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METERING EFFECTS IN POPULATION SYSTEMS

Erika T. Camacho

School of Mathematical & Natural Sciences
Arizona State University,
4701 W. Thunderbird Rd, Glendale, AZ, 85306, USA
and
Mathematical, Computational and Modeling Sciences Center
Arizona State University
P.O. Box 871904, Tempe, AZ, USA 85287-1904, USA

Christopher Kribs-Zaleta

Departments of Mathematics and Curriculum & Instruction
University of Texas at Arlington
P.O. Box 19408, Arlington, TX, 76019-0408, USA
and
Mathematical, Computational and Modeling Sciences Center
Arizona State University
P.O. Box 871904, Tempe, AZ, USA 85287-1904, USA

Stephen Wirkus

School of Mathematical & Natural Sciences
Arizona State University
4701 W. Thunderbird Rd, Glendale, AZ, 85306, USA
and
Mathematical, Computational and Modeling Sciences Center
Arizona State University
P.O. Box 871904, Tempe, AZ, USA 85287-1904, USA

Abstract. This study compares the effects of two types of metering (periodic resetting and periodic increments) on one variable in a dynamical system, relative to the behavior of the corresponding system with an equivalent level of constant recruitment (influx). While the level of the target population in the constant-influx system generally remains between the local extrema of the same population in the metered model, the same is not always true for other state variables in the system. These effects are illustrated by applications to models for chemotherapy dosing and for eating disorders in a school setting.

1. **Introduction.** Many applications involve continuous systems that undergo some type of resetting or external influence that alters the dynamics [29, 39, 40, 41, 42, 45, 53]. Terms that have been used to describe such phenomena include impact models, Filippov systems or piecewise smooth systems, metered preemptive models, phase resetting, pulsed models or periodically pulsed, impulse differential equations, and metered models. In this paper, we will use the phrase "metered model" as an inclusive term that incorporates the pulsed or periodically pulsed models and impulse

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differential equations. We are specifically referring to equations in which a continuous time process is externally influenced at discrete time intervals or stages [7, 8]. While our concern is with biological and sociological applications, we mention here applications of some of the other resetting mechanisms.

Impact models were initially used in the description of mechanical systems and are characterized by phenomena that occur on very different time scales [9]. A recent example from ecology describes a slowly growing forest that is occasionally ravaged by fire [32]. *Metered preemptive models* refer to applications in scheduling when a partially completed job may still have some worth (e.g., a low resolution image that may need some areas done at high resolution but not all requests from users can be satisfied) [13, 16]. Another type of model that is sometimes called a metered model is a Filippov or piecewise smooth system [17]. An example of this type of model is in predator-prey systems in which a predator uses an optimal strategy to go between habitats based on the density of the populations [24, 46]. While these examples are either called metered models or describe a discrete time influence on a continuous system, we do not consider these types of metered models.

The above systems involved a resetting or altering in one or more of the state variables of the model. Another type of application is the control of continuous systems [10, 31, 33, 34, 47], in which the goal is to use metering to control an otherwise unstable behavior. A final type of model that we mention before addressing the interest of the present study is *phase resetting*. In this type of system, metering is done but it is not directed at the state variables. One common biological application involves circadian rhythms that can be altered by light [11, 20, 49].

In this study we distinguish mathematically between two types of metered models: those with periodic *resetting*, in which one or more state variables are reset *to* a fixed value at regular intervals, and those with periodic *increments*, in which one or more state variables are incremented (or decremented) *by* a fixed value at regular intervals. Those models where periodic incrementing is done are also called *pulsed* or *periodically pulsed models* and sometimes *impulse differential equations*. Models in which periodic resetting is done could include the previously mentioned control applications or again the impulse differential equations. There is a wealth of literature on the theory of these types of models [2, 35, 36, 5, 6, 26, 27, 43] as well as numerous biological applications involving them [14, 21, 22, 25, 28, 19, 50, 51, 52].

Our interest in metered models arises from a modeling perspective. Specifically, we would like to know how the solutions of the metered model differ from those models in which a drug or population or other state variable is assumed to enter the system through a constant influx over the given period. To our knowledge, no such comparison of the two modeling approaches has been performed. In the specific case of chemotherapy and periodic incrementing, it is mathematically more tractable to assume a continuous dose of chemotherapy when modeling but clearly unrealistic. Some metered models have considered this application [26, 37, 38] but not in comparison to the continous administration model. In a similar way, if we consider a system in which the state variables are reset to a certain level (an example of periodic resetting), many examples abound but none of the results compare the metered model resetting with the often-used assumption of constant influx [1, 4, 12, 30, 44].

We begin with an analytical comparison of the two approaches in the context of a single equation and then consider the effects of metering in one state variable, on the other variables in a larger system, using examples drawn from the research produced

by Carlos Castillo-Chavez's Mathematical and Theoretical Biology Institute (MTBI, http://mtbi.asu.edu).

2. **Simple models.** A simple example of a system with periodic resetting is a setting such as a school group where new individuals are admitted up to a maximum capacity once per season, but individuals may leave the group at any time. A mathematical model for this system incorporates the rate of departure, say μ, which is the reciprocal of the average stay in the system; the resetting period T; and the size to which the population is reset, which without loss of generality we can assume is the same as the initial population size x_0. Then $dx/dt = -\mu x$ except when time t is a multiple of the period T, at which moments the population is reset to x_0. The initial value problem consisting of the given differential equation and initial condition has solution $x(t) = x_0 e^{-\mu t}$, so that the population size just before resetting is $x(T^-) = x_0 e^{-\mu T}$. Thus the amount by which the population is incremented (to make $x(T^+) = x_0$) is $x_0\left(1 - e^{-\mu T}\right)$. (Thereafter $x(t + kT) = x(t)$ for all whole numbers k.)

A non-metered model which spreads this resetting continuously over the interval $(0, T]$ would have instead the form $dx/dt = \Lambda - \mu x$, where $\Lambda = x_0\left(1 - e^{-\mu T}\right)/T$. The solution of this differential equation (regardless of initial condition) is asymptotically constant to $x^* = \Lambda/\mu = x_0\left(1 - e^{-\mu T}\right)/(\mu T)$. We can then compare the solution to the metered model with that to the non-metered model.

It is straightforward to prove that the behavior of the metered model oscillates about the asymptotically constant solution of the non-metered model, i.e., $x(T^-) < x^* < x(T^+)$, as illustrated in Figure 1. If we denote the dimensionless decay quantity $\mu T > 0$ by z, the first part of this inequality can be (re)written $e^{-z} < (1 - e^{-z})/z$, which is equivalent to $g_1(z) = (z + 1)e^{-z} < 1$. This follows from the fact that g_1 is decreasing in z for $z > 0$, with a maximum at $g(0) = 1$. Likewise, the second half of the inequality can be written $(1 - e^{-z})/z < 1$, which is equivalent to $g_2(z) = z + e^{-z} > 1$. This follows from the fact that g_2 is increasing in z for $z > 0$, with a minimum at $g(0) = 1$.

A simple example of a system with periodic increments is the administration of a drug with constant dosage. In practice, most drugs are administered at discrete, regular intervals (say, once each day), rather than continuously throughout the day (as intravenous fluids are). Meanwhile, the body works on a continuous basis to clear the chemical from the body. This clearance rate corresponds to the departure rate in the previous model and can also be denoted μ. Again the dynamics between administrations can be described by a simple decay equation, $dx/dt = -\mu x$, but in this case the metering is described by a constant increment $\Lambda T = x(T^+) - x(T^-)$. Under the simplifying assumption that drug administration begins at time 0, with $x(0^-) = 0$ and $x(0^+) = x_0 > 0$, this increment can be written simply as x_0. Then the solution to the metered model can be written as follows:

$$x(t) = \begin{cases} x_0 e^{-\mu t}, & 0 < t < T; \\ x_0\left(1 + e^{-\mu T}\right) e^{-\mu(t-T)}, & T < t < 2T; \\ x_0\left(1 + e^{-\mu T} + e^{-2\mu T}\right) e^{-\mu(t-2T)}, & 2T < t < 3T; \\ \cdots & \\ x_0 e^{-\mu(t-nT)} \sum_{k=0}^{n} \left(e^{-\mu T}\right)^k, & nT < t < (n+1)T. \end{cases}$$

As time progresses ($n \to \infty$), the sum of exponential terms approaches the geometric series with constant ratio $e^{-\mu T}$, which converges to $1/(1 - e^{-\mu T})$; thus $x(t)$ is asymptotically periodic to the quantity $x_0 e^{-\mu(t \bmod T)}/(1 - e^{-\mu T})$.

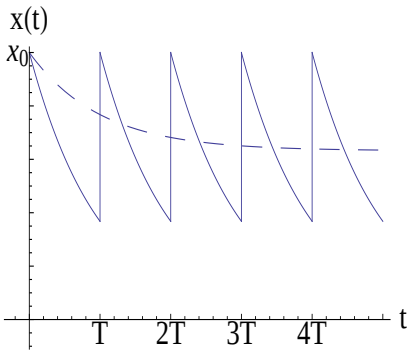

FIGURE 1. Comparison of the solutions to the simple metered model with periodic resetting (solid curve) and the corresponding non-metered model with constant influx (dashed line)

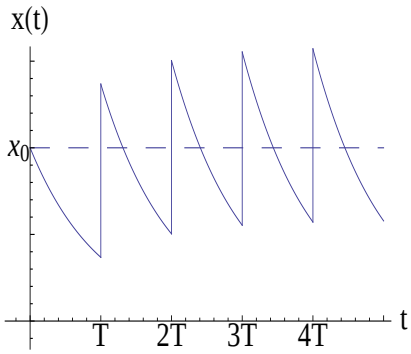

FIGURE 2. Comparison of the solutions to the simple metered model with periodic increments (solid curve) and the corresponding non-metered model with constant influx (dashed line)

Another way to examine the solution to this metered model is via the values just before and after each increment is applied: if we define $x_n^- = x(nT^-)$ and $x_n^+ = x(nT^+)$, then we have

$$\begin{aligned}
x_0^- &= 0, & x_0^+ &= x_0; \\
x_1^- &= x_0 e^{-\mu T}, & x_1^+ &= x_0\left(1 + e^{-\mu T}\right); \\
x_2^- &= x_0\left(e^{-\mu T} + e^{-2\mu T}\right), & x_2^+ &= x_0\left(1 + e^{-\mu T} + e^{-2\mu T}\right); \\
x_3^- &= x_0\left(e^{-\mu T} + e^{-2\mu T} + e^{-3\mu T}\right), & x_3^+ &= x_0\left(1 + e^{-\mu T} + e^{-2\mu T} + e^{-3\mu T}\right); \\
&\vdots & & \\
x_n^- &= x_0 \sum_{k=1}^{n} \left(e^{-\mu T}\right)^k, & x_n^+ &= x_0 \sum_{k=0}^{n} \left(e^{-\mu T}\right)^k;
\end{aligned}$$

so that as $n \to \infty$ $x_n^- \to x_-^* = x_0 e^{-\mu T}/\left(1 - e^{-\mu T}\right)$, and $x_n^+ \to x_+^* = x_0/\left(1 - e^{-\mu T}\right)$.

Meanwhile, a model which assumed continuous administration at the same rate would have $dx/dt = \Lambda - \mu x$, as with the previous example, but where $\Lambda = x_0/T$. The solution to this equation is asymptotically constant to $x^* = \Lambda/\mu = x_0/\mu T$.

We can again compare the behaviors of the solutions to the metered and non-metered models, using the simplifying notation $z = \mu T > 0$. And again the solution to the metered model oscillates about the solution to the non-metered model, with $x_-^* < x^* < x_+^*$, which can be proven as before. The compound inequality can be rewritten

$$\frac{e^{-z}}{1 - e^{-z}} < \frac{1}{z} < \frac{1}{1 - e^{-z}}.$$

The two halves of this inequality are equivalent once more to $g_1(z) < 1$ and $g_2(z) > 1$, which were shown true in the previous example. The oscillation is illustrated in Figure 2.

The consequences of substituting the solution to the simpler non-metered model for that of the metered model can be serious even in these simple examples: if, for instance, the maximum drug concentration a patient's body can tolerate is between x^* and x^*_+, then the non-metered model predicts that a dosage of x_0 units every T units of time is safe, while the metered model predicts (correctly) that a discrete administration of this dosage will be harmful to the patient for a nontrivial period of time following each dose.

These very simple examples illustrate the general principle that metered models capture fluctuations (often asymptotically periodic in nature) ignored by the averaging of comparable non-metered models. These principles also manifest in more complicated systems for some cases, although in such cases they are generally more difficult to identify analytically. In the following sections we consider examples of such complex systems taken from research projects which originated at MTBI (a within-host treatment model and a school setting model). Numerical investigations show that the qualitative behavior of the continuous and metered models with resetting in one state variable is the same only for the class where the resetting takes place. For the other classes simulations reveal that the behavior is more complex.

3. **Within-host treatment.** For an application with periodic increments, we consider a 1999 MTBI breast cancer treatment study [3] that modeled the effects of chemotherapy (where a fixed dosage is administered periodically) on the size of a tumor and the health of a patient.[1] This study tracked the tumor size g (measured in units of 10^{10} cells), the health h of the patient (as a unitless proportion from 0 to 1), and the amount c (in grams) of chemotherapy drug in the body over time. The system denoted Model B in the study (equations (6)–(8)), depicting the amount of drug in the body as exponentially decaying via a constant clearance rate λ, is given by

$$\begin{aligned} \frac{dg}{dt} &= \left[\gamma\left(1 - \frac{g(1-h)}{K}\right) - d_1 c\right] g \\ \frac{dh}{dt} &= \left[r\left(1 - h(1 + (\delta g)^2)\right) - d_2 c\right] h \\ \frac{dc}{dt} &= -\lambda c, \end{aligned} \tag{1}$$

where γ and d_1 give the natural tumor cell proliferation and drug-induced death rates, respectively, K represents a minimal (limited by patient illness $1-h$) carrying capacity for tumor size, r describes the patient's natural health recovery rate while d_2 describes the drug's deleterious effects on patient health, and δ is the coefficient measuring the tumor's deleterious effects on patient health. The logistic growth rates in the first two equations are structured to account for the interaction between tumor size and patient health: tumor growth slows when a patient is dying, and the presence of the tumor impedes the patient from reaching full health [3]. From [3], the parameter estimates are given as $\gamma = \log(2)/200$, $r = 0.1$, $\lambda = 0.33$ (all in

[1]While chemotherapy is typically prescribed with other medications such as steroids, we consider the chemotherapy-only model considered by the MTBI 1999 group in order to illustrate the effects of metering. It is left as future work to obtain a more realistic treatment model from which to analyze periodic increments.

units of 1/day); $d_1 = 0.08$, $d_2 = 0.3$ (both in units of 1/grams); $K = 12 \times 10^{10}$ cells; $\delta = 0.25$ $1/(10^{10}$ cells).

Metered drug administration is modeled via periodic increments of a fixed value c_0, causing discontinuities in $c(t)$ for $t = kT$, $k = 0, 1, 2, \ldots$. The corresponding continuous-dosage model changes the equation for drug amount to

$$\frac{dc}{dt} = \Lambda - \lambda c,$$

where Λ, analogously to the simple model in the previous section, provides an equivalent dose over each period, $\Lambda = c_0/T$.

As expected, the solution curve showing drug amount assuming continuous administration stays bounded within the local extrema of the solution curve corresponding to periodic dosing (i.e., the metered model with periodic increments); see Figure 3. In addition, we observe that the solution curve of the health of the patient, h, also remains within the bounds of its metered counterpart. In contrast, however, the tumor size, g, in the continuous administration system is below that of the periodic incremented system. This is significant because the simpler continuous-influx model overestimates the tumor shrinkage rate, as the constant presence of the drug at a medium level apparently has a greater effect during the times when a periodically administered drug would be largely absent, than the periodically-administered drug has beyond the average level during the period immediately subsequent to its administration.

If we vary the parameters of the system, we can arrange for all three solution curves corresponding to the continuous administration of chemotherapy to lie between the high and low values of their metered counterparts. While this ignores the realistic parameter values used to generate Figure 3, it shows that, mathematically, the relationship between the solution curves for continuous administration and periodic administration of chemotherapy is somewhat dependent on the choice of parameter values; see Figure 4.

For this numerical exploration of periodic incrementing in the case of chemotherapy administration, we observe that whether or not the solution curves of the state variables with continuous administration of a drug remain bounded by the extrema of their metered counterparts is completely dependent on the parameters. Only in the case of the solution curve of the drug can we be sure that it will remain bounded since the equation describing the change in c is decoupled from the other two equations.

4. **School setting.** For an application of periodic resetting, we consider a model of the eating disorder bulimia nervosa in a college population developed in a 2001 MTBI study [23]. This model considers a small population of college females in which peer pressure to conform to unrealistic body ideals drives women to develop bulimia, and the eating disorder is described via two stages: an early stage in which symptoms are light enough to go undetected, and an advanced stage characterized by episodes severe enough to require medical care and thus detection by others, subsequent to which individuals are obliged to enter treatment. Since treatment typically lasts two years or more, a fully recovered phase was omitted from the model. The model considered a continuous influx of students throughout in order to keep the population constant, and assumed that all incoming students were non-bulimic (and had never been bulimic). Onset of early-stage bulimia ("infection") was assumed to occur at a [per capita] rate proportional to the bulimic population

(who propagate the unhealthy ideals/habits), while progression to advanced-stage bulimia was considered automatic. Advanced-stage bulimics were assumed to enter treatment due to both discovery (at a constant rate) and the influence of classmates who had entered treatment (at a rate proportional to the number of women in treatment), while relapse was considered spontaneous. All students were assumed to spend an average of three years in the population (due to transfer students and other effects).

We here modify the model of [23] in two ways: first to incorporate periodic resetting, and second to allow the possibility that some proportion of entering students

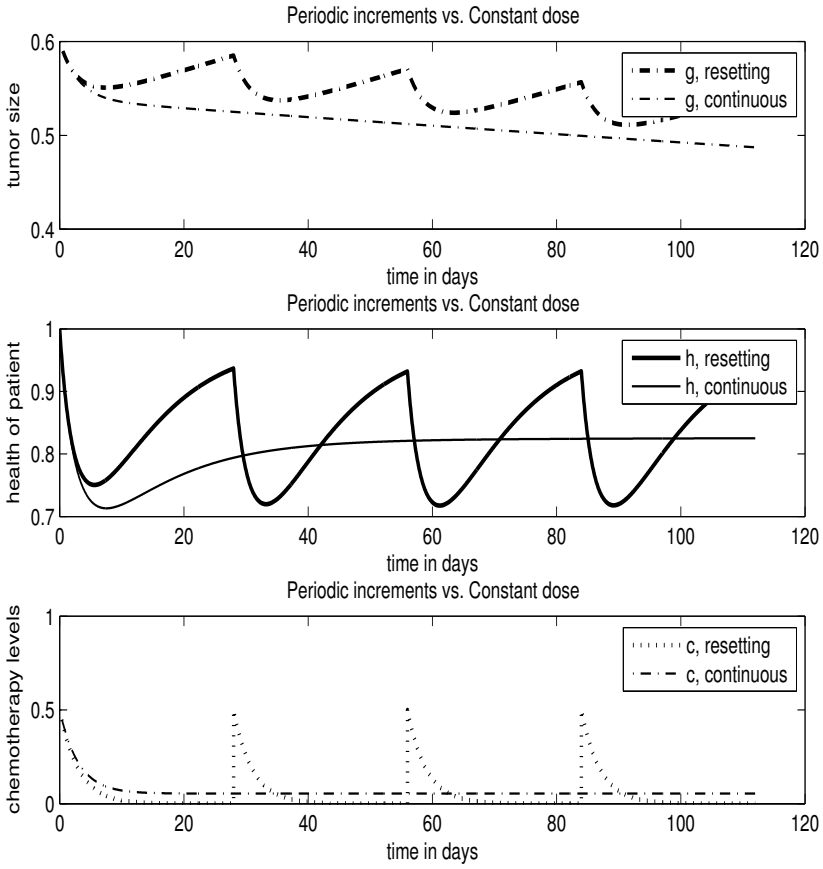

FIGURE 3. Continuous versus periodic dosage administration in the case of chemotherapy for the parameters given after (1). Note that the tumor size predicted by the continuous dosage model does not remain within the extrema of the solution from the metered model counterpart. This is in contrast to the solution curves of the h and c under continous administration, which do remain within the extrema of their metered model counterparts. Only the initial four dosage administrations are shown.

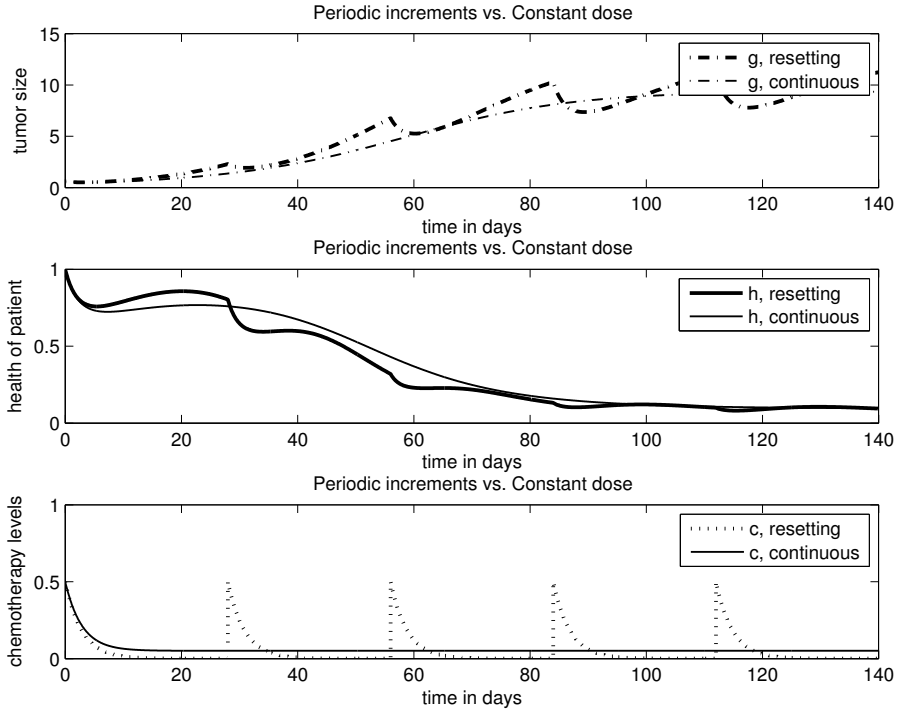

FIGURE 4. Application of periodic incrementing in the case of chemotherapy administration. The values used are $\gamma = \log(2)/10$, $d_1 = .4$, $\delta = .3$, $\lambda = .35$, which result in all three solution curves from continuous administration remaining within the bounds of their respective metered counterparts.

are bulimic (the size to which the total population is reset each period remains independent of this proportion). To incorporate the latter assumption, we assume that a proportion $k_1 \geq 0$ of entering students are early-stage bulimics and a proportion $k_2 \geq 0$ are advanced-stage bulimics, with $k_1 + k_2 < 1$. Since the number of students in high school who have already entered treatment for bulimia is very small we assume this to be negligible and as such there are no new college students entering the treatment class. Allowing new students to enter directly into the treatment class would involve defining a similar proportion k_3, but here we take the proportion entering as susceptibles (non-bulimic) as $1 - k_1 - k_2 > 0$.

The continuous-influx model of [23], in which the sizes of the four classes are rescaled as proportions of the overall population, uses the variables x, y_1, y_2, and z, respectively, to track the susceptible, stage 1 and stage 2 bulimic, and treatment classes. The modified system involving new arrivals entering bulimic classes directly is given by the following equations:

$$\frac{dx}{dt} = (1 - k_1 - k_2)\mu - \alpha x(y_1 + y_2) - \mu x,$$

$$\begin{aligned}\frac{dy_1}{dt} =& k_1\mu + \alpha x(y_1+y_2) - (\mu+\gamma)y_1,\\ \frac{dy_2}{dt} =& k_2\mu + \gamma y_1 - (\mu+\rho)y_2 - \delta y_2 z + \phi z\\ \frac{dz}{dt} =& \rho y_2 + \delta y_2 z - (\mu+\phi)z.\end{aligned} \tag{2}$$

If in addition we wish to incorporate periodic resetting, then we set $\mu = 0$ in the above equations, and at the end of every period T, the proportions are reset as weighted averages:

$$\begin{aligned} x(kT^+) =& \quad x(kT^-)e^{-\mu T} + (1-k_1-k_2)(1-e^{-\mu T}),\\ y_1(kT^+) =& \quad y_1(kT^-)e^{-\mu T} + k_1(1-e^{-\mu T}),\\ y_2(kT^+) =& \quad y_2(kT^-)e^{-\mu T} + k_2(1-e^{-\mu T}),\\ z(kT^+) =& \quad z(kT^-)e^{-\mu T}.\end{aligned}$$

The parameter estimates given in [23] are $\mu = 1/3$, $\alpha = 0.439$, $\gamma = 1.5$, $\rho = 0.13$, $\delta = 0.13$, $\phi = 0.15$ (all rates given in units of 1/yr) together with initial conditions of $x = 0.95$, $y_1 = 0.02$, $y_2 = 0.02$, $z = 0.01$. The continuous influx model in which no one enters the system bulimic ($k_1 = k_2 = 0$) can be shown to have a reproductive number of

$$\begin{aligned} R_0 = \quad & \frac{1}{2}\left[\frac{\alpha}{\mu+\gamma} + \frac{\phi\rho}{(\mu+\phi)(\mu+\rho)}\right.\\ & \left. + \sqrt{\left(\frac{\alpha}{\mu+\gamma} - \frac{\phi\rho}{(\mu+\phi)(\mu+\rho)}\right)^2 + \frac{4\gamma\alpha}{(\mu+\rho)(\mu+\gamma)}}\right]\end{aligned} \tag{3}$$

(derivable using a next-generation approach [18, 48]). This quantity measures the phenomenon's ability to invade a population. (Note that if $k_1 + k_2 > 0$, then R_0 is technically undefined since in this case new "infections" appear in the system even in the complete absence of bulimics). The parameter values given above yield a point estimate for the reproductive number of $R_0 \approx 1.047$.

In contrast to the 1-dimensional analogue, we find some very interesting behavior in our system. The continuous influx model predicts an epidemic when everyone enters into the susceptible class. In contrast, the periodic resetting metered bulimia model in which every incoming student enters into the susceptible class (i.e., no entering students are bulimic, $k_1 = k_2 = 0$) does not predict an epidemic and instead predicts the y_1, y_2, z populations go extinct with everyone eventually in the x class; see Figure 5. This result suggests a seemingly odd control strategy where a school could eliminate a bulimia problem by accepting only non-bulimic students (we ignore the feasibility of a school being able to request such a screening and the accuracy these screens). This prediction of being able to "flush out" a bulimic population even when $R_0 > 1$ has significant consequences. In particular, it predicts that even in a well-mixed population in which differential equations are valid, the manner in which the inflow occurs may be significant. The result is strongly affected by the replacement rate, here $\mu = 1/(3\text{ yr})$, which must be (relatively) high enough to clear bulimic students before they can build a critical mass. Lowering this replacement rate to $\mu = 0.193$/yr ($R_0 \approx 1.32$) still leads, numerically, to no disease while dropping it just a bit further to $\mu = 0.183$/yr ($R_0 \approx 1.34$) will allow the disease to persist in the periodic resetting model. There is clearly a balance between parameters for a given resetting that is required in

order for the metered model to predict an epidemic. As a caveat, though, even if a small portion of the incoming students are bulimic ($k_1 + k_2 > 0$) the metered model will predict an epidemic as well, since there is then a regular influx of bulimics.

We now consider the case when $k_1 + k_2 > 0$, which is not considered in the original paper but is considered here numerically, together with the metered predictions. In this case, all evidence suggests that both the metered model and continuous-influx model predict the persistence of bulimia in the population. Even though the qualitative prediction of the two models is the same, however, the numerical values that result are often lower for the metered model than for the continuous-influx model; see Figure 6. Table 4 shows how changes in the proportions of the incoming classes can affect the final proportion (before resetting for the sake of definiteness since the system rarely reaches a single steady state value in a metered model). More specifically, if the percentage of students entering the first-stage bulimia class is 0.1% (with $k_2 = 0$), the metered model predicts 0.39% and 1.3% as the final percentages present in the y_1 and y_2 classes, respectively, whereas the continuous influx model predicts corresponding values of 4.6% and 25.3%, more than an order of magnitude greater. As the proportion k_1 of entering first-stage bulimics increases (keeping $k_2 = 0$), this difference gradually decreases, but remains significant even for as high as 10% first-stage bulimics among entering students (while the eventual

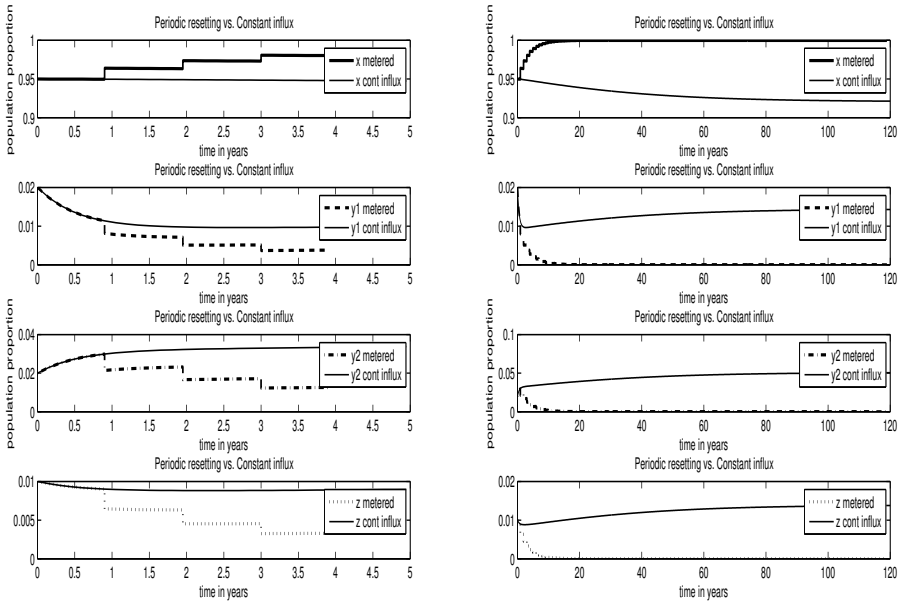

FIGURE 5. Application of periodic resetting for the bulimia model. All the resetting goes into the susceptible class, i.e., no student enters the system as bulimic ($k_1 = k_2 = 0$). Left figures: only the initial 4 years are shown. Right figures: Time is shown to 120 years, where the variables in the continuous influx model near their non-zero steady state values ($R_0 \approx 1.047$).

k_1	k_2	y_1^*	y_2^*	y_1^-	y_2^-
0	0	1.4%	5.1%	0 %	0%
10^{-3}	0	4.6%	25.3%	0.4%	1.3%
10^{-2}	0	4.8%	26.1%	1.8%	5.9%
10^{-1}	0	5.9%	32.0%	5.9%	20.9%
0.05	0.05	5.3%	32.2%	5.1%	21.2%

TABLE 1. Numerical comparison of an increased inflow ($k_1 + k_2 > 0$) into the y_1 and/or y_2 classes. The steady state values are given for the continuous influx model as y_i^* and for the resetting model just before resetting as y_i^-.

y_1 proportions agree in this case at around 6%, the continuous-influx model predicts an eventual proportion of 32% second-stage bulimics compared to only 21% for the periodic resetting model, a difference of over 11%). This distinction remains if we distribute the entering bulimics between y_1 and y_2, as illustrated in the last line of the table, in which each stage receives 5% of the incoming students. As neither set of percentages is significantly different from the previous case, this suggests that it is only necessary to have students incoming into the y_i class and not so important how they are distributed when they arrive.

The prediction of the 1-dimensional model in which the solution of the continuous model is always bounded above and below by the metered model solution does not necessarily hold for all the state variables in higher dimensions. For example, if we have 1% entering y_1 and 53% entering y_2 (or 0% y_1 and 53% or 54% y_2), then the continuous influx solution for y_1 and y_2 will remain bounded by the extrema of its metered counterpart; see Figure 7. However, changing these by even a single percent causes the y_2 to go outside of these bounds (y_1 appears to be far more robust). In the case of x, numerical investigation suggests that the solution from the continuous influx model will always be outside and below its metered counterpart.

5. **Conclusions.** Metering provides a way to model changes in populations better described as periodic and near-instantaneous than continuous. Although all models are gross oversimplifications of reality, confidence in their predictions and explanations derives from the robustness of the results across many different models with similar characteristics. Simplifying metered models by describing influxes as continuous averages predicts target population curves which typically remain within the "bounds" provided by the corresponding metered model (an apparent indication of robustness); however, the examples presented in this study show that other populations in the system may be affected quite differently, with continuous-influx model solutions well outside (above or below) the range of the corresponding metered model solutions. In the models analyzed here, continuous-influx models predicted faster tumor shrinkage than would occur with periodic dosing, and on the other hand persistence of bulimic populations under circumstances when periodic admission of students precludes their survival, or predicts a significantly lower endemic persistence level.

This latter result is significant for epidemic modeling, in that the effects of metering appear to interfere with the ability of an infection's basic reproductive number to measure the infection's ability to invade a population. The periodic "dilution" of infectives by metering seems to reduce the instantaneous infection rate so much

at once that it prevents the epidemic from recovering to its previous level before the next reset, even when it can overcome an equivalent time-averaged continuous removal of infectives. The drug dosing application makes evident the significance to such a spread within a single host, but this result may have implications at the metapopulation level for disease control policies involving discrete, recurring activities. Methods have been developed (e.g., [15]) to generate point estimates of a time-dependent reproductive number, without incorporating explicitly the discontinuities incurred by metering.

Further study is necessary to determine whether there is any consistent difference between the effects of periodic increments and periodic resetting.

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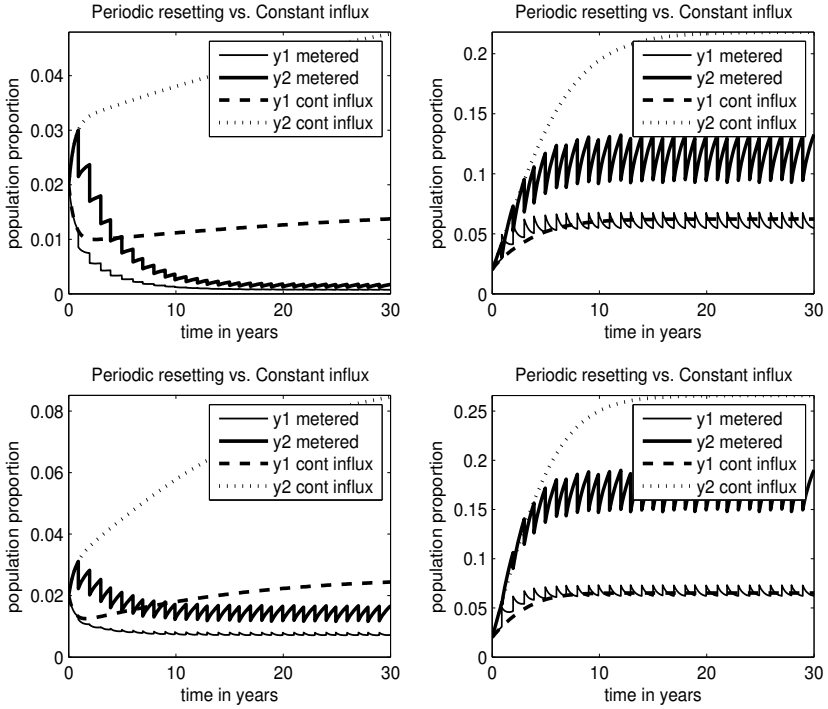

FIGURE 6. Application of periodic resetting for the bulimia model. Above left: $k_1 = 0.001$, $k_2 = 0$. Below left: $k_1 = 0.01$, $k_2 = 0$. Above right: $k = 0.1$, $k_2 = 0$. Below right: $k_1 = 0.1$, $k_2 = 0.05$.

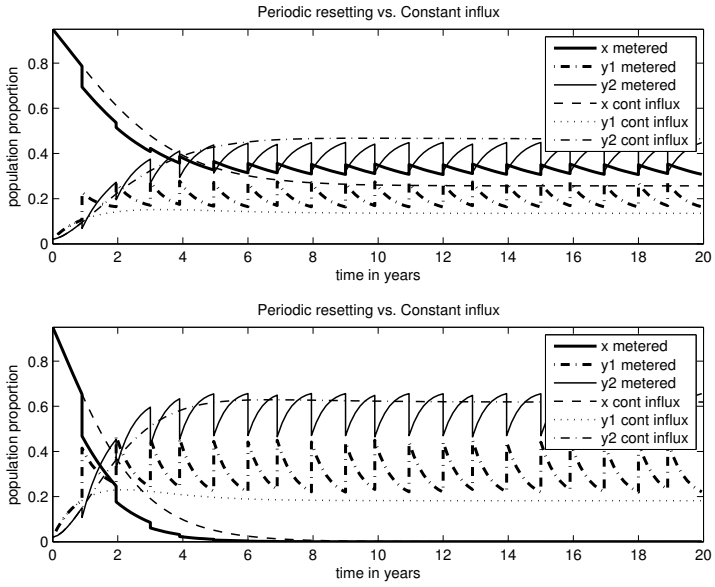

FIGURE 7. Application of periodic resetting for the bulimia model. In the top graph, 54% of new arrivals go into y_2, with the remaining going into x. The steady state solution of the continuous influx model for both y_1 and y_2 are between the extrema of their metered counterparts. In the bottom graph, 99.99% go into y_1 with remaining going into x yet the steady state solution of the continous influx model for x remains below its metered counterpart. Only y_2 is within its metered bounds in this bottom graph.

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E-mail address: erika.camacho@asu.edu
E-mail address: kribs@uta.edu
E-mail address: swirkus@asu.edu