

Dynamical Systems and Delays

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Scalar Linear Example

$$\frac{dx}{dt} = \lambda x, \quad x(0) = x_0 \in \mathbb{R}$$

- This is an *Initial Value Problem*. Initial value is $x_0 \in \mathbb{R}$.
- Solution of IVP is function $x(t)$ that satisfies ODE for $t \geq 0$ and initial value.

Question: How does solution depend on value of x_0 ?

- $\lambda \in \mathbb{R}$ is a parameter. Does not change in time, but we can consider different values.

Question: How does behaviour of solution change with λ ?



Scalar Linear Example

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Solution

$$x(t) = e^{\lambda t} x_0, \quad t \geq 0 \text{ or } t \in \mathbb{R}$$

This solves IVP, but is not the answer to our questions



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Answers:

- If $\lambda < 0$ then $\lim_{t \rightarrow +\infty} x(t) = 0$ and $\lim_{t \rightarrow -\infty} |x(t)| = +\infty$
If $\lambda > 0$ then $\lim_{t \rightarrow +\infty} |x(t)| = +\infty$ and $\lim_{t \rightarrow -\infty} x(t) = 0$
- $\text{sign}(x(t)) = \text{sign}(x_0)$ for all $t \in \mathbb{R}$. Solutions do not cross $x = 0$
- If $x_0 = 0$ then $x(t) = 0$ for all $t \in \mathbb{R}$ is a solution. Its called a *steady state*.
- Steady state at $x = 0$ is stable if $\lambda < 0$ (other solutions approach it), and unstable if $\lambda > 0$.



Scalar Nonlinear Example: The Logistic Equation

$$\frac{dx}{dt} = f(x, \lambda) = \lambda x(1 - x), \quad x(0) = x_0 \in \mathbb{R}$$

- There is again an exact formula for solution of IVP. We don't need it.



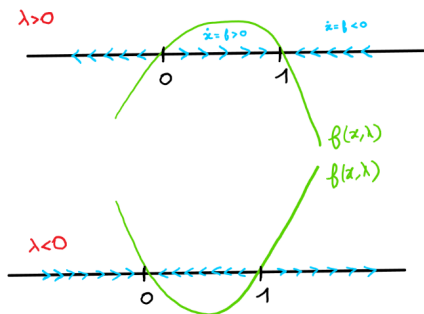
Ordinary Differential Equations as Dynamical Systems

Scalar Nonlinear Example: The Logistic Equation

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Consider:



- Plot $f(x, \lambda)$ against x . Then $\text{sign}\left(\frac{dx}{dt}\right) = \text{sign}(f(x, \lambda))$ which allows us to sketch dynamics on \mathbb{R} .
- Steady states at $x = 0$ and $x = 1$.
- If $\lambda > 0$ then $x = 0$ is unstable and $x = 1$ is stable with $\lim_{t \rightarrow \infty} x(t) = 1$ whenever $x_0 > 0$ and $\lambda > 0$.
- If $\lambda < 0$ then $x = 1$ is unstable and $x = 0$ is stable with $\lim_{t \rightarrow \infty} x(t) = 0$ whenever $x_0 < 1$ and $\lambda < 0$.
- Stable steady states are locally but not globally attracting



Dynamical Systems in Higher Dimensions

Lorenz Equations in \mathbb{R}^3

$$\frac{dx}{dt} = \sigma(y - x)$$

$$\frac{dy}{dt} = rx - y - xz$$

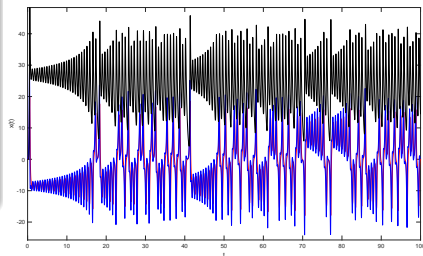
$$\frac{dz}{dt} = xy - bz$$

Parameters: $\sigma = 10$, $b = 8/3$, $r = 28$.

Initial condition: $(x_0, y_0, z_0) \in \mathbb{R}^3$

Solution: $\underline{u}(t) = (x(t), y(t), z(t)) \in \mathbb{R}^3$

Plot solutions components against time t



That's a mess above!



Dynamical Systems in Higher Dimensions

Lorenz Equations in \mathbb{R}^3

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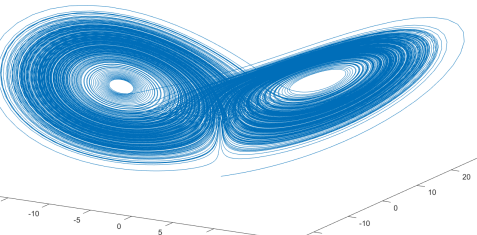
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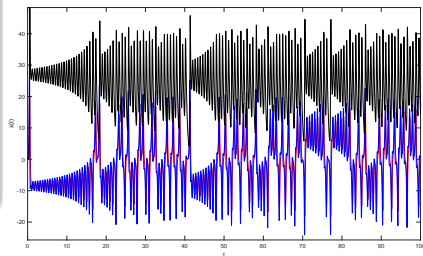
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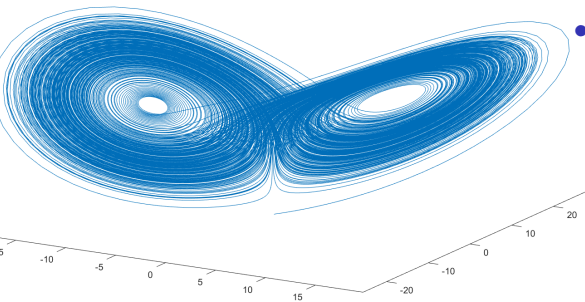


That's a mess above!

Plot solution $(x(t), y(t), z(t))$ as a curve in \mathbb{R}^3 parametrised by t .

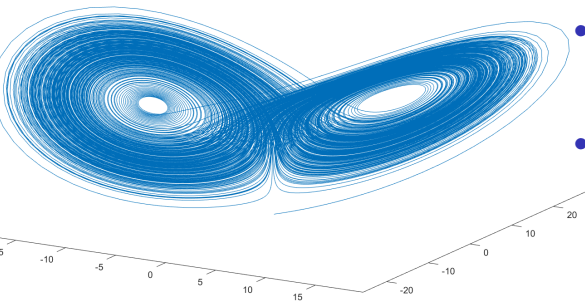
The beautiful Lorenz attractor now appears





- Why is curve $(x(t), y(t), z(t)) \in \mathbb{R}^3$ so elegant?

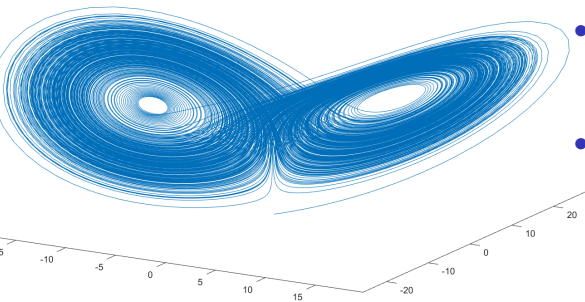




- Why is curve $(x(t), y(t), z(t)) \in \mathbb{R}^3$ so elegant?
- Because
 - $(x_0, y_0, z_0) \in \mathbb{R}^3$ also
 - Initial condition specifies a unique solution of ODE.
 - Uniqueness ensures that solutions do not cross.



Phase Space



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 - Initial condition specifies a unique solution of ODE.
 - Uniqueness ensures that solutions do not cross.

Phase Space

Phase space is the space that the initial conditions belong to.

- Set up needs to ensure that solution of IVP for any $(x_0, y_0, z_0) \in \mathbb{R}^3$ is unique
- Crucial feature: dynamics depends only on position, not on time.

Systems with delay, noise, forcing are excluded (for now).



Evolution Operator

Let U be phase space (\mathbb{R}^n for now).

Evolution operator $S(t)$ maps initial condition $u_0 \in \mathbb{R}^n$ to solutions t time units later,

Commutative Semigroup Property

- 1 $S(t_1)S(t_2) = S(t_2)S(t_1) = S(t_1 + t_2)$ for all $t_1, t_2 \geq 0$ (associative and commutative)
- 2 $S(0) = I$ (identity operator; so a commutative monoid)

Evolution operator allows us to define invariant sets $A \subset U$.



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Invariant Sets Under Dynamics

A is *forward invariant* if $S(t)u \in A$ for all $u \in A$ and all $t \geq 0$.

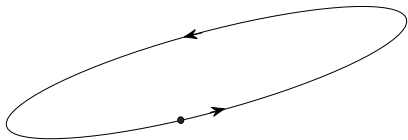
A is *backward invariant* if $S(-t)u \in A$ for all $u \in A$ and all $t \leq 0$.

A is *invariant* if it is both forward and backward invariant.



Invariant Sets include

- Steady states
- Periodic Orbits
- More exotic things, including invariant tori and strange attractors (inc. Lorenz attractor).



Stability of Steady States

For a steady state $u^* \in \mathbb{R}^n$ let $v(t) = u(t) - u^*$ and linearize to obtain

$$\frac{dv}{dt} = Av,$$

where $A \in \mathbb{R}^{n \times n}$ is the $n \times n$ Jacobian matrix of f evaluated at u^* .

- Steady-state is stable if all eigenvalues λ have negative real parts.
- Floquet theory generalises technique to periodic orbits.



Parameter Continuation and Bifurcations

Recall $\frac{du}{dt} = f(u, \mu)$ has parameter(s).

Implicit Function Theorem

If all eigenvalues of Jacobian matrix at steady-state u^* have $Re(\lambda) \neq 0$ then as parameter μ is varied

- u^* varies continuously in phase space
- Number of eigenvalues with positive and negative real parts is constant, so no change in stability.



Parameter Continuation and Bifurcations

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Bifurcation is qualitative change in dynamics as parameter μ is varied.

Bifurcations

Occur when

- Steady-state bifurcation: Real eigenvalue crosses 0. Number and stability of steady states close to u^* changes
- Hopf bifurcation: Complex conjugate pair of eigenvalues cross the imaginary axis. A Periodic orbit is born from the steady state.

There are plenty of more complicated bifurcations



Delays arise in Physics/Engineering

due to

- Transport
- Communication
- Processing Time

Delays in Physiology

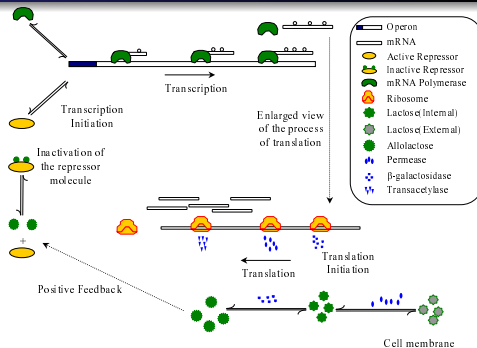
Often blend all three

- Hormone/Antigen must be produced and transported to receptor before signal received
- Maturation/incubation delays often significant
- Its a modelling choice to incorporate a delay, rather than model the entire process leading to that delay.



Goodwin Operon Model

- Protein Production
- mRNA Transcription & Translation
- [GOODWIN 1963,1965] without delay
- τ constant: 1970s, 1980s
- [GEDEON, ARH ET AL, JMB 2022]:



$$\text{MRNA: } \frac{dM}{dt}(t) = \beta_M e^{-\mu\tau_M(t)} \frac{v_M(E(t))}{v_M(E(t - \tau_M(t)))} f(E(t - \tau_M(t))) - \bar{\gamma}_M M(t),$$

$$\text{Intermediate: } \frac{dI}{dt}(t) = \beta_I e^{-\mu\tau_I(t)} \frac{v_I(M(t))}{v_I(M(t - \tau_I(t)))} M(t - \tau_I(t)) - \bar{\gamma}_I I(t),$$

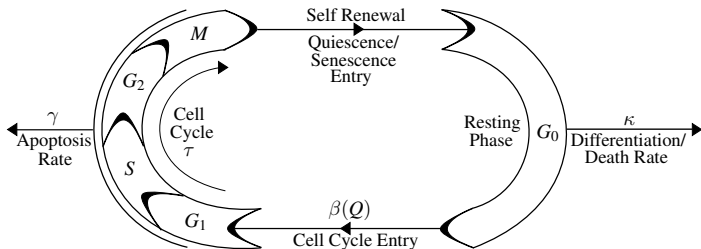
$$\text{Effector: } \frac{dE}{dt}(t) = \beta_E I(t) - \bar{\gamma}_E E(t).$$

$$\text{Threshold delays : } a_j = \int_{t-\tau_j(t)}^t v_j(E(s)) ds, \quad j = M, I.$$



Burns and Tannock G_0 Cell Cycle Model

Cell cycle model: [BURNS & TANNOCK 1970]:



Stem Cell DDE: [MACKEY BLOOD 1978]

$$Q'(t) = -(\kappa + \beta(Q(t)))Q(t) + A\beta(Q(t - \tau))Q(t - \tau),$$

$$\beta(Q) = f \frac{\theta^s}{\theta^s + Q^s}, \quad A = 2e^{-\gamma\tau}$$

- Describes cell division
- Non-monotone delayed feedback



Body produces more than 10^{11} blood cells per day

- That's 10^{11} Burns-Tannock cell cycles per day
- Numerous proteins needed for each cell cycle (Goodwin Model)
- A macro-model is needed that simplifies these processes

Granulopoiesis Model [CRAIG, ARH, MACKEY BMB 16]:

$$\text{Stem Cells : } \frac{dQ}{dt} = -(\kappa_N(G(t)) + \kappa_\delta + \beta(Q(t))) \\ + A_Q(t)\beta(Q(t - \tau_Q))Q(t - \tau_Q)$$

$$\text{Reservoir : } \frac{dN_R}{dt} = A_N(t)\kappa_N(G(t - \tau_N))Q(t - \tau_N) \frac{V_{N_M}(G(t))}{V_{N_M}(G(t - \tau_{N_M}(t)))} \\ - (\gamma_{N_R} + \varphi_{N_R}(G(t)))N_R(t)$$

$$\text{Circulating : } \frac{dN}{dt} = \varphi_{N_R}(G(t))N_R(t) - \gamma_N N(t)$$



Maturation Threshold Condition and Velocity Ratio

Constant V :

$$\frac{dN_R}{dt} = K_N(G(t - \tau_N))Q(t - \tau_N)A_N(t) - (\gamma_{N_R} + \varphi_{N_R}(G(t)))N_R$$



Maturation Threshold Condition and Velocity Ratio

Variable V . Tempting to write

$$\frac{dN_R}{dt} = K_N(G(t - \tau_N(t)))Q(t - \tau_N(t))A_N(t) - (\gamma_{N_R} + \varphi_{N_R}(G(t)))N_R$$

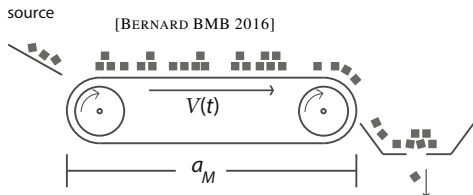
But **wrong**



Maturation Threshold Condition and Velocity Ratio

Variable V . With velocity correction:

$$\frac{dN_R}{dt} = K_N(G(t - \tau_N(t)))Q(t - \tau_N(t))A_N(t) \frac{V_{N_M}(G(t))}{V_{N_M}(G(t - \tau_{N_M}(t)))} - (\gamma_{N_R} + \varphi_{N_R}(G(t)))N_R$$



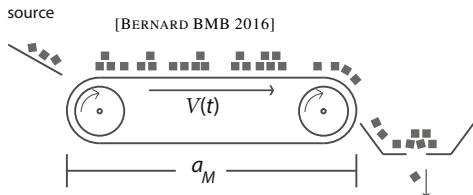
- add bags to conveyor belt at constant rate
- For any constant belt speed they exit at same rate
- Not true if belt speed varies



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- add bags to conveyor belt at constant rate
- For any constant belt speed they exit at same rate
- Not true if belt speed varies

- Differentiate Threshold condition: $\int_{t-\tau_{N_M}(t)}^t V_{N_M}(G(s))ds = a_{N_M}$,

$$\frac{d}{dt}\tau_{N_M}(t) = 1 - \frac{V_{N_M}(G(t))}{V_{N_M}(G(t-\tau_{N_M}(t)))} \text{ and } \frac{d}{dt}(t - \tau_{N_M}(t)) > 0$$

- Same correction term derived in [CRAIG,ARH,MACKEY BMB 2016] from age structured PDE, also as far back as [SMITH MATH BIOSCI '93]. Generalized to random maturation age in [CASSIDY,CRAIG,ARH MATH BIOSCIENG '19]



Constant Delay DDE IVP

$$\dot{u}(t) = f(t, u(t), u(t - \tau)), \quad u(0) = u_0 \in \mathbb{R}^d, \quad u(t) \in \mathbb{R}^d, t \geq t_0$$

For unique IVP solution for $t \geq t_0$

- it is *not* sufficient to specify $u(t_0)$
- To evaluate RHS at t_0 require $u(t_0 - \tau)$
- $\forall s \in [t_0 - \tau, t_0]$ require a value of $u(s)$ to evaluate RHS of DDE at $t = s + \tau \in [t_0, t_0 + \tau]$.

For uniqueness of IVP solution need an initial function

$$u(t) = \varphi(t), \quad \forall t \in [t_0 - \tau, t_0]$$

Provided φ is Lipschitz and $f = f(t, u, v)$ is Lipschitz in its arguments this is sufficient for local existence and uniqueness.

- Recall that phase space is space of initial functions



Breaking Points and Smoothing

$$\begin{aligned}\dot{u}(t) &= f(t, u(t), u(t - \tau)), & t \geq t_0 \\ u(t) &= \varphi(t), & t \in [t_0 - \tau, t_0]\end{aligned}$$

Breaking Point at t_0

Usually $\dot{\varphi}(t_0) \neq f(t_0, \varphi(t_0), \varphi(t_0 - \tau))$
so $\dot{u}(t_0^-) \neq \dot{u}(t_0^+)$. This is a *breaking point*.

Breaking Points at $t_0 + k\tau$

$$\begin{aligned}\ddot{u}(t) &= f_t(t, u(t), u(t - \tau)) + \dot{u}(t)f_u(t, u(t), u(t - \tau)) \\ &\quad + \dot{u}(t - \tau)f_v(t, u(t), u(t - \tau)).\end{aligned}$$

So \ddot{u} generically discontinuous at $t_0 + \tau$ and similarly,
 $u^{(k+1)}(t)$ discontinuous at $t = t_0 + k\tau$ for $k \geq 0$.

- Smoothing: $u(t) \in C^{k+1}$ for $t \geq t_0 + k\tau$
- No such smoothing for neutral problems



DDEs as Dynamical Systems

Phase space of DS is set of (initial) states of system:

$$\{u_t : u_t(\theta) = u(t + \theta), \theta \in [-\tau, 0]\}$$

But for $t \in (t_0, t_0 + \tau) \exists \theta \in (-\tau, 0)$ s.t. $t + \theta = t_0$.
 $u_t(\theta)$ is not differentiable at this θ .

Phase Space of continuous functions

$$\{\varphi : \varphi \in C([-\tau, 0], \mathbb{R}^d)\}$$

Includes all polynomials, so phase space is infinite dimensional even for scalar $d = 1$ problems

Retarded Functional Differential Equations

$$\dot{u}(t) = F(t, u_t), \quad F : \mathbb{R} \times C \rightarrow \mathbb{R}^d$$

- Lack of differentiability is a serious hindrance to theory



Scalar Example

Suppose $f(u, v)$ satisfies $f(0, 0) = 0$ so $u = 0$ is a steady state then

$$\dot{u}(t) = f(u(t), u(t - \tau)) = f_u(0, 0)u(t) + f_v(0, 0)u(t - \tau) + h.o.t$$

and linearization is

$$\dot{u}(t) = f_u(0, 0)u(t) + f_v(0, 0)u(t - \tau) = \mu u(t) + \sigma u(t - \tau)$$

Positing $u(t) = e^{\lambda t}$ gives transcendental *characteristic equation*

$$\lambda - \mu - \sigma e^{-\tau\lambda} = 0.$$

Let $\lambda = x + iy$ and take real and imaginary parts:

$$x - \mu - \sigma e^{-\tau x} \cos(y\tau) = y + \sigma e^{-\tau x} \sin(y\tau) = 0$$

Infinitely many roots, all lie on curve $y = \pm \sqrt{\sigma^2 e^{-2\tau x} - (x - \mu)^2}$

- Laplace transforms show all solutions are exponentials
- Finitely many roots to right of any vertical line in \mathbb{C} ;
- All characteristic roots satisfy $x < |\mu| + |\sigma|$
- Stable manifolds is infinite dimensional



$$\dot{u}(t) = f(u(t), u(t - \tau_1), \dots, u(t - \tau_m))$$

Let $f(u, v_1, \dots, v_m) : \mathbb{R}^d \times \mathbb{R}^{md} \rightarrow \mathbb{R}^d$ satisfy $f(0, 0, \dots, 0) = 0$, so $u = 0$ is a steady state.

Linearization is variational equation

$$\dot{u}(t) = A_0 u(t) + \sum_{j=1}^m A_j u(t - \tau_j),$$

where $A_0 = f_u$ and $A_j = f_{v_j}$ are $d \times d$ matrices evaluated at the steady-state (essentially a Jacobian matrix for each 'delay').

There is nontrivial solution $u(t) = e^{\lambda t} \underline{v} \in \mathbb{R}^d$ with $\Delta(\lambda) \underline{v} = 0$ if

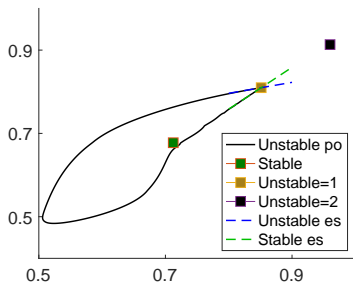
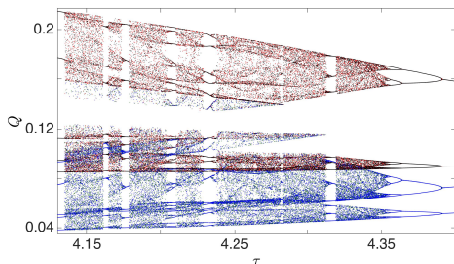
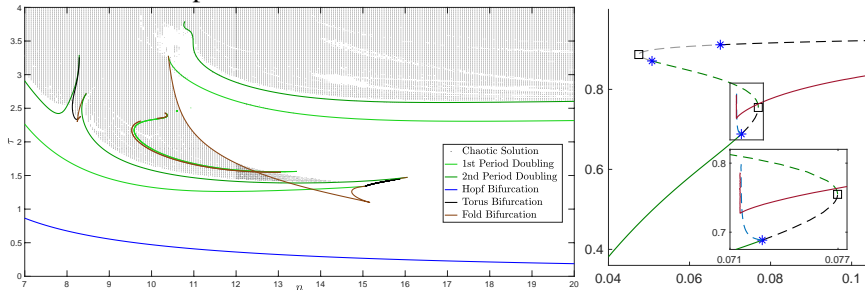
$$0 = \det(\Delta(\lambda)), \quad \Delta(\lambda) = \lambda I_d - A_0 - \sum_{j=1}^m A_j e^{-\lambda \tau_j}.$$

- Characteristic equation has infinitely many roots
- Variational equation soln: $u(t) = \sum_i \alpha_i e^{\lambda_i t} \underline{v}_i$
- Finitely many λ_i with $Re(\lambda_i) > \beta$ for any $\beta \in \mathbb{R}$.
- State-dependent DDEs are linearized by freezing the delays



Bifurcations for Delay Differential Equations

Numerical tools: DDE-Biftool and DDE23 in Matlab for solution and bifurcation computation



Threshold delays are example of distributed delays. Such delays hidden in many models this week. Lets consider infinite delay:

Model Distributed Delay DE

$$\frac{du}{dt} = f\left(t, u(t), \int_{-\infty}^t u(s)g(t-s)ds\right) = f\left(t, u(t), \int_0^{\infty} u(t-\sigma)g(\sigma)d\sigma\right).$$

- PDF:

$$g(t) \geq 0, \quad \int_0^{\infty} g(t)dt = 1, \quad \int_0^{\infty} tg(t)dt = \tau.$$

- Dynamics of $u(t)$ determined by a distribution of previous values.



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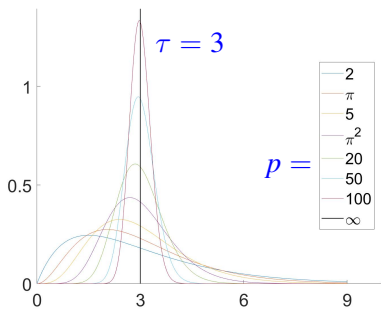
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- Dynamics of $u(t)$ determined by a distribution of previous values.
- **Problem:** Such problems not covered by off the shelf numerical packages for simulation or bifurcation detection
- Should specify a particular PDF.



The Gamma Distribution



PDF: $g_a^p(t) = \frac{a^p}{\Gamma(p)} t^{p-1} e^{-at},$

Mean delay: $\tau = p/a.$

Standard deviation: $\sigma^2 = p/a^2.$

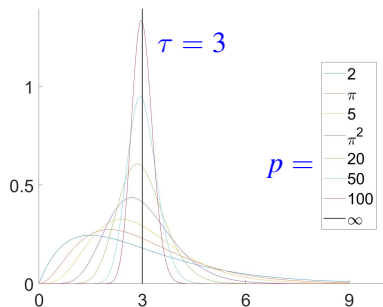
$$\Gamma(n) = (n-1)! \quad n \in \mathbb{N}.$$

$$\Gamma(p) = (p-1)\Gamma(p-1), \quad p \in \mathbb{R}/\mathbb{Z}_-.$$

Erlang distribution is special case of Gamma distribution with $p \in \mathbb{N}$



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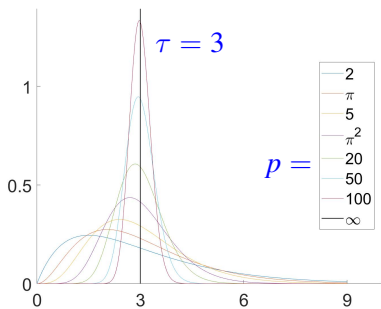
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In limit $p \rightarrow \infty$ with $\tau = p/a$ constant, $\sigma^2 \rightarrow 0$ so $g_a^p(t) \rightarrow \delta(t - \tau)$.

$$\frac{du}{dt} = f\left(t, u(t), \int_{-\infty}^t u(s)g(t-s)ds\right) \rightarrow \frac{du}{dt} = f(t, u(t), u(t-\tau))$$



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$$\Gamma(n) = (n-1)! \quad n \in \mathbb{N}.$$

$$\Gamma(p) = (p-1)\Gamma(p-1), \quad p \in \mathbb{R}/\mathbb{Z}_-.$$

Erlang distribution is special case of Gamma distribution with $p \in \mathbb{N}$

Differentiation Property

$$\frac{d}{dt} g_a^p(t) = \begin{cases} a(g_a^{p-1}(t) - g_a^p(t)), & p \neq 1 \\ -a g_a^1(t), & p = 1. \end{cases}$$

Gives closed system if $p \in \mathbb{Z}_+$.



Distributed Delay DE

$$\dot{u}(t) = f\left(t, u(t), \int_0^\infty u(t - \sigma) g_a^n(\sigma) d\sigma\right)$$



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$$\dot{u}(t) = f\left(t, u(t), \int_0^\infty u(t-\sigma)g_a^n(\sigma)d\sigma\right) = f(t, u(t), T_n(t))$$

Where we let

$$T_j(t) = \int_0^\infty u(t-s)g_a^j(s) ds, \quad j = 1, \dots, n.$$



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Equivalent ODE System

$$\dot{u}(t) = f(t, u(t), T_n(t))$$

$$\frac{dT_j}{dt} = \begin{cases} a(T_{j-1}(t) - T_j(t)), & j = \{2, 3, \dots, n\}, \\ a(u(t) - T_1(t)), & j = 1. \end{cases}$$

$$\tau = n/a \text{ and } \sigma^2 = n/a^2.$$

- This is linear chain technique

[VOGEL PROC. INT. SYMP. NONLINEAR VIB. '61],

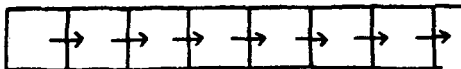
[MACDONALD TIME LAGS IN BIOLOGICAL MODELS '78],...



Linear Chain Trick

- Equivalent ODE is a **transit compartment model**. They have a long history:

$x = 0 \quad 1 \quad 2 \quad 3 \quad 4 \quad 5 \quad 6$



[MCKENDRICK PROC ED MATH SOC '25]

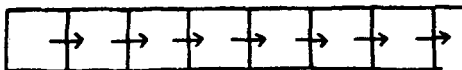
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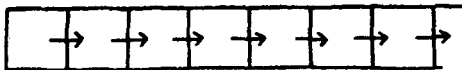
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- These models are finite dimensional, but become discrete delays in limit of infinitely many compartments
- Compartment model requires n integer : distributed DDE does not.
- Given estimates of $\tau \in \mathbb{R}_+$ and $\sigma^2 \in \mathbb{R}_+$,
No reason to suppose $n = \tau^2/\sigma^2 \in \mathbb{Z}_+$.



Ultradian Model

$$\frac{dG}{dt} = f_4(h_n) + I_G(t) - f_2(G) - f_3(I_i)G$$

$$\frac{dh_j}{dt} = \begin{cases} a(h_{j-1}(t) - h_j(t)), & j = \{2, 3, \dots, n\}, \\ a(I_p(t) - h_1(t)), & j = 1. \end{cases}$$

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Linear Chain Trick Equivalence

- Delay $\tau = n/a = 3t_d$
- Standard deviation: $\sigma^2 = n/a^2 = 3t_d^2$
- These are there in the model in whichever formulation, just obscured in ODE formulation.
- Q?: Why $n = 3$ Will?



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Linear Chain Trick Equivalence

- Equivalent Distributed DDE:

$$\frac{dG}{dt} = f_4(h_n) + I_G(t) - f_2(G) - f_3(I_i)G$$

$$h_n(t) = \int_0^\infty I_p(t-s)g_a^n(s) ds,$$

- In this direction its equivalent to solving the linear ODEs



Transit Compartment Models: Hidden Delays

An ODE Neutrophil Model generalised from [QUARTINO ET AL, PHARM RES 2014] (who had $a = k_{tr}$)

$$\dot{P} = P(k_p(1 - E_{Drug})(G/G_0)^\gamma - k_{tr}(G/G_0)^\beta)$$

$$\dot{T}_1 = a(G/G_0)^\beta(k_{tr}P - aT_1)$$

$$\dot{T}_j = a(G/G_0)^\beta(T_{j-1} - T_j), \quad j = 2, \dots, n$$

$$\dot{N} = a(G/G_0)^\beta T_n - k_{circ}N$$

$$\dot{G} = k_{in} - (k_e + k_{ANC}N)G,$$

- If $G = G_0$, constant, rewrite model as a distributed DDE using linear chain technique, with mean **delay** $\tau = n/a$.
- Original paper has wrong delay and wrong production rate.



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- If $G = G_0$, constant, rewrite model as a distributed DDE using linear chain technique, with mean **delay** $\tau = n/a$.
- Original paper has wrong delay and wrong production rate.
- For general $G(t)$, compartment transit rate is $a(G(t)/G_0)^\beta$, state-dependent and linear chain trick does not apply.
- [CAMARA, ..., ARH, JPKPD 2018] rescale time and apply linear chain trick to get distributed DDE even for state-dependent delay [CASSIDY, CRAIG, ARH, MATH BIOSCI & ENG 2019] apply generalised linear chain technique to avoid inelegant time rescaling.



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[CAMARA, ARH SIADS 2019], [CASSIDY, CRAIG, ARH MATH BIOSCI & ENG 2019],
[GEDEON, ARH ET AL JMB 2022], [DURUISSEAU, ARH JCD 2022]

Conclusions

- Delays allow to simplify physiological modelling
- Delay Differential Equations Define Infinite Dimensional Dynamical Systems. These are tractable numerically and theoretically
- Even scalar DDEs can display very interesting dynamics
- Equations which depend on a distribution of past state values, or where the value of the delay is discrete but depends on state of the system are interesting and tractable.



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