Homework Assignment 23: Due at the beginning of class 5/1/02.

This homework assignment is intended to be a review of the techniques that you learned for finding solutions to differential equations at the beginning of the semester. While working on this assignment you might be worried that a mistake in Question 1 will reduce your chances for getting full credit on any of the subsequent questions. This is not the case – as long as you complete Questions 2-5 in a correct manner using the equation(s) that you obtained in Question 1, you will be eligible for full credit on each question.

If you have a lot to do at the moment, skip to page 3.

Figure 1: Daffodils in bloom.

The daffodil (see Figure 1[1]) – perhaps one of the most tangible signs that the reign of Winter is coming to an end. The appearance of daffodils is probably one of the most tangible signs of the approaching spring, and the promise of new life that this season of rebirth brings.

It is somewhat ironic that the daffodil - lovely to behold - is highly toxic to humans if ingested, being infused with an alkaloid compound that causes nerve and respiratory paralysis. This combination of beauty and death is thought to be the origin of the species name for daffodils (*Narcissus*), named for the youth of Greek myth who fell in love with his own beautiful reflection, and who drowned while trying to embrace this reflection in a clear stream.

Many associations between death and beauty have appeared in art and literature, such as the early twentieth century print "All Is Vanity" (see Figure 2[2]) by an unknown American artist. Viewed from afar, this print appears to depict a human skull, yet when examined closely reveals a beautiful young woman sitting in front of a mirror applying make-up.

Figure 2: The early twentieth century print, "All Is Vanity."

[1] Image source: http://www.poison.org/plantox.htm

[2] Image source: http://www.plantationhome.com/

The title of this print recalls the words of Koheleth, the son of David and king in Jerusalem:

> "Vanity of vanities, saith Koholeth, vanity of vanities, all is vanity … I have seen all the works that are done under the sun; and, behold, all is vanity and a striving after wind. That which is crooked cannot be made straight …" (excerpted from Ecclesiastes[3] 1:1-15)

In accord with[4] Koholeth's despairing assessment of life on Earth, approximately two weeks ago the FDA approved the drug Botox®[5] (see Figure 3 [6]). The first three paragraphs of the FDA press release[7] are quoted below.

Figure 3: The drug Botox®, manufactured by Allergan, Inc.

"FDA today announced the approval of Botulinum Toxin Type A (Botox Cosmetic) to temporarily improve the appearance of moderate to severe frown lines between the eyebrows (glaellar lines), a medical condition that is not serious. The product's manufacturer, Allergan, Inc., Irvine, California, is now allowed to market Botulinum Toxin Type A for this new indication.

Boutlinum Toxin Type A is a protein produced by the bacterium *Clotrdium botulinum*[8]. When used in medical settings as an injectable form of sterile, purified botulinum toxin, small doses of the toxin are injected into the affected muscles[9] and block the release of the chemical acetylcholine that would otherwise signal the muscle to contract. The toxin thus paralyzes or weakens the injected muscle.

Botox was first approved in December 1989, to treat two eye muscle disorders (blepharospasm and strabismus) and in December 2000 to treat cervical distonia, a neurological movement disorder causing severe neck and shoulder contractions."

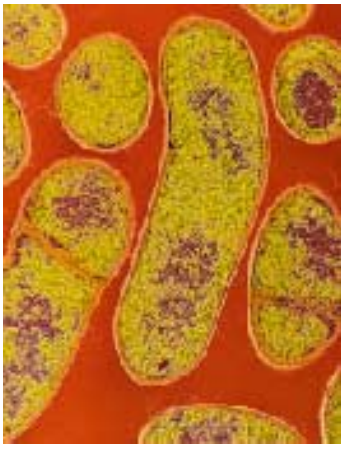


Figure 4: The bacterium *Clotridium botulinum*.

As reported in the *Las Vegas Sun*[10] FDA approval of Botox® has been eagerly awaited by many members of the public.

> "Not since the early days of Viagra has a lifestyle drug garnered so much attention as Botox.
>
> Botox has erased early wrinkles on young women[11], flattened the furrowed brows of middle-aged TV anchormen, removed

[3] The source of this translation is: http://www.mechon-mamre.org/

[4] Or perhaps, "In rebuttal to…" depending on your opinion of cosmetic surgery.

[5] Botox® is a registered trademark of Allergan, Inc. 2525 Dupont Drive, Irvine CA 92715.

[6] Image source: http://www.southshoreneurologic.com/

[7] Source: U.S. Food and Drug Administration. "FDA approves Botox to treat frown lines." *FDA Talk Paper* T02-20, April 15, 2002.

[8] See Figure 4. (This image was not part of the original press release.) The image source for Figure 4 was: http://www.nature.com/

[9] See Figure 5. (This image was not part of the original press release.) The source of the image used in Figure 5 is: http://celebrate2000.cjonline.com/

[10] Source: "Allergan awaits FDA Botox approval." *Las Vegas Sun*, April 2, 2002.

[11] See Figure 6. (This image was not part of the original report in the newspaper.) Source of image for Figure 6: http://www.skinjsc.com/

sweat stains under the arms of young runway models and even erased gamblers' unwanted facial expressions.

In the process, the muscle-paralyzing substance has become one of the most profitable products for Allergan, Inc., which first sold the drug more than a decade ago for treating crossed eyes.

Botox is a laboratory refined strain of botulinum toxin – the cause of botulism[12] and one of the most poisonous substances on earth."

Figure 5 (above): Botox(R) is normally applied via injection directly into facial muscles.

Figure 6 (right): Facial wrinkles (a) before and (b) after treatmen with Botox(R).

Before this unique marriage of beauty and death[13] could be offered to the wrinkled American public, Allergan, Inc. was required to perform extensive clinical trials of Botox®, including trials on mice, monkeys and humans. In humans, Botox® is normally injected into the muscles rather than into the bloodstream. Nevertheless, there is a chance that the drug could accidentally be introduced into the blood stream, and a serious part of the clinical research involved determining what effects the drug might cause if it were to get into the blood. During one of the experiments in an early phase of the clinical trials Botox® was slowly introduced into the blood of a monkey at a rate of 0.0121 units per hour. Measurements of the amount of botulinum toxin the monkey's blood suggested that the drug was eliminated at a rate proportional to the amount of botulinum toxin

[12] (This foot note was not present in the original text.) Botulism is a form of food poisoning that can easily prove lethal. According to the *Mortality and Morbidity Weekly Newsletter* produced by the Centers for Disease Control and Prevention, there are usually between 10 and 50 cases of botulism reported each year in the United States.

[13] As noted in the *Las Vegas Sun* story, Botox® is one of the most poisonous substances known to medical science. In another interesting twist, Allergan, Inc., do not give standard units (such as mg or ml) for the amount of Botox®. Instead amounts of this drug are given in "units." The definition of one "unit" is that one unit of Botox® is equal to the amount of Botox® that will kill 50% of the mice that are injected with it.

present in the monkey's blood[14]. The constant of proportionality was measured to be 0.00031. At the beginning of the experiment the monkey did not have any botulinum toxin in its body.

1. The prototypical differential equation that usually serves as a good starting point for putting information on rates together to form a differential equation is:

Rate at which Drug accumulates In body	=	*Rate at which enters body*	–	*Rate at which is eliminated from body*

Let:

- T = the number of hours since the mouse was started on Botox®.
- $B(T)$ = the amount (in "units") of Botox® in the monkey's body.

Formulate a differential equation and an initial condition that describe how the amount of Botox® in the monkey's body changed as the clinical trial of the new drug was conducted.

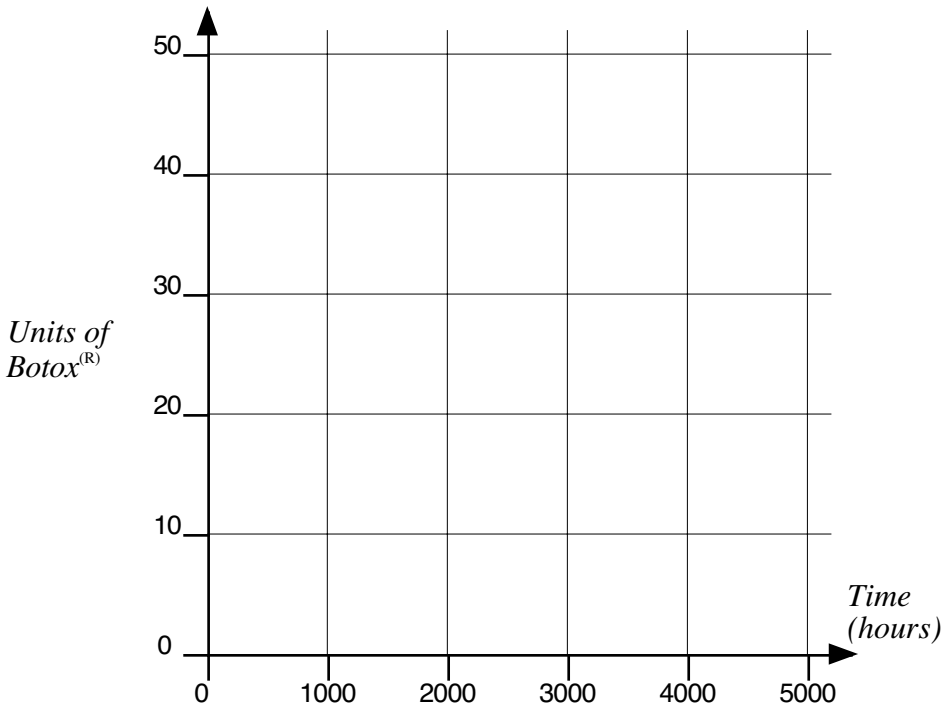
2. Use the differential equation, the initial condition (both from Question 1) and the table given below to estimate the amount of Botox® in the monkey's body three hours into the clinical trial of the drug.

Time (hours)	Amount of Botox® ("units")	Rate of change	Change in amount of Botox® in next 30 minutes	New amount of Botox® ("units")
0				
0.5				
1				
1.5				
2				
2.5				

[14] Source: http://www.drugeruptiondata.com/

3. Is the estimate that you found in Question 2 an over-estimate or an under-estimate of the actual amount of Botox® in the monkey's body after three hours? You must supply compelling evidence to support your answer.

4. Use the differential equation (that you set up in Question 1) together with the axes provided below to draw a slope field. When you have finished the slope field, use it and the initial value (that you determined in Question 1) to sketch a graph showing the amount of Botox® in the monkey's body as a function of time.



5. An equation for a function, $B(T)$, is given below. Determine whether or not this function is a solution of either your differential equation or initial condition (from Question 1). Show full details of any calculations that you do.

$$B(T) = 39.032 - 39.032 \cdot e^{-0.00031 \cdot T}$$

Extra Credit – Up to 5 points available.

The body mass[15] of an adult rhesus monkey is about 7 kg. The 50% lethal dose (LD 50) of Botox® in monkeys is about 39 units per kg. Would the experiment described in this homework be likely (probability ≥ 0.5) to kill an adult rhesus monkey if such an animal was used as the experimental subject? If so, about how long would you expect the monkey to survive the experiment? Provide evidence to support your conclusions.

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[15] Source of data: http://www.nuffieldfoundation.org/ and http://www.southshoreneurologic.com/