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DISTRIBUTED DELAY DIFFERENTIAL EQUATION REPRESENTATIONS OF CYCLIC DIFFERENTIAL EQUATIONS*

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Abstract. Compartmental ordinary differential equation (ODE) models are used extensively in mathematical biology. When transit between compartments occurs at a constant rate, the well-known linear chain trick can be used to show that the ODE model is equivalent to an Erlang distributed delay differential equation (DDE). Here, we demonstrate that compartmental models with nonlinear transit rates and possibly delayed arguments are also equivalent to a scalar distributed DDE. To illustrate the utility of these equivalences, we calculate the equilibria of the scalar DDE, and compute the characteristic function—without calculating a determinant. We derive the equivalent scalar DDE for two examples of models in mathematical biology and use the DDE formulation to identify physiological processes that were otherwise hidden by the compartmental structure of the ODE model.

Key words. delay differential equations, infinite delay equations, mathematical biology, linear chain trick

AMS subject classifications. 92D25, 92B05, 45J05, 34K17, 34A05

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1. Introduction.

Multicompartment models, where changes in one population propagate through a chain of successive stages, have been used extensively in mathematical biology. Examples include inhibitory (and excitatory) neuronal feedback loops [19, 21, 39, 45], cellular reproduction [2, 4, 7, 48, 49], enzymatic production [1, 23, 60], infectious disease epidemiology [9, 29, 32, 44], and many others. It is well established that, when the relationship between stages is linear, these compartmental models "hide" delays [4, 6, 25, 51, 53]. Recently, there has been increased interest in establishing the equivalence between models that explicitly include delays, like renewal or distributed delay differential equations (DDEs), and multistage ordinary differential equation (ODE) models [9, 13, 14, 15, 28].

In general, these multistage models follow a chainlike structure, with one population influencing the next. When there is feedback between the first and last populations, these chainlike structures close and become cyclic. Here, we formalize the relationship between these cyclic differential equations and distributed DDEs. Specifically, we establish the equivalence between a scalar distributed DDE and the general, possibly delayed, cyclic differential equation

$$\frac{\mathrm{d}}{\mathrm{dt}}x_i(t) = f_i\left(\int_0^\infty x_{i-1}(t-\varphi)K_i(\varphi)\mathrm{d}\varphi\right) - \left(\mu(x_n(t))\right)x_i(t) \quad \text{for} \quad i = 1,\dots,n, \tag{1.1}$$

where the indices i are taken mod n. Equation (1.1) includes the convolution integral

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term

$$\int_0^\infty x_i(t-\varphi)K_i(\varphi)\mathrm{d}\varphi,$$

where each $K_i(\varphi)$ is a probability density function (PDF) that satisfies

$$K_i(\varphi) \geqslant 0 \quad \forall \varphi \geqslant 0 \quad \text{and} \quad \int_0^\infty K_i(\varphi)\mathrm{d}\varphi = 1.$$

Thus, we study the relationship between scalar distributed DDEs and multistage models that potentially include nonlinearities and delays. In particular, two specific formulations of (1.1) have been extensively studied. First, by choosing $K_i(\varphi) = \delta(\varphi - \tau_i)$, where, here and in what follows, $\delta(\varphi)$ is the Dirac delta distribution at $\varphi = 0$, (1.1) becomes the system of cyclic discrete DDEs with delays τ_i given by

$$\frac{\mathrm{d}}{\mathrm{dt}}x_i(t) = f_i\left(x_{i-1}(t-\tau_i)\right) - \left(\mu(x_n(t))\right)x_i(t) \quad \text{for} \quad i = 1,\ldots,n, \tag{1.2}$$

where, once again, the indices i are taken mod n.

The system (1.2) has been studied in depth by a number of authors [3, 30, 41]. Previously derived results include a Poincaré–Bendixson theorem for the discrete system of DDEs (1.2) when $\mu(x_n(t)) = 0$ [41], and the existence of periodic solutions of (1.2) under modest assumptions on the specific feedback functions f_i [3, 30]. We consider a particular example of (1.2), used in the context of lac-operon dynamics [60] in section 4.

Conversely, (1.1) is quite common in mathematical modeling in the delay free case: after setting $K_i(\varphi) = \delta(\varphi)$, the delay in (1.1) vanishes, and the system becomes a multicompartment ODE. Then, the equivalence of an Erlang, or gamma type distribution with an integer shape parameter, distributed DDE, and a system of ODEs has been known since at least the 1960s [53]. The linear chain trick, or linear chain technique (LCT), establishes the equivalence between Erlang distributed DDEs and transit compartment ODE models with a constant transition rate [36, 51]. Recently, a number of authors have generalized the LCT to other distributions and model formulations [14, 15, 28]. Often, these transit compartment ODE models take the form, for some function F,

$$\begin{cases} \dfrac{\mathrm{d}}{\mathrm{dt}}x_1(t) = \dfrac{\beta(x_n(t))}{V^*} - V^*x_1(t), \\ \dfrac{\mathrm{d}}{\mathrm{dt}}x_i(t) = V^*\left[x_{i-1}(t) - x_i(t)\right] \quad \text{for} \quad i = 2,3,\ldots,n-1, \\ \dfrac{\mathrm{d}}{\mathrm{dt}}x_n(t) = F(x_n(t), V^*x_{n-1}(t)), \end{cases} \tag{1.3}$$

where, for the constant transit rate between compartments V^*, we see that $f_i(x_{i-1}(t)) = V^*x_{i-1}(t)$ and $\mu(x_n(t))x_i(t) = V^*x_i(t)$, while $f_1(x_n(t)) = \beta(x_n(t))/V^*$ acts as the recruitment rate into the chain of transit compartments. The LCT consists of replacing the transit compartment chain $\{x_i(t)\}_{i=1}^{n-1}$ with the distributed delay term

$$x_{n-1}(t) = \int_0^\infty \frac{\beta(x_n(t-s))}{V^*}g_{V^*}^{n-1}(s)\mathrm{d}s, \tag{1.4}$$

where $g_{V^*}^{n-1}(s)$ is the PDF of the gamma distribution with scale parameter V^* and shape parameter $n-1$:

$$g_{V^*}^{n-1}(s) = \frac{(V^*)^{n-1}s^{n-2}e^{-V^*s}}{(n-2)!}.$$

The linchpin of the LCT is the ability to write the functions $\{g_{V^*}^i(s)\}_{i=1}^{n-1}$ as the solution of a system of differential equations

$$\frac{\mathrm{d}}{\mathrm{d}s}g_{V^*}^1(s) = -V^*g_{V^*}^1(s) \quad \text{and} \quad \frac{\mathrm{d}}{\mathrm{d}s}g_{V^*}^i(s) = V^*[g_{V^*}^{i-1}(s) - g_{V^*}^i(s)],$$

which is an explicit example of a sufficient condition to replace a distributed DDE by a system of ODEs [20, 54], namely, that there exist functions $\{a_i(t)\}_{i=0}^{n-1}$ such that the delay kernel $K(t)$ satisfies

$$\frac{\mathrm{d}^n}{\mathrm{d}t^n}K(t) + \sum_{i=0}^{n-1} a_i(t)\frac{\mathrm{d}^i}{\mathrm{d}t^i}K(t) = 0.$$

Often, particularly in the pharmaceutical sciences, the transit rate and clearance terms are not constant, but rather determined through an external or environmental variable, $E(t)$, so $f_i(x_{i-1}(t), E(t)) = V(E(t))x_{i-1}(t)$ and $\mu(x_n(t), E(t)) = V(E(t))x_i(t)$ [4, 27, 34, 49]. Naively including a variable transit rate, $V(E(t))$ in (1.3) gives

$$\begin{cases} \dfrac{\mathrm{d}}{\mathrm{dt}}x_1(t) = \dfrac{\beta(x_n(t))}{V(E(t))} - V(E(t))x_1(t), \\ \dfrac{\mathrm{d}}{\mathrm{dt}}x_i(t) = V(E(t))\left[x_{i-1}(t) - x_i(t)\right] \quad \text{for} \quad i = 2, 3, \ldots, n-1, \\ \dfrac{\mathrm{d}}{\mathrm{dt}}x_n(t) = F(x_n(t), V(E(t))x_{n-1}(t)). \end{cases} \tag{1.5}$$

Cassidy, Craig, and Humphries [6] established the equivalence between (1.5) and a state dependent gamma distributed DDE by explicitly considering the age-structured partial differential equation modeling the underlying maturation process. In the variable transit rate case, where V^* acts as a fixed scaling velocity to ensure that the homeostatic ageing rate is unity, the distributed delay term (1.4) becomes

$$x_{n-1}(t) = \int_0^\infty g_{V^*}^{n-1}\left(\int_{t-\varphi}^t \frac{V(E(s))}{V^*}\mathrm{d}s\right)\frac{\beta(x_n(t-\varphi))}{V(E(t-\varphi))}\mathrm{d}\varphi.$$

While the results developed in this work translate to models that include external control, we do not focus on state dependent distributed DDEs.

The model ingredients necessary to derive equations such as (1.3) or (1.5) were considered in [14, 15, 25]. Broadly speaking, creating a model like (1.3) or (1.5) requires determining the birth (or appearance) rate $\beta(x_n(t))$, the death (or growth rate) $\mu(x_n(t))$, and the ageing (or transit rate) $V(E(t))$. These model ingredients are precisely those catalogued by Diekmann, Gyllenberg, and Metz in their work on physiologically structured equations [14, 15]. In brief, these model ingredients allow for the development of a physiologically structured model. In their recent work, Diekmann, Gyllenberg, and Metz derived necessary and sufficient criteria to determine if the,

typically infinite dimensional, physiologically structured models can be reduced to a finite dimensional system of ODEs without the loss of relevant information [13, 14, 15].

The physiologically structured models considered by Diekmann, Gyllenberg, and Metz offer a framework to study the role of individual level heterogeneity on population level dynamics. These structured models allow for individuals to be continuously distributed in "trait" (i.e., age, size, maturity,...) space, rather than imposing the artificial binning that would be necessary in the ODE case. In general, these structured population models describe the evolution of a density p over the set of possible traits, which provides the physiological structure, Ω. Often, the population distribution across the possible states determines the model output and is a density over Ω, so $p \in L_1(\Omega)$. It is then natural to consider the population level dynamics, given by the time evolution of

$$N(t) = \int_\Omega \psi(x)p(t,x)\mathrm{d}x.$$

The function ψ acts as a weight function in mapping the distribution of individual states to the population, equivalently, the mapping $L_1(\Omega) \to \mathbb{R}^k$. Through careful bookkeeping, it is sometimes possible to cast the evolution of $N(t)$ as a delay, or renewal, equation [16, 17]

$$N(t) = F(N_t),$$

where $N_t(\theta) = N(t+\theta)$ for $\theta \in (-\infty, 0]$ and, for $\rho > 0$, solutions live in the natural phase space [12]

$$L_{1,\rho} = \left\{ f \;\middle|\; \int_{-\infty}^{0} |f(\varphi)|e^{\rho\varphi}\mathrm{d}\varphi < \infty \right\}.$$

Here, we employ a similar bookkeeping strategy when considering the cyclic system (1.1) to obtain a scalar distributed DDE. Effectively, by tracking the appearance or recruitment rate into each compartment and measuring the expansion or contraction of each cohort, we write down a componentwise solution of the transit stages in the cyclic differential equation (1.1) in section 2. Then, similarly to the LCT, we are left with a scalar distributed DDE. However, unlike the classical LCT and existing variants, our technique extends to models with both nonlinear clearance rates and the delayed terms from (1.1). We then show how recasting the system of n DDEs as the equivalent scalar distributed DDE simplifies model analysis by establishing nonnegativity of solutions and giving an explicit expression for equilibria. We calculate the characteristic equation by making extensive use of the chain rule for Fréchet derivatives to replace the $n \times n$ determinant typically involved in the calculation of the characteristic function in section 3. Next, we consider two biological systems and corresponding mathematical models which take the form of (1.1) in section 4. In particular, these examples elucidate how the chainlike structure of (1.1) hides delayed processes that are crucial in the physiological system, and offer the opportunity to illustrate the general theory established in the preceding sections while demonstrating how the equivalence between a cyclic differential equation and a scalar distributed DDE can be implemented in practice. We finish with a discussion of the mathematical and biological advantages and limitations of our work in a brief conclusion.

2. Generalized LCT. In this section, we demonstrate how to reduce (1.1) to a scalar distributed DDE. As mentioned, the theory for scalar DDEs is quite well

developed, so this reduction enables simpler analysis of the equivalent system. We note that the case of (1.1) with no explicit delays has been extensively studied and catalogued by Diekmann, Gyllenberg, and Metz [13, 14, 15]. For ease of notation, we separate our analysis into two cases: the first with only one explicit delay in (1.1) and the second with multiple explicit delays. In what follows, we use $x_{i,t}$ to denote the function segment $x_{i,t}(\theta) = x_i(t+\theta)$ for $\theta \in (-\infty, 0]$.

In the first case, to avoid cumbersome notation, we consider a specific case of (1.1) with $n = 3$:

$$\begin{cases} \dfrac{\mathrm{d}}{\mathrm{dt}} x_1(t) = f_1\left(\displaystyle\int_0^\infty x_3(t-\varphi)K_1(\varphi)\mathrm{d}\varphi\right) - \left(\mu(x_3(t))\right) x_1(t) \\ \dfrac{\mathrm{d}}{\mathrm{dt}} x_i(t) = f_i\left(x_{i-1}(t)\right) - \mu(x_3(t))x_i(t) \quad \text{for} \quad i = 2 \text{ and } 3. \end{cases} \tag{2.1}$$

We note that the differential equation for $x_1(t)$ in (2.1) is linear in x_1 and, otherwise, is a possibly nonlinear function of $x_{3,t}$. Specifically, the term

$$f_1\left(\int_0^\infty x_3(t-\varphi)K_1(\varphi)\mathrm{d}\varphi\right),$$

which is independent of $x_1(t)$, can be thought of as the recruitment rate at time t, while the factor $\mu(x_3(t))$ gives the growth or contraction rate of $x_1(t)$ at time t. Then, using Leibniz's rule, it is possible to verify that

$$\begin{aligned} x_1(t) &= \int_0^\infty f_1\left(\int_0^\infty x_3(t-s-\varphi)K_1(\varphi)\mathrm{d}\varphi\right)\exp\left(-\int_{t-s}^t \mu(x_3(u))\mathrm{d}u\right)\mathrm{d}s \\ &= \int_{-\infty}^t f_1\left(\int_0^\infty x_3(\sigma-\varphi)K_1(\varphi)\mathrm{d}\varphi\right)\exp\left(-\int_\sigma^t \mu(x_3(u))\mathrm{d}u\right)\mathrm{d}\sigma. \end{aligned}$$

We note that $x_1(t)$ is entirely determined by $x_3(t)$ and that the expression

$$f_1\left(\int_0^\infty x_3(t-s-\varphi_1)K_1(\varphi_1)\mathrm{d}\varphi_1\right)\exp\left(-\int_{t-s}^t \mu(x_3(u))\mathrm{d}u\right)$$

is the product of the recruitment into x_1 at time $t-s$ and the expansion or contraction, determined by the sign of μ, of that cohort between time $t-s$ and t. Using the same technique for $x_2(t)$, we obtain

$$\begin{aligned} x_2(t) &= \int_0^\infty f_2\left(x_1(t-r)\right)\exp\left(-\int_{t-r}^t \mu(x_3(u))\mathrm{d}u\right)\mathrm{d}r \\ &= \int_{-\infty}^t f_2\left(x_1(r)\right)\exp\left(-\int_r^t \mu(x_3(u))\mathrm{d}u\right)\mathrm{d}r. \end{aligned}$$

Now, using the expression for $x_1(t)$, we see that

$$\begin{aligned} x_2(t) = \int_{-\infty}^t f_2\left[\int_{-\infty}^r f_1\left(\int_0^\infty x_3(\sigma-\varphi_1)K_1(\varphi_1)\mathrm{d}\varphi_1\right)\exp\left(-\int_\sigma^r \mu(x_3(u))\mathrm{d}u\right)\mathrm{d}\sigma\right] \\ \times \exp\left(-\int_r^t \mu(x_3(u))\mathrm{d}u\right)\mathrm{d}r. \end{aligned}$$

Once again, we note that $x_2(t)$ is entirely determined by $x_3(t)$ alone, so we finally obtain the scalar distributed DDE

$$\begin{aligned}\frac{\mathrm{d}}{\mathrm{dt}}x_3(t) &= f_3\left(x_2(t)\right) - \left(\mu(x_3(t))\right)x_3(t)\\ &= f_3\left(\int_{-\infty}^{t} f_2\left[\int_{-\infty}^{r} f_1\left(\int_0^{\infty} x_3(\sigma-\varphi_1)K_1(\varphi_1)\mathrm{d}\varphi_1\right)\exp\left(-\int_{\sigma}^{r}\mu(x_3(u))\mathrm{d}u\right)\mathrm{d}\sigma\right]\right.\\ &\quad\left.\times\exp\left(-\int_{r}^{t}\mu(x_3(u))\mathrm{d}u\right)\mathrm{d}r\right) - \left(\mu(x_3(t))\right)x_3(t).\end{aligned}$$

We begin formalizing the relationship between the chain structure of (1.1) and a scalar distributed DDE by partially solving the differential equations for the transit compartments.

LEMMA 2.1. *Assume that* $[x_1(t), x_2(t), \ldots, x_n(t)]$ *solves* (1.1). *Then* $x_i(t) = F_i(x_{i-1,t}, x_{n,t})$ *for* $i \geqslant 2$, *where*

$$F_i(x_{i-1,t}, x_{n,t}) = \int_0^{\infty} f_i\left[\int_0^{\infty} x_{i-1}(t-s-\varphi)K_i(\varphi)\mathrm{d}\varphi\right]\exp\left(-\int_{t-s}^{t}\mu(x_n(u))\mathrm{d}u\right)\mathrm{d}s.$$

Proof. The proof is a straightforward application of the arguments used in the above treatment of (2.1). ∎

We now show that, since $x_1(t)$ is entirely determined by $x_{n,t}$ through

(2.2)
$$x_1(t) = \int_0^{\infty} f_1\left(\int_0^{\infty} x_n(t-s-\varphi)K_1(\varphi)\mathrm{d}\varphi\right)\exp\left(-\int_{t-s}^{t}\mu(x_n(u))\mathrm{d}u\right)\mathrm{d}s = G_1(x_{n,t}),$$

the cyclic nature of (1.1) allows us to write each intermediate variable x_i as a function of the final stage x_n, as in the LCT.

THEOREM 2.2. *Let* $[x_1(t), x_2(t), \ldots, x_n(t)]$ *satisfy* (1.1). *Then,* $x_n(t)$ *satisfies the scalar distributed DDE*

$$\frac{d}{dt}x_n(t) = f_n\left(\int_0^{\infty} G_{n-1}(x_n(t-\varphi))K_n(\varphi)\mathrm{d}\varphi\right) - \left(\mu(x_n(t))\right)x_n(t),$$

where the G_i *are defined iteratively with* $G_1(x_{n,t})$ *in* (2.2) *and*

$$G_i(x_{n,t}) = F_i(G_{i-1}(x_{n,t}), x_{n,t}) \quad \textit{for} \quad i \geqslant 2.$$

Proof. Using (2.2) and Lemma 2.1, we write

$$x_1(t) = G_1(x_{n,t}) \quad \text{and} \quad x_i(t) = F_i(x_{i-1,t}, x_{n,t}).$$

Then, as $x_1(t) = G_1(x_{n,t})$, it follows that $x_2(t) = F_2(G_1(x_{n,t}), x_{n,t}) = G_2(x_{n,t})$. Now, we can repeat this for $i = 3, \ldots, n-1$, and obtain

$$x_{n-1}(t) = F_{n-1}(x_{n-2,t}, x_{n,t}) = F_{n-1}(G_{n-2}(x_{n,t}), x_{n,t}) = G_{n-1}(x_{n,t}),$$

so that

$$\frac{\mathrm{d}}{\mathrm{d}t}x_n(t) = f_n\left(\int_0^\infty x_{n-1}(t-\varphi)K_n(\varphi)\mathrm{d}\varphi\right) - (\mu(x_n(t)))\,x_n(t)$$
$$= f_n\left(\int_0^\infty G_{n-1}(x_n(t-\varphi))K_n(\varphi)\mathrm{d}\varphi\right) - (\mu(x_n(t)))\,x_n(t). \qquad \square$$

We have shown that the dynamics of the cyclic system (1.1) is determined by the dynamics of the final stage $x_n(t)$. In what follows, for notational convenience, when considering the scalar DDE reduction of the cyclic system in (1.1), we drop the index n and instead write $x_n(t) = y(t)$, where

$$\frac{\mathrm{d}}{\mathrm{d}t}y(t) = f_n\left(\int_0^\infty G_{n-1}(y(t-\varphi))K_n(\varphi)\mathrm{d}\varphi\right) - (\mu(y(t)))\,y(t).$$

To complete the equivalence between the scalar distributed DDE and the system of cyclic differential equations (1.1), we must map the initial data from one formulation to the other. This mapping can be slightly complicated, as the dimensions of phase space may be different in each formulation. For example, the classic LCT establishes the equivalence between an Erlang distributed DDE with initial data in the corresponding infinite dimensional probability space with a system of ODEs with finite dimensional phase space. Thus, we discuss the implications of the slightly restrictive general requirement following the theorem.

THEOREM 2.3. *There is a mapping between solutions* $\{x_i(t)\}_{i=1}^n$ *of the cyclic differential equation* (1.1) *with initial data* $\{\xi_i(s)\}_{i=1}^n$ *for* $s < 0$ *and the scalar distributed DDE for* $y(t)$ *given by*

(2.3)
$$\frac{d}{dt}y(t) = f_n\left(\int_0^\infty G_{n-1}(y(t-\varphi))K_n(\varphi)\mathrm{d}\varphi\right) - (\mu(y(t)))\,y(t), \quad y(s) = \psi(s) \quad \textit{for} \quad s < 0,$$

where $G_{n-1}(y(t))$ *is given in Theorem* 2.2 *if the initial data satisfy*

$$\xi_i(s) = G_i(\psi_s) \quad K_i\textit{-almost everywhere} \quad \textit{with} \quad \xi_n(s) = \psi(s). \tag{2.4}$$

Proof. Assume that $\{x_i(t)\}_{i=1}^n$ is a solution of (1.1) with initial data $\{\xi_i(s)\}_{i=1}^n$. Then, we set $y(t) = x_n(t)$, and it follows from the construction of the G_i that $y(t)$ solve (2.3) with $y(s) = \psi(s)$ for $s < 0$ with $\psi(s) = \xi_n(s)$.

Now, assume that $y(t)$ solves (2.3) with $y(s) = \psi(s)$. Then, Theorem 2.2 ensures that $x_n(t) = y(t)$ and $x_i(t) = G_i(x_{n,t})$ for $i = 2, 3, \ldots, n-1$ solve the differential equation (1.1) with initial data given by (2.4). $\square$

Remark 2.4 (on the compatibility of initial data). In general, a system of DDEs like (1.1) takes initial data in the infinite dimensional phase space [12]

$$C_{0,\rho,} = \left\{ f \in C_0 \;\middle|\; \lim_{\varphi\to-\infty} f(\varphi)e^{\rho\varphi} = 0 \right\}.$$

As the phase space of the cyclic differential formulation and the scalar distributed DDE are both infinite dimensional, the strict condition on the history functions ξ_i in (2.4) is perhaps unsurprising. Nevertheless, while (2.4) appears restrictive, it is directly linked to the cyclic structure of the system (1.1). Specifically, we have shown that the dynamics of (1.1) are driven by the final stage, and (2.4) encodes this dependence in the history of the system by enforcing that the initial data follow this

relationship. In practice, the modeler needs only to determine the history of the final stage—which is the stage that drives the dynamics of the entire system—and then read off the corresponding history of the remaining $n-1$ compartments from (2.4). When considering biological or physical systems, this corresponds to assuming that perturbations (such as therapies or other interventions) to the cyclic structure of the system do not occur in the past, and is satisfied in many (if not most) models [4, 9, 34].

A specific version of the constraint (2.4) appears in the transit compartment case where (1.1) does not include explicit delays, so $K_i(\varphi) = \delta(\varphi)$. In this case, the initial data are the vector $[\xi_1^0, \dots, \xi_n^0] \in \mathbb{R}^n$ and the equivalent constraint to (2.4) appears throughout the literature; setting $\xi_i^0 = G_i(\psi_0)$ maps a given history function ψ to the initial conditions ξ_i^0 [9, 13, 51]. The inverse mapping is more delicate. For arbitrary $[\xi_1^0, \dots, \xi_n^0]$, we must construct a function ψ such that $\xi_i^0 = G_i(\psi_0)$ holds. In general, ξ_i^0 must belong to the range of G_i but deriving more specific conditions is model dependent. However, in models similar to the classic transit compartment case where $K_i(\varphi) = \delta(\varphi)$ and each f_i is linear, then it is possible to construct infinitely many such ψ for arbitrary $[\xi_1^0, \dots, \xi_n^0]$ [7].

3. Properties of the scalar distributed DDE. Equation (1.1) has been extensively studied in both the discrete delay case, where $K_i(s) = \delta(s - \tau_i)$, and the no delay case where $K_i(s) = \delta(s)$ [3, 30, 41]. As we are primarily interested in biological systems exhibiting a cyclic nature, we begin by demonstrating that, for modest assumptions on the functions f_i, solutions of (1.1) evolving from nonnegative initial data remain nonnegative.

PROPOSITION 3.1. *Assume that μ is bounded above so $\mu(y) \leqslant \mu_{max}$ and that the initial data ξ_n satisfy*

$$\int_{-\infty}^{0} \xi_n(0-\varphi) K_i(\varphi) \mathrm{d}\varphi > 0 \quad \textit{for} \quad i = 1, 2, \dots, n$$

with $\xi_n(0) \geqslant 0$. Further, assume that each f_i satisfies

$$f_i(x) > 0 \quad \textit{if} \quad x > 0 \quad \textit{and} \quad f_i(0) = 0, \quad i = 1, 2, \dots, n.$$

Then, the solution of the IVP (2.3) satisfies $y(t) \geqslant 0$ for all $t > 0$.

Proof. To begin, we note that if $G_{n-1}(y_t) \geqslant 0$ K_n-almost everywhere, then

$$\frac{\mathrm{d}}{\mathrm{d}t} y(t) \geqslant -\mu(y(t)) y(t) \geqslant -\mu_{max} y(t)$$

and Gronwall's inequality gives

$$y(t) \geqslant y(0) \exp\left(-\mu_{max} t\right) \geqslant 0.$$

Therefore, to establish the claim, it is sufficient to show that $G_{n-1}(y_t) \geqslant 0$. From

$$\begin{aligned} G_i(y_t) &= F_i(G_{i-1}(y_t), y_t) \\ &= \int_0^\infty f_i \left[\int_0^\infty G_{i-1}(y_{t-s-\varphi}) K_i(\varphi) \mathrm{d}\varphi \right] \exp\left(- \int_{t-s}^{t} \mu(y(u)) \mathrm{d}u \right) \mathrm{d}s, \end{aligned}$$

and the assumption on f_i, if $G_{i-1}(y_t) \geqslant 0$ K_i-almost everywhere, then $G_i(y_t) \geqslant 0$.

Now, consider

$$G_1(y_0) = \int_0^\infty f_1\left(\int_0^\infty \xi_n(0-s-\varphi)K_1(\varphi)\mathrm{d}\varphi\right)\exp\left(-\int_{-s}^0 \mu(\xi_n(u))\mathrm{d}u\right)\mathrm{d}s,$$

which is strictly positive by the assumptions on f_1 and ξ_n, and note that if $y_t \geqslant 0$, then $G_1(y_t) \geqslant 0$. We consider two distinct cases.

Case I. Assume that $\xi_n(0) > 0$, and let t^* be the first time such that $y(t^*) = 0$. Then, for $s \in [0, t^*]$, $y(s) \geqslant 0$ and we obtain $G_i(y_s) \geqslant 0$. Then, for $t \in [0, t^*]$, we have

$$\frac{\mathrm{d}}{\mathrm{d}t}y(t) \geqslant -\mu_{max}y(t),$$

and Gronwall's inequality gives

$$0 = y(t^*) \geqslant \xi_n(0)\exp(-\mu_{max}t^*) > 0,$$

which is a contradiction so no t^* can exist.

Case II. Assume that $\xi_n(0) = 0$. Now, if $G_{n-1} = 0$ K_n-almost everywhere for all $t > 0$, then $y = 0$ is the solution of the differential equation. Alternatively, let $\hat{t}$ be the first time such that

$$\int_0^\infty G_{n-1}(y_{\hat{t}-\varphi})K_n(\varphi)d\varphi > 0,$$

so

$$\frac{\mathrm{d}}{\mathrm{d}t}y(t)\bigg|_{t=\hat{t}} = f_n\left(\int_0^\infty G_{n-1}(y_{\hat{t}-\varphi})K_n(\varphi)d\varphi\right) > 0,$$

so y becomes positive at time $\hat{t}$ and we return to Case I. ∎

After establishing a mathematical model, a first step is often the study of equilibria. In (1.1), an equilibrium solution is a vector of constant functions $[x_1^*, x_2^*, \ldots, x_n^*]$ such that

$$\left[\frac{\mathrm{d}}{\mathrm{d}t}x_1(t), \frac{\mathrm{d}}{\mathrm{d}t}x_2(t), \ldots, \frac{\mathrm{d}}{\mathrm{d}t}x_n(t)\right]\bigg|_{[x_1(t),\ldots,x_n(t)]=[x_1^*,\ldots,x_n^*]} = [0, 0, \ldots, 0].$$

Consequently, calculating the equilibrium solution involves simultaneously finding the zeros of n nonlinear multivariate functions. This calculation is simplified by the fact that (1.1) admits a Jacobian matrix with zeroes below the first subdiagonal. The Jacobian is thus an upper Hessenberg matrix and is particularly amenable to iterative solvers such as Newton's method despite the nonlinearities present in (1.1) [52]. Conversely, equilibria y^* of (2.3) satisfy the single variable equation

$$0 = f_n\left(G_{n-1}(y^*)\right) - \mu(y^*)y^*. \tag{3.1}$$

In the case of (3.1), we can use techniques from single variable calculus such as the intermediate and mean value theorems to analytically establish the existence and uniqueness of an equilibrium solution. As (1.1) and (2.3) are equivalent, we can then exploit the favorable Hessenberg structure of the Jacobian to numerically calculate the equilibrium values.

We define the equilibrium clearance rate by

$$\mu^* = \mu(y^*), \tag{3.2}$$

and returning to the definition of $G_i(y^*)$, we calculate

$$G_1(y^*) = \int_0^\infty f_1\left(\int_0^\infty y^* K_1(\varphi)\mathrm{d}\varphi\right)\exp\left(-\mu^* s\right)\mathrm{d}s = \frac{f_1(y^*)}{\mu^*}$$

and

$$\begin{aligned} G_i(y^*) &= \int_0^\infty f_i\left[\int_0^\infty G_{i-1}(y^*)K_i(\varphi)\mathrm{d}\varphi\right]\exp\left(-\mu^* s\right)\mathrm{d}s \\ &= \frac{f_i(G_{i-1}(y^*))}{\mu^*} = \frac{f_i}{\mu^*}\circ\frac{f_{i-1}}{\mu^*}\circ\cdots\circ\frac{f_1(y^*)}{\mu^*}. \end{aligned}$$

We note that $f_i(x^*_{i-1})/\mu^* = f_i(G_{i-1}(y^*))/\mu^*$ is precisely the term that would be obtained by solving (1.1) for the n different components of an equilibrium solution.

3.1. Characteristic function of the scalar distributed DDE. Once an equilibrium solution has been found, often the next step is to study the local stability of the equilibrium. As shown by Diekmann and Gyllenberg [12], the local stability of an equilibrium y^* is determined via the position of zeros of the characteristic function. For cyclic systems (1.1) of n DDEs given by

$$\frac{\mathrm{d}}{\mathrm{d}t}u(t) = F(u(t), u_t),$$

the characteristic function is determined by solving a transcendental eigenvalue problem arising from the $n \times n$ determinant

$$\det\left[\lambda I - A - \mathcal{L}[B](\lambda)\right],$$

where A and B are the Fréchet derivatives of F with respect to u and u_t evaluated at the equilibrium point u^* and $\mathcal{L}[B](\lambda)$ denotes the Laplace transform of B evaluated at λ. From the cyclic structure of (1.1), the Jacobian matrix $A + \mathcal{L}[B](\lambda)$ is an upper Hessenberg matrix, where $\mathcal{L}[B](\lambda)$ involves the calculation of a Fréchet derivative for each delayed term on the right-hand side of (1.1). Many efficient numerical methods exist for matrices with this special structure and the determinant of $A + \mathcal{L}[B](\lambda)$ can be expressed analytically as a recursive relationship by expanding the matrix along the final column [52]. However, if, as in the model of white blood cell production considered in section 4.2, modelers wish to vary the number of compartments n, then the recursive definition only allows for limited carryover from case to case. Further, the stability of an equilibrium is determined by the solutions of a nonlinear eigenvalue problem due to the dependence $\mathcal{L}[B](\lambda)$ on λ (which is typically not polynomial in λ), so in both the system and scalar case, the eigenvalue problem is often numerically solved by Newton iteration and without exploiting any possible decompositions of $A + \mathcal{L}[B](\lambda)$.

We now demonstrate how the reduced scalar distributed DDE can simplify the calculation of the characteristic equation. Assume that y^* solves (3.1) and μ^* is given by (3.2), so

$$f_n\left(G_{n-1}(y^*)\right) = \mu^* y^*,$$

and define $z(t) = y(t) - y^*$ with

$$\begin{aligned} \frac{\mathrm{d}}{\mathrm{d}t}z(t) &= f_n\left(\int_0^\infty G_{n-1}(y(t-\varphi))K_n(\varphi)\mathrm{d}\varphi\right) - \mu(y(t))y(t) \\ &= f_n\left(\int_0^\infty G_{n-1}(y^* + z(t-\varphi))\mathrm{d}\varphi\right) - \mu(y^* + z(t))(y^* + z(t)). \end{aligned} \tag{3.3}$$

To complete the linearization, we first consider nondelayed arguments of the right-hand side of (3.3) with linear approximation

$$\mu(y^* + z(t))(y^* + z(t)) = \mu^* y^* + \mu^* z(t) + \mu'(y^*)z(t)y^* + \mathcal{O}(z^2).$$

We now turn to the delayed argument in (3.3), and must compute the Fréchet derivative of the operator H that maps $\psi \in C_{0,\rho}$:

$$H : \psi(t) \to f_n\left(\int_0^\infty G_{n-1}(\psi(t-\varphi))K_n(\varphi)\mathrm{d}\varphi\right).$$

The chain rule for Fréchet derivatives gives

$$\begin{aligned} DH(\psi) &= f_n'(G_{n-1}(\psi))DG_{n-1}(\psi) \\ &= f_n'(G_{n-1}(\psi))DG_{n-1}(G_{n-2}(\psi))\dots DG_2(G_1(\psi))DG_1(\psi). \end{aligned}$$

Now, expanding $G_1(y^* + \psi)$ about y^* gives

$$\begin{aligned} DG_1(y^*)\psi(t) = &\int_0^\infty f_1'(y^*)\left[\int_0^\infty \psi(t-s-\varphi)K_1(\varphi)\mathrm{d}\varphi\right]e^{-\mu^* s}\mathrm{d}s \\ &+ \int_0^\infty e^{-\mu^* s} f_1(y^*)\left[\int_{t-s}^t \mu'(y^*)\psi(x)\mathrm{d}x\right]\mathrm{d}s \end{aligned}$$

and after setting $\psi(t) = Ce^{\lambda t}$, we get

$$\begin{aligned} DG_1(\psi(t)) &= \mathcal{L}[K_1](\lambda)\left(\frac{f_1'(y^*)}{\mu^* + \lambda}\right)Ce^{\lambda t} \\ &\quad + \mu'(y^*)f_1(y^*)\left[\int_0^\infty e^{-\mu^* s}\left(\frac{Ce^{\lambda t} - Ce^{\lambda(t-s)}}{\lambda}\right)\mathrm{d}s\right] \\ &= \mathcal{L}[K_1](\lambda)\left(\frac{f_1'(y^*)}{\mu^* + \lambda}\right)Ce^{\lambda t} + \mu'(y^*)f_1(y^*)\left(\frac{1}{\mu^*} - \frac{1}{\mu^* + \lambda}\right)\frac{Ce^{\lambda t}}{\lambda} \\ &= \left(\mathcal{L}[K_1](\lambda)\left(\frac{f_1'(y^*)}{\mu^* + \lambda}\right) + \frac{\mu'(y^*)f_1(y^*)}{\mu^*(\mu^* + \lambda)}\right)\psi(t). \end{aligned}$$

As the above calculation holds for $i = 2, 3, \dots, n-1$, it follows from induction that

$$DH(y^*)\psi = f_n'(G_{n-1}(y^*))\prod_{i=1}^{n-1}\left(\mathcal{L}[K_i](\lambda)\left(\frac{f_i'(G_{i-1}(y^*))}{\mu^* + \lambda}\right) + \frac{\mu'(y^*)f_i(G_{i-1}(y^*))}{\mu^*(\mu^* + \lambda)}\right)\psi,$$

where $\psi(t) = Ce^{\lambda t}$. Then, $z(t) = y(t) - y^*$ satisfies the linear differential equation

$$\frac{\mathrm{d}}{\mathrm{d}t}z(t) = DH(y^*)z - [\mu^* z(t) + \mu'(y^*)z(t)y^*]$$

which, using the ansatz $z = Ce^{\lambda t}$ and the resulting expression for DH, becomes

$$\begin{aligned} \lambda z(t) = &f_n'(G_{n-1}(y^*))\prod_{i=1}^{n-1}\left(\mathcal{L}[K_i](\lambda)\left(\frac{f_i'(G_{i-1}(y^*))}{\mu^* + \lambda}\right) + \frac{\mu'(y^*)f_i(G_{i-1}(y^*))}{\mu^*(\mu^* + \lambda)}\right)z(t) \\ &- [\mu^* + \mu'(y^*)y^*]\,z(t). \end{aligned}$$

Cancelling the $z(t)$ terms gives the characteristic equation

$$\lambda = f_n'(G_{n-1}(y^*)) \prod_{i=1}^{n-1} \left(\mathcal{L}[K_i](\lambda) \left(\frac{f_i'(G_{i-1}(y^*))}{\mu^* + \lambda} \right) + \frac{\mu'(y^*) f_i(G_{i-1}(y^*))}{\mu^* (\mu^* + \lambda)} \right) \tag{3.4}$$

$$- \left[\mu^* + \mu'(y^*) y^* \right], \tag{3.5}$$

whose roots can be determined using singe variable Newton iteration. Further, we note that the Laplace transforms are of the delay kernels K_i. These Laplace transforms are precisely the moment generating the functions of the random variable with density K_i and are known for most common kernels.

While these computations are cumbersome due to the notation involved, if we were to add an additional stage to (1.1) as in the model of white blood cells mentioned earlier and analyzed in section 4.2, updating the characteristic equation (3.5) would be straightforward. In particular, we avoid calculating an $(n+1) \times (n+1)$ determinant, and simply multiply one extra factor in the product. In section 4, we illustrate the simplicity of calculating the characteristic equation of the scalar distributed DDE for equations arising in biological modeling.

In general, expanding the product of Laplace transforms yields n different convolutions. In many biological examples, the growth or clearance rate is not state dependent, so $\mu'(y^*) = 0$ and the product in (3.5) becomes

$$\prod_{i=1}^{n-1} \mathcal{L}[K_i](\lambda) \left(\frac{f_i'(G_{i-1}(y^*))}{\mu^* + \lambda} \right) = \mathcal{L}[K_1 * K_2 * \cdots * K_{n-1}](\lambda) \prod_{i=1}^{n-1} \left(\frac{f_i'(G_{i-1}(y^*))}{\lambda + \mu^*} \right).$$

The convolution of the PDFs K_i represents the concatenation of the delayed processes wherein changes in x_1 propagate to x_n in the cyclic differential equation formulation given by (1.1). As the densities $K_i(\varphi)$ are only defined for $\varphi > 0$, the convolution of Laplace transforms is the moment generating function for the random variable modeling the time delay between the first and the nth compartment. As the sojourn times in each stage are independent, this random variable is the sum of the random variables defining the sojourn time in each stage. Consequently, the mean delay between the first and nth compartment is precisely the sum of the mean sojourn times in each compartment, as would be expected. Consequently, this form of the characteristic equation emphasizes the concatenation of delayed processes modeled by the system of cyclic differential equations (1.1), and allows modelers to both identify otherwise hidden delayed processes and ensure that the delays are consistent between the model and experimental system. For completeness, we note that this term is present in the more general case where $\mu'(y^*) \neq 0$.

4. Examples. The form of (1.1) is quite general and encompasses a large number of mathematical models of physiological processes, including those mentioned earlier. Here, we consider models of two distinct biological processes to illustrate the general technique derived in section 2. We begin with a model of the dynamics of the lac-operon, in which sequential expression of intermediate proteins controls the ability to use lactose an energy source. We consider Goodwin's ODE model of lac-operon dynamics, as well as a discrete DDE form of the same model, and reduce these models to scalar distributed DDEs. The calculations shown here easily generalize to cyclic systems with $n \geqslant 4$ and demonstrate how to adapt our results to models with compartment specific clearance rates and where the final compartment depends more generally on the other components than in (1.1).

We next consider a recent article studying white blood cell production [33]. The hematopoietic, or blood production, system has been modeled extensively, and these models often include explicit or implicit delays. As mentioned by Knauer, Stiehl, and Marciniak-Czochra [33], a compartmental system with linear feedback regulation implicitly includes a distributed delay, and the coupling of this delay with feedback is enough to produce oscillations. These oscillations are of particular interest in hematopoiesis due to the so called "dynamical diseases" [38]. Here, we show that the Knauer, Stiehl, and Marciniak-Czochra [33] model with maturation compartments and nonlinear feedback also encodes a gamma type delay.

4.1. Models of lac-operon dynamics. The lac-operon facilitates the use of lactose as a fuel source in certain types of bacteria and was one of the first genetic regulatory mechanisms to be understood. This regulatory mechanism is controlled by the presence of allolactose. In the presence of allolactose, mRNA transcription occurs and leads to the production of β-galactosidase, which converts allolactose to glucose. This conversion of allolactose eventually inhibits the production of mRNA and results in bistability in the operon. The lac-operon was one of the first genetic regulatory mechanisms to display such bistability.

Yildirim et al. [60] proposed a reduced model of lac-operon dynamics to study the importance of β-galactosidase on the bistability of the operon. The structure of the reduced model proposed by Yildirim et al. [60] is similar to Goodwin's model of repressible dynamics [23]. Before considering the Yildirim's DDE model of lac-operon dynamics, we study the simpler Goodwin [23] model. Goodwin's model includes a metabolite controlled enzyme and intermediate stage and is known to produce oscillatory dynamics [23].

Goodwin's model is a system of three differential equations modeling mRNA, $M(t)$; intermediate protein, $I(t)$; and effectors, $E(t)$ [23]. The Goodwin model is a simple example of cyclic dynamics, where the production of one population is self-regulating through the dynamics of the other two. By showing that the Goodwin model can be reduced to a scalar distributed DDE, we make this self-regulation explicit. The ODE model is

$$\begin{cases} \dfrac{\mathrm{d}}{\mathrm{dt}}M(t) = F[E(t)] - \gamma_M M(t), \\ \dfrac{\mathrm{d}}{\mathrm{dt}}I(t) = \alpha_I M(t) - \gamma_I I(t), \\ \dfrac{\mathrm{d}}{\mathrm{dt}}E(t) = \alpha_E I(t) - \gamma_E E(t). \end{cases} \tag{4.1}$$

The parameters α_j and γ_j are positive real numbers for $j = M, I, E$ and represent the production and clearance of the jth species, respectively. $F[E(t)]$ represents mRNA production driven by either an inducible or repressible operon, with the monotonicity of F determining the type of feedback. As a first example of how to apply Theorem 2.2 in a cyclic feedback structure, we first reduce (4.1) to a distributed DDE where the effector $E(t)$ population is self-regulating.

Equation (4.1) is in a similar form to (1.1) for $[x_1(t), x_2(t), x_3(t)] = [I(t), E(t), M(t)]$ and $K_1(s) = K_2(s) = \delta(s)$ so that

$$f_1\left(\int_0^\infty x_3(t-s)K_1(s)\mathrm{d}s\right) = \alpha_I M(t) \quad \text{and} \quad f_2\left(\int_0^\infty x_1(t-s)K_2(s)\mathrm{d}s\right) = \alpha_E I(t).$$

However, the clearance rates differ between compartments with $\mu_1(x_3(t))x_1(t) = \gamma_I I(t)$ and $\mu_2(x_3(t))x_2(t) = \gamma_E E(t)$. Using the technique from the proof of

Lemma 2.1, we easily obtain

$$I(t) = \int_{-\infty}^{t} \alpha_I M(\varphi) e^{-\gamma_I (t-\varphi)} \mathrm{d}\varphi = \int_0^{\infty} \alpha_I M(t-\varphi) e^{-\gamma_I \varphi} \mathrm{d}\varphi$$

and

$$E(t) = \int_0^{\infty} \alpha_E \underbrace{\int_{-\infty}^{t-\theta} \alpha_I M(\varphi) e^{-\gamma_I (t-\theta-\varphi)} \mathrm{d}\varphi}_{I(t-\theta)} e^{-\gamma_E (t-\theta)} \mathrm{d}\theta.$$

Then, we immediately obtain the equivalent distributed DDE for the ODE model (4.1)

$$\frac{\mathrm{d}}{\mathrm{dt}} M(t) = F\left[\int_0^{\infty} \alpha_E \underbrace{\int_{-\infty}^{t-\theta} \alpha_I M(\varphi) e^{-\gamma_I (t-\theta-\varphi)} \mathrm{d}\varphi}_{I(t-\theta)} e^{-\gamma_E (t-\theta)} \mathrm{d}\theta \right] - \gamma_M M(t). \tag{4.2}$$

There is no obvious ageing structure in the chain of enzyme, metabolite, and intermediate protein. However, as mentioned, the cascade from metabolite to enzyme to intermediate protein defines a "cyclic" model structure. In this sense, the metabolite controls it's own expression through (4.2).

4.1.1. Delayed lac-operon model. Having shown how to reduce Goodwin's model of repressible dynamics to a scalar distributed DDE, we now consider the reduced Yildirim et al. model of the delayed lac-operon [60]. This model is given by three discrete DDEs:

$$\begin{cases} \dfrac{\mathrm{d}}{\mathrm{dt}} M(t) = F\left[e^{-\nu_E \tau_M} E(t-\tau_M)\right] - \gamma_M M(t), \\ \dfrac{\mathrm{d}}{\mathrm{dt}} I(t) = \alpha_I M(t-\tau_I) e^{-\nu_M \tau_I} - \gamma_I I(t), \\ \dfrac{\mathrm{d}}{\mathrm{dt}} E(t) = \alpha_E I(t) - \beta_E I(t) \dfrac{E(t)}{K_E + E(t)} - \gamma_E E(t). \end{cases} \tag{4.3}$$

The model in (4.3) is slightly more complicated due to the presence of discrete delays and the nonlinearity in the equation for $E(t)$. Due to the nonlinear Hill term in the differential equation for $E(t)$, we construct the cyclic structure in a different order than for (4.1), namely, $[x_1(t), x_2(t), x_3(t)] = [M(t), I(t), E(t)]$, and include this example to extend the framework in Theorem 2.2 to more general differential equations for $x_n(t)$. To apply Theorem 2.2, we define $K_1(s) = \delta(s - \tau_M)$ and $K_2(s) = \delta(s - \tau_I)$ which gives

$$\begin{aligned} f_1\left(e^{-\nu_E \tau_M} \int_0^{\infty} x_3(t-s) K_1(s) \mathrm{d}s\right) &= F\left[e^{-\nu_E \tau_M} E(t-\tau_M)\right], \\ f_2\left(e^{-\nu_M \tau_I} \int_0^{\infty} x_1(t-s) K_2(s) \mathrm{d}s\right) &= \alpha_I M(t-\tau_I) e^{-\nu_M \tau_I}, \end{aligned}$$

and the clearance rates $\mu_1(x_3(t))x_1(t) = \gamma_M M(t)$ and $\mu_2(x_3(t))x_2(t) = \gamma_I I(t)$. We thus immediately obtain

$$M(t) = \int_0^{\infty} F\left[e^{-\nu_E \tau_M} E(t-\varphi-\tau_M)\right] e^{-\gamma_M \varphi} \mathrm{d}\varphi \tag{4.4}$$

and

$$I(t) = \int_0^\infty \alpha_I M(t-\theta-\tau_I) e^{-\nu_M \tau_I} e^{-\gamma_I(\theta)} \mathrm{d}\theta$$

(4.5)

$$= \int_0^\infty \alpha_I \left[\int_0^\infty F\left[e^{-\nu_E \tau_M} E(t-\theta-\varphi-\tau_I-\tau_M)\right] e^{-\gamma_M \varphi} \mathrm{d}\varphi \right] e^{-\nu_M \tau_I} e^{-\gamma_I \theta} \mathrm{d}\theta.$$

Now, using (4.4) and (4.5), the system (4.3) becomes the following scalar distributed DDE for $E(t)$:

(4.6)

$$\begin{cases} \dfrac{\mathrm{d}}{\mathrm{dt}} E(t) = \displaystyle\int_{-\infty}^{t} \alpha_I \left[\int_{-\infty}^{\theta-\tau_I} F\left[e^{-\nu_E \tau_M} E(\varphi-\tau_M)\right] e^{-\gamma_M(\theta-\tau_I-\varphi)} \mathrm{d}\varphi \right] e^{-\nu_E \tau_I} e^{-\gamma_I(t-\theta)} \mathrm{d}\theta \\ \qquad\qquad \times \left[\alpha_E - \beta_E \dfrac{E(t)}{K_E + E(t)} \right] - \gamma_E E(t). \end{cases}$$

The product of (4.5) and the Hill function in (4.6) illustrates a simple extension of the generic form of (1.1) to differential equations that include more general terms in the final stage.

4.1.2. Linearization of the delayed lac-operon model. Equation (4.3) is a discrete DDE, so the canonical choice for the phase space is $\mathcal{C}(-\max[\tau_i, \tau_M], 0)$ and equilibrium solutions are constant functions satisfying the implicit condition

$$\gamma_E E^* = \left(\alpha_E - \beta_E \frac{E^*}{K_E + E^*} \right) \left(\frac{\alpha_I}{\gamma_I} \right) \frac{F\left[e^{-\nu_E \tau_M} E^*\right]}{\gamma_M} e^{-\nu_E \tau_I}.$$

To compute the characteristic equation and emphasize the more general dependence on the final stage in this example, we rewrite (4.6) as

$$\frac{\mathrm{d}}{\mathrm{dt}} E(t) = (HE) \left[\alpha_E - \beta_E \frac{E(t)}{K_E + E(t)} \right] - \gamma_E E(t),$$

where

$$H : E \to \int_0^\infty \alpha_I \left[\int_0^\infty F\left[e^{-\nu_E \tau_M} E(t-\theta-\varphi-\tau_I-\tau_M)\right] e^{-\gamma_M \varphi} \mathrm{d}\varphi \right] e^{-\nu_M \tau_I} e^{-\gamma_I \theta} \mathrm{d}\theta.$$

Using $x(t) = E(t) - E^*$ and making the ansatz $x(t) = Ce^{\lambda t}$, the linearization of (4.6) about the equilibrium solution E^* is therefore

$$\lambda x(t) = \left(\alpha_E - \frac{\beta_E E^*}{K_E + E^*} \right) \times DHx - \left(\bar{E}^* \frac{\beta_E K_E}{(K_E + E^*)^2} + \gamma_E E^* \right) x(t), \tag{4.7}$$

where $\bar{E}^* = HE^*$ and we use the generic characteristic equation (3.5) with the specific forms of f_i and K_i to obtain

$$DHx = \left(\partial_x F(e^{-\nu_E \tau_M} E^*) e^{-\nu_M \tau_I} \right) \left(\frac{\alpha_I}{\gamma_I + \lambda} \right) \left(\frac{e^{-\lambda(\tau_I + \tau_M)}}{\gamma_M + \lambda} \right) x(t).$$

In particular, we note that $\mu_I' = \mu_M' = 0$, and, after rearranging (4.7), we obtain the

characteristic equation

$$0 = \left(\lambda + \frac{\beta_E \bar{E}^* K_E}{(K_E + E^*)^2} + \gamma_E\right)(\lambda + \gamma_I)(\lambda + \gamma_M) - \left(\alpha_E - \beta_E \frac{E^*}{K_E + E^*}\right) \partial_x F(e^{-\nu_E \tau_M} E^*) e^{-\nu_M \tau_I} \alpha_I e^{-\lambda(\tau_I + \tau_M)},$$

which is exactly the characteristic equation found by [60] (after undoing their nondimensionalization). Thus, we have shown how to reduce a system of three discrete DDEs to a scalar differential equation and have computed the characteristic equation without computing Jacobian matrices or determinants.

4.2. Compartmental white blood cell model. The human hematopoietic system is responsible for blood cell production and is tightly regulated by circulating cytokine concentrations. This cytokine control of blood cell production, maturation, and release into the circulation ensures that the hematopoietic system is able to respond to challenges such as infection, blood loss, and hypoxemia. There has been extensive interest in mathematical modeling of the control mechanisms underlying the regulatory control of the hematopoietic system [37, 47]. In general, a circulating population of blood cells controls the production of precursors through a negative feedback loop mediated by cytokine signaling. In the absence of exogeneous cytokine administration, it is common to use a quasi-steady-state approximation to discard a model for the cytokine signaling and simply use the circulating concentration of blood cells to control precursor production. Accordingly, these models typically exhibit the form of (1.1).

The production of neutrophils, the most common type of white blood cell in humans, has been extensively modeled over the past half century [11, 40, 47, 50]. Neutrophil precursors progress through a number of distinct proliferation and maturation stages before entering a reservoir of mature cells in the bone marrow and passing into circulation. It is common to model each of these stages separately, leading to a system of ODEs [48, 49, 50, 55]. Consequently, these models can be transformed to a distributed DDE through the LCT [4, 6], where the distributed delay represents the time required for nascent neutrophil precursors to pass from the hematopoietic stem cell populations through proliferation and maturation stages before reaching the circulation.

Marciniak-Czochra et al. [42] introduced a compartmental model of hematopoietic stem cell regeneration that has since been adapted to study bone marrow transplantation, resistance to therapy in leukemia, and other disorders of the hematopoietic system. Recently, the model was thoroughly analyzed for two compartments in [22], who showed that the homeostatic equilibrium point is globally stable when it exists. Knauer, Stiehl, and Marciniak-Czochra [33] considered a multicompartment version of the model and demonstrated the existence of a supercritical Hopf bifurcation that leads to oscillatory circulating blood concentrations, similar to those observed in cyclic neutropenia [10, 24, 46, 58]. Interestingly, the supercritical Hopf bifurcation and resulting periodic orbit is not present in a similar model without the multiple maturation stages but rather results from the inclusion of a multistage maturation process [22, 33]. This multistage maturation process results in the multicompartment nature of the Knauer, Stiehl, and Marciniak-Czochra [33] model, where each compartment corresponds to a distinct stage in the differentiation process. As the authors mention, these multicompartment models have a long history in modeling cyclic neutropenia, and typically are structured to implicitly (or explicitly) induce a delay in the feed-

back. The Knauer, Stiehl, and Marciniak-Czochra [33] model is the following three compartment model:

$$\begin{cases} \dfrac{\mathrm{d}}{\mathrm{dt}}u_1(t) = \left(2\dfrac{a_1}{1+ku_3(t)} - 1\right)p_1u_1(t), \\ \dfrac{\mathrm{d}}{\mathrm{dt}}u_2(t) = \left(2\dfrac{a_2}{1+ku_3(t)} - 1\right)p_2u_2(t) + 2\left(1 - \dfrac{a_1}{1+ku_3(t)}\right)p_1u_1(t), \\ \dfrac{\mathrm{d}}{\mathrm{dt}}u_3(t) = 2\left(1 - \dfrac{a_2}{1+ku_3(t)}\right)p_2u_2(t) - d_3u_3(t). \end{cases} \tag{4.8}$$

Here, we show that the maturation stage in the compartmental model (4.8) acts to impose a distributed delay and we reduce (4.8) to a coupled ODE and distributed DDE. This is a departure from earlier examples in which we completely reduced the system to a scalar distributed DDE. While we are only reducing the number of free variables in (4.8) by one in this example, our results immediately apply to models with the same structure as (4.8) with $n > 3$ compartments that have been used extensively in hematopoietic modeling [43, 56, 57, 59]. Moreover, this example contains a nonconstant $\mu(x_n(t))$ and the resulting exponential integral. These nonconstant exponential integrals occur naturally in other DDE models of hematopoiesis that arise from physiologically structured models [4, 6, 8, 35]. In these models, the linearization was performed on a model by model basis, so we include this example to demonstrate how the characteristic function (3.5) can be obtained for these physiologically structured models.

We note that the reduction to a scalar DDE is possible for (4.8), but with an additional complication as the differential equation for u_1 is homogeneous in u_1 with $f_1(u_3(t)) = 0$. Consequently, the scalar DDE for u_3 obtained by applying Theorem 2.2 explicitly depends on the initial condition $u_1(0)$. This explicit dependence on initial conditions has a simple biological explanation: $u_1(0)$ represents the initial population of hematopoietic stem cells which are only produced through self-renewal of the existing stem cell population. Thus, the circulating concentration of white blood cells will influence the growth or decay rate of the hematopoietic stem cells but cannot independently drive the production of new hematopoietic cells without hematopoietic stem cell self-renewal. Therefore, we reduce (4.8) to a system for the hematopoietic stem cell population and the circulating neutrophil concentration by replacing the intermediate compartment u_2 with a distributed delay, which leaves a system of differential equations for u_1 and u_3.

We consider $[x_1(t), x_2(t)] = [u_2(t), u_3(t)]$ in (4.8), where the effective proliferation rate of cells in compartment i is given by p_i with a fraction,

$$\left(2\frac{a_i}{1+ku_3(t)} - 1\right),$$

of these cells self-renewing and remaining in the ith compartment, while the remaining fraction,

$$2\left(1 - \frac{a_i}{1+ku_3(t)}\right),$$

progresses to the subsequent compartment and mature cells are cleared from circulation linearly at a rate d_3.

We begin with the differential equation for u_2,

$$\frac{\mathrm{d}}{\mathrm{d}t}u_2(t) = 2\left(1 - \frac{a_1}{1+ku_3(t)}\right)p_1u_1(t) + \left(\frac{2a_2}{1+ku_3(t)} - 1\right)p_2u_2(t),$$

and note that this differential equation has precisely the form of (1.1) with $K_2(s) = \delta(s)$,

$$f_2\left(\int_0^\infty x_1(t-s)K_2(s)\mathrm{d}s\right) = 2\left(1 - \frac{a_1}{1+ku_3(t)}\right)p_1u_1(t) \quad \text{and} \quad \mu(x_n(t)) = p_2\left(\frac{2a_2}{1+ku_3(t)} - 1\right).$$

Thus, it follows that

(4.9)
$$u_2(t) = \int_0^\infty 2\left(1 - \frac{a_1}{1+ku_3(t-\sigma)}\right)p_1u_1(t-\sigma)\exp\left[p_2\int_{t-\sigma}^t\left(\frac{2a_2}{1+ku_3(x)} - 1\right)\mathrm{d}x\right]\mathrm{d}\sigma.$$

To facilitate the following computations, let

$$h_1(y) = 2p_1\left(1 - \frac{a_1}{1+ky}\right) \quad \text{and} \quad h_2(y) = p_2\left(\frac{2a_2}{1+ky} - 1\right)$$

so we can write (4.9) as

$$u_2(t) = \int_0^\infty h_1(u_3(t-\sigma))(u_1(t-\sigma))\exp\left[\int_{t-\sigma}^t h_2(u_3(x))\mathrm{d}x\right]\mathrm{d}\sigma,$$

and the Knauer, Stiehl, and Marciniak-Czochra [33] model reduces to

$$\text{(4.10)} \qquad \begin{cases} \dfrac{\mathrm{d}}{\mathrm{d}t}u_1(t) = \left(2\dfrac{a_1}{1+ku_3(t)} - 1\right)p_1u_1(t), \\ \dfrac{\mathrm{d}}{\mathrm{d}t}u_3(t) = \left(\displaystyle\int_0^\infty h_1(u_3(t-\sigma))(u_1(t-\sigma))\exp\left[\int_{t-\sigma}^t h_2(u_3(x))\mathrm{d}x\right]\mathrm{d}\sigma\right) \\ \qquad\qquad \times 2p_2\left(1 - \dfrac{a_2}{1+ku_3(t)}\right) - d_3u_3(t). \end{cases}$$

In the preceding calculation, we have implicitly assumed that $u_1(0) \neq 0$. Now, if $u_1(0) = 0$, then $u_1(t) = 0$ for all $t > 0$ and the 3 compartment model (4.8) becomes

$$\text{(4.11)} \qquad \begin{cases} \dfrac{\mathrm{d}}{\mathrm{d}t}u_2(t) = \left(2\dfrac{a_2}{1+ku_3(t)} - 1\right)p_2u_2(t), \\ \dfrac{\mathrm{d}}{\mathrm{d}t}u_3(t) = 2\left(1 - \dfrac{a_2}{1+ku_3(t)}\right)p_2u_2(t) - d_3u_3(t). \end{cases}$$

Then, the preceding discussion regarding the biological interpretation of $u_1(0)$ for (4.8) can be repeated verbatim for (4.11) but now with $u_2(0)$.

4.2.1. Equilibria and linearization. In the DDE form of the Knauer model given by (4.10), equilibria solutions are the constant functions $(u_1(t), u_3(t)) = (u_1^*, u_3^*)$ such that the right-hand side of (4.10) is zero. Immediately, we see that

$$u_1^* = 0 \quad \text{or} \quad u_3^* = \frac{2a_1 - 1}{k}.$$

Using the equilibrium value of u_3^*, the nonzero equilibria value of u_1^* is given by

$$\begin{aligned} d_3 u_3^* &= 4p_1p_2\left(1 - \frac{a_1}{1+ku_3^*}\right)\left(1 - \frac{a_2}{1+ku_3^*}\right)u_1^*\int_0^\infty \exp\left[p_2\left(\frac{2a_2}{1+ku_3^*} - 1\right)\sigma\right]\mathrm{d}\sigma \\ &= \frac{p_1\left(2 - \frac{a_2}{a_1}\right)u_1^*}{1 - \frac{a_2}{a_1}}, \end{aligned}$$

which is the value found by [33] and only exists if $a_2 < a_1$ so $h_2(u_3^*) = p_2(a_2/a_1 - 1) < 0$ and $h_1(u_3^*) = p_1$. Now, to linearize about the equilibrium solution, we must calculate the 2×2 Jacobian matrix A such that $z(t) = u(t) - u^*$ satisfies

$$\frac{\mathrm{d}}{\mathrm{d}t}z(t) = Az(t).$$

As we are considering the coupled system (4.10), the linearization differs from previous examples where we obtained a scalar linearized differential equation. We begin with the computation of the linear approximation of the delayed term

$$\int_0^\infty h_1(u_3^* + z_3(t-\sigma))(u_1^* + z_1(t-\sigma))\exp\left[\int_{t-\sigma}^t h_2(u_3^* + z_3(x))\mathrm{d}x\right].$$

Taylor expanding the above expression in z_1 and z_3 gives

$$\begin{aligned} &\int_0^\infty [h_1(u_3^*) + h_1'(u_3^*)z_3(t-\sigma)](u_1^* + z_1(t-\sigma))e^{h_2(u_3^*)\sigma} \\ &\quad\times\left(1 + \int_{t-\sigma}^t h_2'(u_3^*)z_3(x)\mathrm{d}x\right)\mathrm{d}\sigma + \mathcal{O}(z^2) \\ &= \frac{h_1(u_3^*)u_1^*}{h_2(u_3^*)} + \int_0^\infty [h_1'(u_3^*)u_1^*z_3(t-\sigma) + h_1(u_3^*)z_1(t-\sigma)]e^{h_2(u_3^*)\sigma}\mathrm{d}\sigma \\ &\quad + \int_0^\infty h_1(u_3^*)u_1^*e^{h_2(u_3^*)\sigma}\left[\int_{t-\sigma}^t h_2'(u_3^*)z_3(x)\mathrm{d}x\right]\mathrm{d}\sigma + \mathcal{O}(z^2). \end{aligned}$$

We discard the nonlinear terms and insert the ansatz $z(t) = Ce^{\lambda t}$ to find

$$\begin{aligned} &\frac{h_1(u_3^*)u_1^*}{h_2(u_3^*)} + \int_0^\infty [h_1'(u_3^*)u_1^*z_3(t-\sigma) + h_1(u_3^*)z_1(t-\sigma)]e^{h_2(u_3^*)\sigma}\mathrm{d}\sigma \\ &\quad + \int_0^\infty h_1(u_3^*)u_1^*e^{h_2(u_3^*)\sigma}\left[\int_{t-\sigma}^t h_2'(u_3^*)z_3(x)\mathrm{d}x\right]\mathrm{d}\sigma + \mathcal{O}(z^2) \\ &= \frac{h_1(u_3^*)u_1^*}{h_2(u_3^*)} + \frac{h_1'(u_3^*)u_1^*}{\lambda + h_2(u_3^*)}z_3(t) + \frac{h_1(u_3^*)}{\lambda + h_2(u_3^*)}z_1(t) \\ &\quad + \int_0^\infty h_1(u_3^*)u_1^*e^{h_2(u_3^*)\sigma}\left[\int_{t-\sigma}^t h_2'(u_3^*)z_3(x)\mathrm{d}x\right]\mathrm{d}\sigma. \end{aligned}$$

Then, following the calculation of (3.5), we obtain the linear differential equation for $z_3(t)$:

$$\begin{aligned}\frac{\mathrm{d}}{\mathrm{dt}}z_3(t) &= -d_3(z_3(t)+u_3^*) + \left[2p_2\left(1-\frac{a_2}{1+ku_3^*}\right) + 2p_2\frac{ka_2}{(2a_1)^2}z_3(t) + \mathcal{O}(z^2)\right] \\ &\quad \times \left[\frac{h_1(u_3^*)u_1^*}{p_2(1-a_2/a_1)} + \left(\frac{u_1^*[h_1'(u_3^*)h_2(u_3^*)+h_1(u_3^*)h_2'(u_3^*)]}{h_2(u_3^*)[\lambda+p_2(1-a_2/a_1)]}\right)z_3(t)\right. \\ &\quad \left. + \left(\frac{h_1(u^*)}{\lambda+p_2(1-a_2/a_1)}\right)z_1(t) + \mathcal{O}(z^2)\right] \\ &= \left[-d_3 + 2p_2\frac{ka_2}{(2a_1)^2}\frac{h_1(u_3^*)u_1^*}{p_2(1-a_2/a_1)}\right. \\ &\quad \left. + 2p_2\left(1-\frac{a_2}{1+ku_3^*}\right)\left(\frac{u_1^*[h_1'(u_3^*)h_2(u_3^*)+h_1(u_3^*)h_2'(u_3^*)]}{h_2(u_3^*)[\lambda+p_2(1-a_2/a_1)]}\right)\right]z_3(t) \\ &\quad + \left(2p_2\left(1-\frac{a_2}{1+ku_3^*}\right)\frac{h_1(u^*)}{\lambda+p_2(1-a_2/a_1)}\right)z_1(t).\end{aligned}$$

From which we get the linearization matrix A,

$$A(\lambda) = \begin{bmatrix} 0 & \left(1-\frac{1}{2a_1}\right)\frac{d_3}{2-a_2/a_1}(1-a_2/a_1) \\ p_2\left(2-\frac{a_2}{a_1}\right)\frac{h_1(u^*)}{\lambda+p_2(1-a_2/a_1)} & d_3\left[\left(1-\frac{1}{2a_1}\right)\frac{a_2}{a_1}\frac{1}{2-\frac{a_2}{a_1}}-1\right]+A_{22}(\lambda) \end{bmatrix},$$

where

$$A_{22}(\lambda) = 2p_2\left(1-\frac{a_2}{1+ku_3^*}\right)\left(\frac{u_1^*[h_1'(u_3^*)h_2(u_3^*)+h_1(u_3^*)h_2'(u_3^*)]}{h_2(u_3^*)[\lambda+p_2(1-a_2/a_1)]}\right).$$

Following [33] and rescaling time by $\hat{t} = tp_1$, we have $h_1(u_3^*) = 1$, so

$$A_{22}(\lambda) = p_2d_3\left(1-2\frac{a_2}{a_1}\right)\left(1-\frac{1}{2a_1}\right)\left(\frac{1}{\lambda+p_2(1-a_2/a_1)}\right).$$

Then, computing $\det[\lambda I - A]$ gives the same characteristic equation as was found in [33]:

$$\begin{aligned}0 &= \lambda^3 + \left[\left(1-\frac{a_2}{a_1}\right)p_2 + \left(1-\frac{a_2}{a_1}\right)\left(1-\frac{1}{2a_1}\right)\frac{1}{2-\frac{a_2}{a_1}}\right]\lambda^2 \\ &\quad + \left[\left(1-\frac{a_2}{a_1}\right)\left(1-\frac{a_2}{a_1}\left(1-\frac{1}{2a_1}\right)\frac{1}{2-\frac{a_2}{a_1}}\right) - \left(1-\frac{1}{2a_1}\right)\left(1-2\frac{a_2}{a_1}\right)\right]d_3p_2\lambda \\ &\quad + \left(1-\frac{1}{2a_1}\right)\left(1-\frac{a_2}{a_1}\right)d_3p_2.\end{aligned}$$

4.2.2. Biological interpretation. Oscillations in mathematical models of hematopoiesis have been extensively studied, with cyclic neutropenia being a canonical example of a dynamical disease. These mathematical models often include delayed feedback from the circulation to the immature precursor cells, either indirectly through a quasi-steady-state assumption or explicitly through external control via

models of cytokine dynamics. The in-depth anaylsis of Getto et al. [22] demonstrates that the Knauer, Stiehl, and Marciniak-Czochra [33] model without the maturation compartment *cannot* produce oscillatory solutions. However, the multistage compartment model in (4.8) undergoes a Hopf bifurcation and produces solutions that compare favorably with observed data from patients with cyclic neutropenia. Knauer, Stiehl, and Marciniak-Czochra state that a nonlinear model without explicit delays has not been used to model oscillatory behavior in the hematopoietic system. Here, we show that the Knauer, Stiehl, and Marciniak-Czochra [33] model also shares the framework of delayed feedback between circulating and precursor hematopoietic cells by explicitly constructing the equivalent distributed DDE. Taken with the results of [22], this result supports the conclusion that a delay between signal and response in the feedback loop is necessary to recapture the oscillatory dynamics observed in the hematopoietic system.

5. Conclusion. In this work, we have formalized the relationship between cyclic differential equations and distributed DDEs. This relationship is well known in the case of transit compartment models as the LCT, and has been shown to lead to state dependent distributed DDEs in the variable transit rate case [6]. However, both of these equivalences require linear transit between compartments, which is not the case in our work. At the heart of the LCT is the ability to write down a closed form integral solution of the transit compartment model. Here, we use the same idea in a more general setting to establish the equivalence between general cyclic differential equations that include both nonlinearities and delays, and scalar distributed DDEs by writing an integral form solution of the transit compartments. In essence, we demonstrate how sequentially solving the transit compartment system naturally leads to a scalar distributed DDE.

As discussed throughout the text, the reduction of a generic cyclic model to a scalar distributed DDE has a number of advantages. Mathematically, determining the existence of equilibria in n dimensional systems typically requires solving n simultaneous equations, and it is, in general, difficult to determine a priori if an equilibrium point exists. Conversely, both de Souza et al. and Cassidy, Craig, and Humphries demonstrate that the distributed DDE formulation of transit compartment models can be more tractable to analytical techniques [4, 6]. In general, the equivalence derived in this work allows modelers to use analytical techniques from single variable calculus to prove the existence of an equilibrium solution in the scalar formulation and then use the efficient numerical solvers to numerically calculate their value using the special structure of the cyclic system. Once an equilibrium solution has been found, studying the local stability properties of the equilibrium in the cyclic formulation involves calculating the $n \times n$ determinant of the Jacobian matrix. Consequently, if modeling biological data indicates the need for the inclusion of an additional intermediate modeling stage, as in the model of hematopoiesis mentioned earlier, it is necessary to recalculate the now $(n+1) \times (n+1)$ Jacobian matrix and it's determinant. Conversely, when working with the equivalent scalar distributed DDE, studying the local stability of these equilibria corresponds to calculating a Fréchet derivative. As we have shown, this calculation replaces the calculation of the determinant of the $n \times n$ Jacobian matrix with the chain rule of Fréchet derivatives, and is much more amendable to the inclusion of new modeling stages.

Biologically, the scalar distributed DDE explicitly identifies delays between signal and response that are otherwise hidden in the equivalent cyclic system. Moreover, each intermediate stage represents another quantity that should be compared to data

when validating a mathematical model. However, these intermediate stages are either often difficult to measure or do not represent specific physiological compartments. To emphasize this point, we considered two examples that represent biological systems without obvious delays, and showed that identifying the otherwise hidden delays can suggest necessary model ingredients to recapture biological phenomena, as in section 4.2. Conversely, when considering the equivalent scalar distributed DDE, the model output may be easier to compare against biological data. In a related point, using the scalar distributed DDE formulation can alleviate nonbiological modeling assumptions. For example, using a transit compartment ODE model to replace a distributed DDE imposes a nonbiological constraint on the delayed process. Namely, imposing that the delayed process be Erlang distributed constrains one of the two parameters of the gamma distribution. As the mean, τ, and variance, σ^2, of a delayed process precisely determine the shape and scale parameters of the gamma distribution, imposing that the shape parameter is an integer leads to an overdetermined system for the remaining scale parameter and artificially enforces $\tau^2 = m\sigma^2$ for integer m. For example, when modeling the duration of the cell cycle using an Erlang distributed DDE, modelers can capture the mean or the variance of the delayed process, but not generally both [5, 31]. This limitation is alleviated when using the more general distributed DDE.

In summary, we formalized the equivalence between cyclic systems of differential equations with delay and scalar distributed DDEs. However, the distributed DDE formulation of cyclic models has some limitations. The most striking of these is the lack of established numerical techniques for the simulation and bifurcation analysis of infinite delay models. Given the multitude of tools available for discrete or no delay systems, the main area of application for our results is thus cyclic systems that already include more general distributed delays. In these cases, it may be preferable to apply the recently developed techniques from [18, 26] to the scalar distributed DDE (2.3) rather than to each component of the cyclic system. All told, the equivalence established in this work allows researchers to study the mathematical model in whichever form is most convenient, and may elucidate otherwise hidden delayed processes.

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