Delay-induced uncertainty: Mathematics and physiological implications

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Outline

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Motivation

Successful medical intervention requires reliable prediction.

- Uncertainty about exact patient state
- Uncertainty about the intervention itself
- Sensitivity of treatment to timing
- Repeatability of treatment outcomes

If prediction reliability fails for a physiological system:

- Mechanisms?
- Mathematical characterization?
- Clinial impact?
- Mitigation?

Take-home messages

Prediction reliability can fail for the glucose-insulin system.

- Induced by delay
- Precisely characterized by shear-induced uncertainty (SIU) theory

SIU is subtle:

- May or may not occur in a given physiological setting
- Difficult to detect
- Renders mysterious the reasons for treatment failure (interpretability)

Outline

Take-home messages

Shear-induced uncertainty

SIU in glucose-insulin dynamics

Future work

SIU recipe

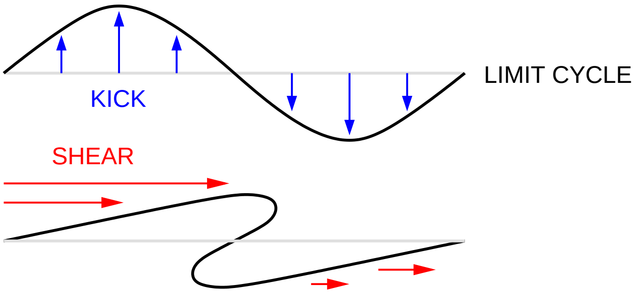
Ingredients:

1. Weakly stable invariant dynamical structure (e.g. limit cycle)
2. Shear
3. External forcing
4. Interaction between external forcing and shear

Results:

1. Temporally-persistent dynamical instability (positive Lyapunov exponent)
2. Complex attractors
3. Genuine nonuniformly hyperbolic dynamics
4. Strong statistical properties (e.g. large deviations principle, exponential decay of correlations)

Linear shear flow - geometry



Phase space: $(\theta, z) \in \mathbb{S}^1 \times \mathbb{R}$

Intrinsic system

$$\begin{cases} \dfrac{d\theta}{dt} = 1 + \sigma z \\ \dfrac{dz}{dt} = -\lambda z \end{cases}$$

Forced system

$$\begin{cases} \dfrac{d\theta}{dt} = 1 + \sigma z \\ \dfrac{dz}{dt} = -\lambda z + \alpha \Phi(\theta) \displaystyle\sum_{n=0}^{\infty} \delta(t - nT) \end{cases}$$

σ: shear λ: contraction α: kick amplitude T: relaxation time

Key diagnostic $\dfrac{\sigma\alpha}{\lambda} = \dfrac{\text{(shear)(kick amplitude)}}{\text{(contraction)}}$

$$\begin{cases} \dfrac{d\theta}{dt} = 1 + \sigma z \\ \dfrac{dz}{dt} = -\lambda z + \alpha\Phi(\theta) \displaystyle\sum_{n=0}^{\infty} \delta(t - nT) \end{cases}$$

Properties of the time-T map H_T

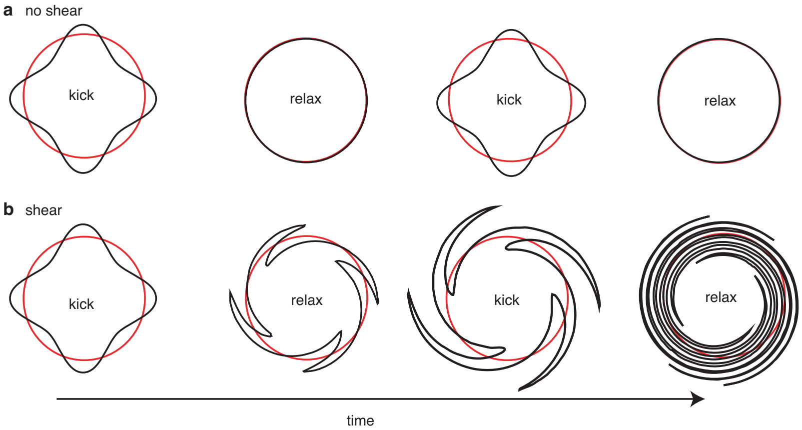
1. $\frac{\sigma\alpha}{\lambda}$ small: invariant curve (diffeomorphic to $\mathbb{S}^1$) attracts every trajectory
2. $\frac{\sigma\alpha}{\lambda}$ large: SIU for a set of T-values of positive Lebesgue measure (Wang/Young 2003)

Analyze the '$T \to \infty$' singular limit:

$$g_a(\theta) := \lim_{k\to\infty} H_{k+a}(\alpha\Phi(\theta))$$

$$g_a(\theta) = \theta + a + \frac{\sigma\alpha}{\lambda}\Phi(\theta)$$

Kick-relax cycle



Shear quantification in nonlinear oscillatory systems

- $2D$ simple mechanical systems (Wang/Young 2002)
- Hopf limit cycles (Wang/Young 2003)
- Limit cycles in dimension N (Ott/Stenlund 2010)
  - Introduce shear integrals
- Hopf bifurcations for parabolic PDEs (Lu/Wang/Young 2013)
- If delay is present?

Outline

Ultradian model

$$\begin{cases} \frac{dI_p}{dt} = f_1(G) - E(\frac{I_p}{V_p} - \frac{I_i}{V_i}) - \frac{I_p}{t_p} \\ \frac{dI_i}{dt} = E(\frac{I_p}{V_p} - \frac{I_i}{V_i}) - \frac{I_i}{t_i} \\ \frac{dG}{dt} = f_4(h_3) + I_G(t) - f_2(G) - f_3(I_i)G \end{cases}$$

$$\begin{cases} \frac{dh_1}{dt} = \frac{1}{t_d}(I_p - h_1) \\ \frac{dh_2}{dt} = \frac{1}{t_d}(h_1 - h_2) \\ \frac{dh_3}{dt} = \frac{1}{t_d}(h_2 - h_3) \end{cases}$$

$I_G(t)$: Nutritional drive t_d : Delay timescale

Nutritional drive

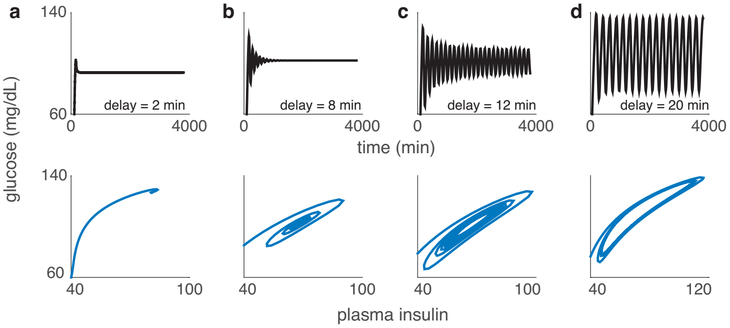
$$I_G(t) = I_0 + \sum_{n \in \mathbb{N}} A_n \delta(t - T_n)$$

- I_0: Basal nutritional input
- A_n: Carbohydrate content of meal n
- T_n: Time of meal n

Delay-induced supercritical Hopf bifurcation (No kicks!)

$$I_G(t) = I_0 + \underbrace{\sum_{n \in \mathbb{N}} A_n \delta(t - T_n)}_{\text{OFF}}$$

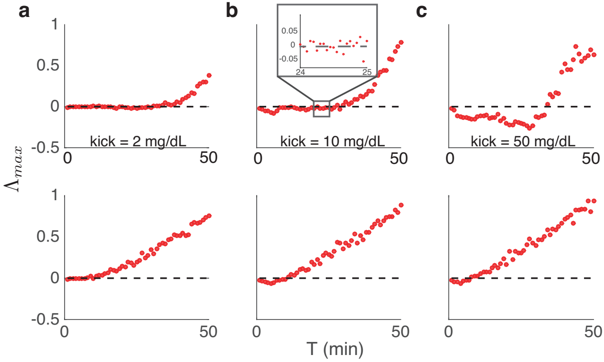
Increasing t_d produces oscillations



Top Lyapunov exponent indicates SIU emergence

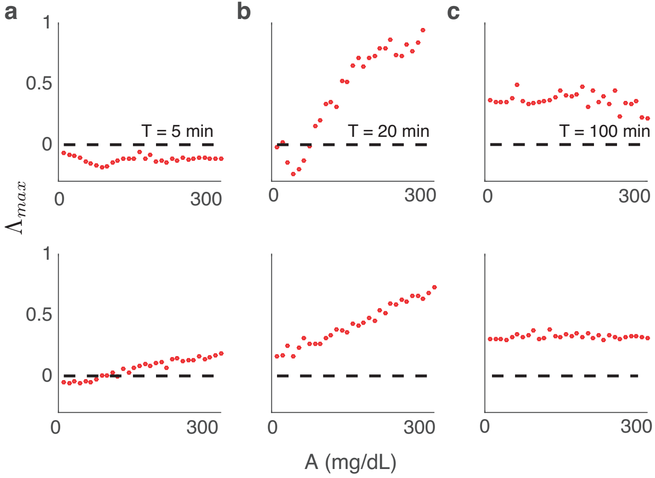
$$I_G(t) = I_0 + \sum_{n \in \mathbb{N}} A\delta(t - T_n)$$

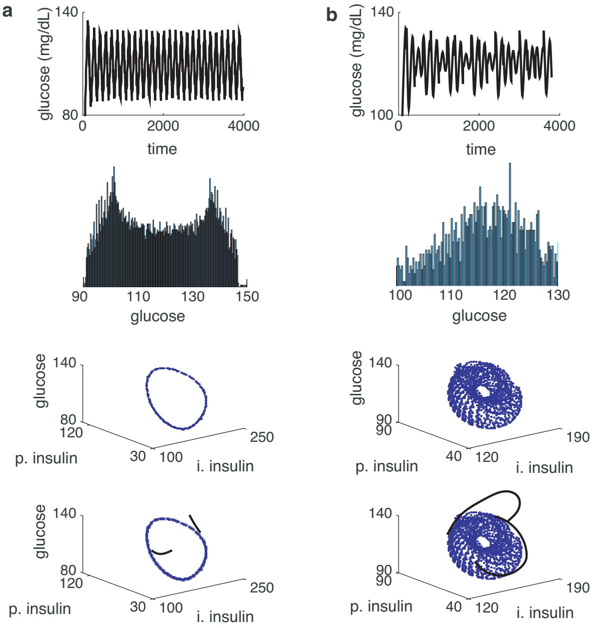
Top: Periodic kicks ($T_n = nT$)
Bottom: Poisson kicks ($T_{n+1} - T_n$ IID exponential with mean T)



$$I_G(t) = I_0 + \sum_{n \in \mathbb{N}} A\delta(t - T_n)$$

Top: Periodic kicks   Bottom: Poisson kicks

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glucose (mg/dL)
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2000
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time
90
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130
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glucose
glucose
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p. insulin
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i. insulin
250
glucose
140
80
120
p. insulin
30
100
i. insulin
250
b
glucose (mg/dL)
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100
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2000
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time
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130
glucose
glucose
140
90
90
p. insulin
40
120
i. insulin
190
140
90
90
p. insulin
40
120
i. insulin
190

Outline

Future work

- Modeling
  - Complex drives
  - Insulin kicks
  - Control protocols
- Anchor to data!
- Rigorous SIU theory for delay systems
  - Fixed delay
  - Random (distributed) delay
- Implications of stochasticity in the delay?