

Non-dimensionalization of Tumor-Immune ODE System *

L.G. de Pillis and A.E. Radunskaya

August 22, 2002

*This work was supported in part by a grant from the W.M. Keck Foundation

0-0

NON-DIMENSIONALIZATION

Overview

1. Importance of Non-dimensionalizing
2. A Simple Example
3. General Process
 - Define Dimensionless Variables
 - Choose Non-dimensionalizing Constants
 - Define New Dimensionless Parameters

Non-Dimensionalization

Rescaling and Dimensionless Variables

Why is it important to rescale and non-dimensionalize?

- To **SIMPLIFY** the equations by reducing the number of variables.
- To analyze the behavior of the system, regardless of the **UNITS** used to measure the variables. **Example:** The Reynolds number of a fluid or Tumor growth/normal growth.
- To rescale the parameters and variables so that all computed quantities are of relatively similar **MAGNITUDES**.

2

Non-Dimensionalization

Notes for Rescaling and Dimensionless Variables slide:

Answers:

(1) simplify

(2) units **Note:** The Reynolds number is the ratio of inertial force to the viscous force, and is defined as:

$$R = \frac{UL}{\nu}$$

where U is the speed of a fluid element, L is a characteristic wave length, and ν is the kinematic viscosity. As an illustration, compare an airplane moving through air, which has a *high* Reynolds number (U is large, while ν is small), to a ship moving through water, which has a *low* Reynolds number, (U is small, while ν is large, relative to that of air). Another example that might be mentioned here, which is more relevant to our model, is that we might be more concerned with *relative* growth rates of cells: (Tumor Cell Growth Rate)/(Normal Cell Growth Rate), rather than rates measured in absolute time units.

(3) magnitudes **Note:** In some cases, certain quantities are inexorably of vastly different sizes. Knowing this, in fact, helps the analysis of the model by showing which variables, or rates of change, can be thought of as 'small' or even 'negligible' relative to others.

2-1

References: See [LS74], [Ban98]

An Additional Example: The following example is included in case this material is unfamiliar, but may be omitted. It might also be given as an exercise, providing a review of simple initial value problems. A more involved problem is given in the exercises.

2-2

Non-Dimensionalization

A Simple Preliminary Example

Suppose that we want to test an exponential model of tumor growth against a list of data collected in an oncologist's office. We are ignoring the effect of the immune system, as well as the competition between tumor cells for nutrients.

Let T denote the number of tumor cells, and r the growth rate *per cell*. Thus, the differential equation describing growth is:

$$\frac{dT}{dt} = rT \text{ (probably realistic enough for small tumors).}$$

The data consist of the number of tumor cells at the time the tumor was first detected, determined by the volume of the tumor. The time between detection and the previous doctor's visit is also recorded.

The Problem: Determine the tumor's rate of growth from these two pieces of data.

⇒ continued

Non-Dimensionalization

A Simple Preliminary Example (continued)

Suppose the detection threshold for tumors is approximately 10^5 cells. Therefore, the number of tumor cells present at the previous visit is $T_0 < 10^5$ cells. If T_1 is the number of tumor cells at the time of detection, and τ is the time between visits, we can find the **MINIMUM** rate of growth by solving the initial value problem:

$$\frac{dT}{dt} = rT, \quad T(0) = 10^5,$$

which gives: $T(t) = T_0 e^{rt}$.

This problem has 4 “variables”, or “unknowns”: T_0 , T_1 , τ and r .

4

Non-Dimensionalization

Notes for A Simple Preliminary Example (continued) slide:

Answers:

(1) rT **Note:** Ignoring the crowding term in the equation for tumor growth may be quite realistic for small tumors growing in isolation, i.e. *in vitro*.

(2) 10^5 .

(3) minimum

(4) $T_0 e^{rt}$.

(5) T_0 (6): T_1 (7): τ

(8) r **Note:** The term “variable” is in quotes because, in this context, it refers to *all* of the unknowns of the problem: state variables, system parameters, and initial values. We use it here to conform with common usage, but perhaps “unknown” is a more informative term.

Non-Dimensionalization

Preliminary Example: Dimensionless Variables

Introduce the **dimensionless** variable: $Y = T/T_0 = \frac{T}{10^5 \text{ cells}}$ (The *numbers* are rescaled, and the *units* disappear.)

Similarly, define a **DIMENSIONLESS** variable $s = \frac{\ln 2}{D}t$, our new 'time', where D is the doubling time of normal cells (≈ 10 days).

Using the chain rule, the differential equation in terms of the dimensionless variables is:

$$\frac{dY}{ds} = kY \quad \text{where } k = \frac{D}{\ln 2}r$$

5

Non-Dimensionalization

Notes for Preliminary Example Dimensionless Variables slide:

Answers:

(1) $T/(10^5 \text{ cells})$ **Note:** This rescaling has the effect of reducing the order of magnitude of this variable.

(2) dimensionless **Note:** This may seem an odd choice of rescaling, but it simplifies the end result. The factor of $\ln 2$ comes in because the rate, r , is in the exponent, and measurements are usually made in terms of doublings, i.e. powers of 2, rather than powers of e .

(3) $\frac{D}{\ln 2}r$

Details:

$$\frac{dY}{ds} = \frac{dY}{dT} \frac{dT}{dt} \frac{dt}{ds} = \frac{dY}{dT} \frac{dt}{ds} \frac{dT}{dt} = \frac{1}{T_0} \frac{D}{\ln 2} r T = \frac{1}{T_0} \frac{D}{\ln 2} r Y T_0 = \frac{D}{\ln 2} r Y = kY$$

Note: $\frac{dY}{ds} = kY$ has the solution $Y_0 e^{ks}$.

Non-Dimensionalization

Preliminary Example: Non-dimensionalized Solution

Let s_τ be the time-data, to the time between doctor visits, (τ) expressed in terms of the variable s , i.e. $s_\tau = \tau \frac{\ln 2}{D}$. Then the solution in terms of the new variable is:

$Y(s_\tau) = Y(0)e^{ks_\tau} = e^{ks_\tau}$ (since $Y(0) = 1$). The number of variables has been reduced to **THREE** and the rate we are looking for is: $k = \ln\left(\frac{Y(s_\tau)}{s_\tau}\right)$.

What have we gained by this procedure?

- We can normalize a long list of data all at once, leaving us with one less parameter.
- k is in terms *relative* to the growth rate of normal cells, ($k = 1 \Rightarrow$ tumor cell doubling time = **D (Normal Cell Doubling Time)**).
- The values of Y are $O(1)$, as opposed to $O(10^5)$.

6

Non-Dimensionalization

Notes for Preliminary Example Non-dimensionalized Solution slide:

Answers:

(1) $\tau \frac{\ln 2}{D}$, i.e. substitute in τ for t since τ is when visit 1 happened, so s_τ is when visit 1 happened in rescaled time. D is the doubling time of normal cells ≈ 10 days

(2) 1

(3) three **They are:** $k, Y(s_\tau), s_\tau$.

(4) $\frac{\ln(Y(s_\tau))}{s_\tau}$.

Details: Previously, k was $\frac{D}{\ln 2}r$. So find: $e^{ks_\tau} = \frac{T_1}{10^5} = Y(s_\tau)$ (where e^{ks_τ} is the solution at the time of detection and $Y(s_\tau) = \frac{T_1}{10^5}$ is the rescaled tumor detected) and

solve for k to get $k = \frac{\ln\left(\frac{T_1}{10^5}\right)}{s_\tau} = \frac{\ln(Y(s_\tau))}{s_\tau}$.

(5) **D Note:** That is, when $k = 1$, the tumor cell doubling equals the normal cell doubling time.

Details: We know that $Y(s) = e^{ks}$ since $Y_0 = Y(0) = 1$. To find the doubling time, $Y(s_D) = e^{ks_D} = 2Y_0 = 2$, which gives that $s_D = \frac{\ln 2}{k}$. So, if $k = 1$ then

6-1

$s_D = \ln 2$. Using $s_D = \left(\frac{\ln 2}{D}\right) t_D$, rearranging and solving for t_D finds that the doubling time occurs at $t_D = D$. The “point” is that k gives the relative doubling time. If $k = 1$, the tumor cells and normal cells double at the same rate however if $k > 1$, the tumor cells double at a faster rate.

Notes: To summarize, there are three major advantages to nondimensionalizing. They are:

1. The total number of parameters is reduced.
2. The meaning of the nondimensionalized parameters may be more transparent, so that, for example, a value of 1 is “normal”.
3. The actual numbers tend to be scaled to allow for better numerics.

A short discussion of why it is desirable to avoid numbers which are either very large or very small in numerical simulations might be appropriate here.

6-2

Non-Dimensionalization

Step 1: Define Dimensionless Variables of the Tumor-Immune System

Recall the differential equations:

$$\frac{dE}{dt} = s + \frac{pET}{g + T} - mET - dE$$

$$\frac{dT}{dt} = aT(1 - bT) - nET$$

Write these differential equations in terms of the new variables:

$$E^* = \hat{E}E \quad T^* = \hat{T}T \quad t^* = \hat{t}t$$

where the unit-carrying quantities \hat{E} , \hat{T} and \hat{t} will be chosen later. Using the chain rule:

$$\begin{aligned} \frac{dE^*}{dt^*} &= \frac{s\hat{E}}{\hat{t}} + \frac{p}{\hat{t}} \frac{E^*T^*}{g\hat{T} + T^*} - \frac{mE^*T^*}{\hat{T}\hat{t}} - \frac{d}{\hat{t}}E^* \\ \frac{dT^*}{dt^*} &= \frac{a}{\hat{t}}T^*(1 - \frac{b}{\hat{T}}T^*) - \frac{n}{\hat{t}\hat{E}}E^*T^*. \end{aligned}$$

Non-Dimensionalization

Notes for Step 1 Define Dimensionless Variables of the Tumor-Immune System slide:

Answers:

$$(1) \frac{s\hat{E}}{\hat{t}} + \frac{p}{\hat{t}} \frac{E^*T^*}{g\hat{T} + T^*} - \frac{mE^*T^*}{\hat{T}\hat{t}} - \frac{d}{\hat{t}}E^*$$

$$(2) \frac{a}{\hat{t}}T^* \left(1 - \frac{b}{\hat{T}}T^*\right) - \frac{n}{\hat{t}\hat{E}}E^*T^*$$

Details: Apply the chain rule, to get:

$$\frac{dE^*}{dt^*} = \frac{dE^*}{dE} \frac{dt}{dt^*} \frac{dE}{dt} = \frac{\hat{E}}{\hat{t}} \frac{dE}{dt}$$

and a similar equation for dT^*/dt^* . After substituting the expressions for the starred variables on the right hand sides, rearrange to get the new equations. **Note:** “unit-carrying” means, for example, \hat{E} and \hat{T} will be some quantity of cells, and \hat{t} is some number of days.

7-1

Non-Dimensionalization

Step 2: Choose the Non-dimensionalizing Constants

We have **3** choices to make, and our goal is to reduce the number of **PARAMETERS** while rescaling very large and very small quantities.

One option (among many):

- Let $\hat{t} = a$, i.e. scale time relative to **THE TUMOR GROWTH RATE**.
- Let $\hat{E} = n/\hat{t} = n/a$, i.e. scale the immune population relative to **THE NUMBER OF TUMOR CELLS INACTIVATED BY EACH IMMUNE CELL (PER UNIT OF RESCALED TIME)**.
- Let $\hat{T} = b$, i.e. scale the tumor population relative to **THE MAXIMUM TUMOR POPULATION (TUMOR CARRYING CAPACITY)**.

Non-Dimensionalization

Notes for Choose the Non-dimensionalizing Constants slide:

Answers:

- (1) three (\hat{E} , \hat{T} , and \hat{t}).
- (2) parameters **Note:** There are many ways to choose these constants. The class might come up with different choices, which could then be compared. Our choice of constants differs from that of Kuznetsov [KMTP94]. We comment on this further in a later slide.
- (3) the tumor growth rate
- (4) the number of tumor cells inactivated by each immune cell **per unit of rescaled time**
- (5) the maximum tumor population **the tumor carrying capacity**

Question: What are the units of each of these quantities? **Answer:** \hat{E} and \hat{T} are in units of cells^{-1} , while \hat{t} is in units of days^{-1} .

8-1

Non-Dimensionalization

Step 3: Define New (Dimensionless) Parameters

Define new system parameters in order to *simplify* the equations:

$$\sigma = \frac{s\hat{E}}{\hat{t}} = \frac{sn}{a^2}, \quad \rho = \frac{p}{a}, \quad \eta = g\hat{T} = gb,$$
$$\mu = \frac{m}{ab}, \quad \delta = \frac{d}{a}$$

In order to perform numerical simulations or further analysis, we recompute the parameters in terms of the new scaling:

$$\sigma = \mathbf{0.4414}, \quad \rho = \mathbf{0.6917}, \quad \eta = \mathbf{0.04038}, \quad \mu = \mathbf{0.9506}, \quad \delta = \mathbf{0.2289}.$$

Non-Dimensionalization

Notes for Define New (Dimensionless) Parameters slide:

Answers:

- (1) .04414
- (2) .6917
- (3) .04038
- (4) .9506
- (5) .2289

Question: What are the dimensions of each new parameter?

Answer: None of the parameters (or variables) have dimension. (Verify this.)

Note: In the paper [KMTP94] a different non-dimensionalization is used. The choice of non-dimensionalizing constants presented in these slides, in contrast, results in simpler non-dimensional equations than those in [KMTP94]. This choice also has the advantage of highlighting the relevant relationships between the original parameters. For example, the parameter δ now represents the death rate of the immune cells, (original parameter: d), relative to the birth rate of the tumor cells (original parameter: a). When the equations are in this form, it is clearer that it is the *ratio* of these two quantities which

9-1

will determine the fate of the system, rather than the values themselves. Since we have reduced the number of parameters as much as possible, and we are left with five, we say that this system has “five degrees of freedom”. See [EK88, chapter 4.4, p.126].

9-2

Non-Dimensionalization

The Equations in Final Form

Step 4: Write the non-dimensionalized equations:

$$\begin{aligned}\frac{dE^*}{dt^*} &= \sigma + \frac{\rho E^* T^*}{\eta + T^*} - \mu E T - \delta E^* \\ \frac{dT^*}{dt^*} &= T^*(1 - T^*) - T^* E^*\end{aligned}$$

Remark: From now on, we will drop the stars for convenience.

10

Non-Dimensionalization

Notes for The Equations in Final Form slide:

Answers:

$$\begin{aligned}(1) \quad &\sigma + \frac{\rho E^* T^*}{\eta + T^*} - \mu E T - \delta E^* \\ (2) \quad &T^*(1 - T^*) - T^* E^*\end{aligned}$$

Note for bifurcation analysis: Our choice of parameters leaves the equation for the evolution of the tumor cell population invariant under parameter changes. This has the effect of fixing the tumor-nullcline. The effector-nullcline, in contrast, will shift as parameters shift. We note that with Kuznetsov's choice of non-dimensionalization, both the tumor-nullcline and the effector-nullcline are parameter dependent. The effect of parameter changing on Kuznetsov's non-dimensionalized equations is discussed in the section on bifurcation analysis.

We point out that either choice of non-dimensionalization is valid, since it is always the *relative* orientation of the null-clines which is important.

Suggested Exercise: As an exercise, have the students go through Kuznetsov's [KMTP94] non-dimensionalization, in preparation for the section on bifurcation analysis in which we return to using Kuznetsov's equations.

10-1

References

- [Ban98] Robert Banks. *Towing Icebergs, Falling Dominoes, and Other Adventures in Mathematics*. Princeton University Press, 1998.
- [EK88] Leah Edelstein-Keshet. *Mathematical Models in Biology*. Random House/Birkhauser, 1988.
- [KMTP94] Vladimir A. Kuznetsov, Iliya A. Makalkin, Mark A. Taylor, and Alan S. Perelson. Nonlinear dynamics of immunogenic tumors: Parameter estimation and global bifurcation analysis. *Bulletin of Mathematical Biology*, 56(2), 1994.
- [LS74] C. C. Lin and L. A. Segel. *Mathematics Applied to Deterministic Problems in the Natural Sciences*. Macmillan Publishing Co., Inc., 1974.