is the idea of Laws – that are general principles that lead to mathematical statements. One of his laws of motion (the second) states that $f = ma$. That is, there is a balance between forces applied on an object and the acceleration of the objects mass. So Equation 1.3 is really a translation of Newton's second law (with a bit of algebra),

$$\begin{aligned} ma &= f, \\ \frac{d^2y(t)}{dt^2} &= \frac{f}{m}, \\ &= -g. \end{aligned}$$

This is a model of the position of an object under constant acceleration. From a modeling standpoint, we started with a very broad 'law' – Newton's second law – and then translated this in the case of assuming only (constant) gravitational attraction. This model can be completely solved for predictions. The next tasks depend on many things including the goals of the model, how the predictions compare to observations; however, for all good models, there are testable predictions.

In this case, we could predict the maximum height of an object that is thrown, the time at which the object reaches that height, when the object hits the ground, etc. But what if we talk to an experimentalists and we are asked what the terminal velocity is? This is the constant speed that an object reaches when falling. But a look at this model indicates that there is no such thing. In fact, this model assumes the velocity increases like the square of the time! As modelers, we have to ask what is wrong – our prediction does not match observations. A little exploration uncovers the trouble. There are many other forces that act on the object. There is air-resistance, coriolis force, even forces at the atomic scales. We have to consider which to include and which to exclude. Do we need to include relativistic effects? This is a commonly accepted model of motion that appears at odds with Newton's model.

There is no complete answer for this. In principle all forces need to be accounted for, but this is like a 1-1 scale map. It does not really help matters. But we can work at estimating which forces matter the most. In this case, unless the velocity gets very large, or the mass of the object is tiny or huge, the main forces that matter when considering terminal velocity is drag. We can then develop a model for drag and go back to our experimental colleague and compare our new, revised prediction with their observations. This loop between observations leading to models leading to predictions leading to revised observations is one of the most successful ways for science to progress. Modeling is a crucial step to this leading to quantitive questions (how fast does an object have to move before constant acceleration deviates from observations by more than 5%) that drive experimental design and insight.

In this book, we will also consider a less standard view of models. In many situations, we *know* that there are many interactions. Consider a gene network schematic shown in Figure 1.1. Clearly there is a lot going on. For complicated networks, the models get extremely large - think thousands of equations with tens of thousands of parameters. How can we possibly assess such a model?

We will show how to use sensitivity analysis to reduce the model and make simplifications that greatly aid the connection between models and experiments. This has a different philosophy than used to understand projectile motion. In that situation, we had a simple model that may or may not reflect observations. If the predictions are inaccurate, we look for additional terms. We could think of this as a bottom up approach where you start small and add to the model as need. A top down approach takes a large amount of current knowledge and tries to pinpoint the most relevant parts for specific predictions. Both standpoints are valid and useful and we will move back and forth between them but it is very useful to know the differences between them.

An additional issue that mathematical biologists have to grapple with is the lack of universal laws in biology. There are very few principles that can be viewed in a way that is similar to Newton's laws of motion. Instead, we have to work a bit harder to develop principles that can be translated into theoretical models. Some principles are broad – we use conservation laws in many of the chapters. Some are known from other disciples – the law of mass action has been well developed

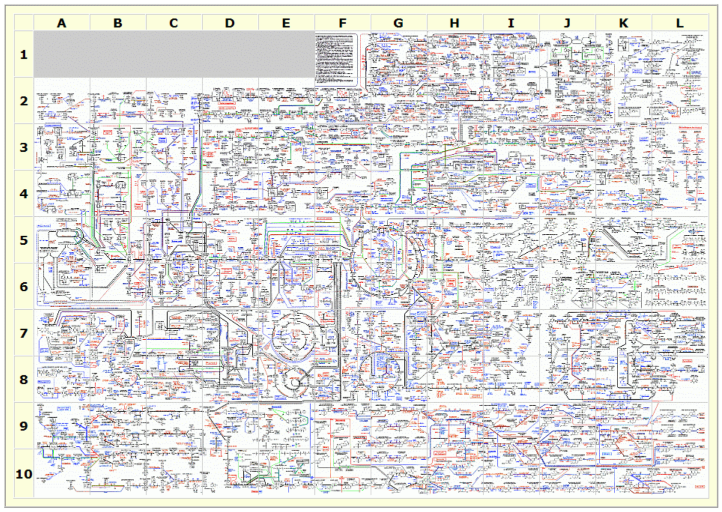


Figure 1.1: Example of a network diagram

in chemistry. Other principles that guide models is the philosophy that mathematics is portable and that some aspects of models are in some way generic – Biological ‘switches’ often follow the form of Fitzhugh-Nagumo like dynamics. In all of these cases it is very helpful to have a library of models that we know. Therefore many of the examples in the chapters begin with historically important models that set a framework to work within.

For most of the models developed in this book, we will start with simple models and add to them as needed. This has certain specific limitations that we should all be aware of. The main limitation that we will acknowledge is the massive amount of mathematics that can be brought to bear on biological questions. Topics ranging from statistics, calculus, differential equations, machine learning, topology, abstract algebra, graph theory, number theory, geometry, numerical analysis and others have all been used to obtain important insight into biological processes. There is no one book that will cover the diversity of topics. Even so, there is no one researcher who uses all of these methods. For about the past two hundred years, methods from calculus have been extremely effective in translating hypotheses concerning the natural world into mathematical language which can be used to analyze, predict and quantify observations. We will focus almost exclusively on differential equation models – for historical reasons they are the most prevalent but they are also quite flexible.

## 1.3 Problems

**Problems 1.1** *Show that if an object is accelerating due to gravity, there is no maximum velocity*

**Problems 1.2** *Suppose an object is thrown in the air from a height of zero. What is the maximal height that is reached if the initial velocity is 3 ft/s?*

**Problems 1.3** *Drag force or air resistance is one of the forces that is neglected in simple projectile motion. One difficulty in modeling air resistance is that direction of the force depends on the velocity. For a projectile fired into the air, the drag force acts in the same direction as gravity when the projectile is moving upwards and in the opposite when the object is moving downwards.*

*(a)* *Show that the force $F = -v^2 sgn(v)$ is consistent with this where $sgn(v)$ is 1 if $v > 0$ or -1 if $v < 0$.*

*(b)* *Consider a ball dropped from rest at height, h. Find the solution to the position as a function of time including air resistance. What is the terminal velocity? Does the concept make sense?*

*(c)* *How fast does an object need to be traveling before air resistance is 10% of the force of gravity?*