Canard-Induced Mixed Mode Oscillations
In Pituitary Lactotrophs

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SIAM LIFE SCIENCES CONFERENCE
AUGUST 10, 2012
MMOs In A 3-Timescale System

Theo Vo

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MMO Model
Bifurcations

1-Fast/3-Slow
Layer Flow
Reduced Flow
Canards

3-Fast/1-Slow
G.S.P.T
Dynamic MMOs
Averaging

3-Timescale
Double Limit
Inheritance

Summary

Motivation

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(a) http://www.empowher.com/media/reference/apoplexy

(b) http://www.scholarpedia.org/article/Models_of_hypothalamus
By contrast, application of the Ca$^{2+}$ channel blockers, nifedipine and Cd$^{2+}$, prolonged depolarization is required to be sufficient to trigger secretion, whereas in neuroendocrine cells prolonged depolarization is required to be sufficient to trigger secretion, whereas in neuroendocrine cells.
Motivation

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Pituitary Lactotroph Model

\[ C_m \frac{dV}{dt} = -(I_{Ca} + I_K + I_{SK} + I_A) \]

\[ \frac{dn}{dt} = \frac{n_\infty(V) - n}{\tau_n} \]

\[ \frac{de}{dt} = \frac{e_\infty(V) - e}{\tau_e} \]

\[ \frac{dc}{dt} = -f_c(\alpha I_{Ca} + k_c c) \]

\[ I_{Ca} = g_{Ca} m_\infty(V)(V - V_{Ca}) \]

\[ I_K = g_K n(V - V_K) \]

\[ I_{SK} = g_{SK} s_\infty(c)(V - V_K) \]

\[ I_A = g_A a_\infty(V)e(V - V_K) \]
Dynamic and Calcium-Clamped MMOs
Bifurcation Structure

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A 3-Timescale Problem

\[ \varepsilon \frac{dV}{dt_L} = f(V, n, e, c) \]
\[ \frac{dn}{dt_L} = g_1(V, n) \]
\[ \frac{de}{dt_L} = g_2(V, e) \]
\[ \frac{dc}{dt_L} = \delta h(V, c) \]
\[ \tau_V = \frac{C_m}{g} < 1 \text{ ms} \]
\[ \tau_n \approx 43 \text{ ms} \]
\[ \tau_e \approx 20 \text{ ms} \]
\[ \tau_c = \frac{1}{f_c k_c} \approx 625 \text{ ms} \]

\[ 0 < \varepsilon = \frac{\tau_V}{\tau_e} \ll 1, \quad 0 < \delta = \frac{\tau_e}{\tau_c} \ll 1 \]
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**Summary**

**‘SLOW’ SYSTEM**

\[
\begin{align*}
\epsilon \frac{dV}{dt_I} &= f(V, n, e, c) \\
\frac{dn}{dt_I} &= g_1(V, n) \\
\frac{de}{dt_I} &= g_2(V, e) \\
\frac{dc}{dt_I} &= \delta h(V, c)
\end{align*}
\]

**FAST SYSTEM**

\[
\begin{align*}
\frac{dV}{dt_F} &= f(V, n, e, c) \\
\frac{dn}{dt_F} &= \epsilon g_1(V, n) \\
\frac{de}{dt_F} &= \epsilon g_2(V, e) \\
\frac{dc}{dt_F} &= \epsilon \delta h(V, c)
\end{align*}
\]

\[t_F = \epsilon t_I\]
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Geometric Singular Perturbation Theory

'SLOW' SYSTEM

\[ \varepsilon \frac{dV}{dt_I} = f(V, n, e, c) \]
\[ \frac{dn}{dt_I} = g_1(V, n) \]
\[ \frac{de}{dt_I} = g_2(V, e) \]
\[ \frac{dc}{dt_I} = \delta h(V, c) \]

\[ \varepsilon \quad \downarrow \quad 0 \]

FAST SYSTEM

\[ \frac{dV}{dt_F} = f(V, n, e, c) \]
\[ \frac{dn}{dt_F} = \varepsilon g_1(V, n) \]
\[ \frac{de}{dt_F} = \varepsilon g_2(V, e) \]
\[ \frac{dc}{dt_F} = \varepsilon \delta h(V, c) \]

\[ \varepsilon \quad \downarrow \quad 0 \]

3D REDUCED PROBLEM

\[ 0 = f(V, n, e, c) \]
\[ \frac{dn}{dt_I} = g_1(V, n) \]
\[ \frac{de}{dt_I} = g_2(V, e) \]
\[ \frac{dc}{dt_I} = \delta h(V, c) \]

1D LAYER PROBLEM

\[ \frac{dV}{dt_F} = f(V, n, e, c) \]
\[ \frac{dn}{dt_F} = 0 \]
\[ \frac{de}{dt_F} = 0 \]
\[ \frac{dc}{dt_F} = 0 \]
The Layer Problem

\[
\begin{align*}
\frac{dV}{dt_F} &= f(V, n, e, c) \\
\frac{dn}{dt_F} &= 0 \\
\frac{de}{dt_F} &= 0 \\
\frac{dc}{dt_F} &= 0
\end{align*}
\]

\[S = S_a \cup L \cup S_r = \{(V, n, e, c) \in \mathbb{R}^4 : f(V, n, e, c) = 0\}\]

Attracting branch, \(S_a := \{(V, n, e, c) \in S : f_V < 0\}\)

Repelling branch, \(S_r := \{(V, n, e, c) \in S : f_V > 0\}\)

Fold surface, \(L := \{(V, n, e, c) \in S : f_V = 0\}\)

CAUTION: THESE PLOTS SHOW 3D SLICES OF A 4D PHASE SPACE
The Reduced System

**Reduced System**

\[ 0 = f(V, n, e, c) \]
\[ \frac{dn}{dt_I} = g_1(V, n) \]
\[ \frac{de}{dt_I} = g_2(V, e) \]
\[ \frac{dc}{dt_I} = \delta h(V, c) \]

**Projection**

\[-f_V \frac{dV}{dt_I} = F_\delta(V, n, e, c) \]
\[ 0 = f(V, n, e, c) \]
\[ \frac{de}{dt_I} = g_2(V, e) \]
\[ \frac{dc}{dt_I} = \delta h(V, c) \]

\[ F_\delta(V, n, e, c) := f_n g_1 + f_e g_2 + \delta f_c h \]
The Reduced System

**Reduced System**

\[-f_V \frac{dV}{dt_i} = F_\delta(V, n, e, c)\]

\[\frac{de}{dt_i} = g_2(V, e)\]

\[\frac{dc}{dt_i} = \delta h(V, c)\]

**Desingularized**

\[\frac{dV}{dt_i^*} = F_\delta(V, n, e, c)\]

\[\frac{de}{dt_i^*} = -f_V g_2(V, e)\]

\[\frac{dc}{dt_i^*} = -\delta f_V h(V, c)\]

- Ordinary singularities
  \[E := \{(V, n, e, c) \in S : g_1 = g_2 = h = 0\}\]

- Folded singularities
  \[M_\delta := \{(V, n, e, c) \in S : f_V = F_\delta = 0\}\]
Singular Orbit Construction

CAUTION: We are plotting 3D projections of a 4D system!
Perturbations – Mixed Mode Oscillations

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Summary
Perturbations – Slow Manifolds

$\varepsilon = 0$

S\textsubscript{a}

S\textsubscript{r} \cap \Sigma

S\textsubscript{a} \cap \Sigma

V (mV)

0.225 0.23 0.235

−18

−15

−12

0.24 0.22 0.20

Summary

Inheritance

Dynamic MMOs

Average

G.S.P.T

3-Fast/1-Slow

Reduced Flow

Flow

Layer Flow

1-Fast/3-Slow

Bifurcations

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MMOs In A 3-Timescale System
Perturbations – Slow Manifolds

\[ \varepsilon = 0.0005 \]
MMOs In A 3-Timescale System

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**Motivation**

- MMO Model
- Bifurcations

**1-Fast/3-Slow**

- Layer Flow
- Reduced Flow
- Canards

**3-Fast/1-Slow**

- G.S.P.T
- Dynamic MMOs
- Averaging

**3-Timescale**

- Double Limit
- Inheritance

**Summary**

Perturbations – Slow Manifolds

$\varepsilon = 0.001$

![Graph showing perturbations and slow manifolds](graph.png)
Perturbations – Slow Manifolds

\[ \varepsilon = 0.002 \]

\[ S^\varepsilon_a \]

\[ S^\varepsilon_r \]

\[ S^\varepsilon_r \cap \Sigma \]

\[ S^\varepsilon_a \cap \Sigma \]
Perturbations – Canards

\[ \varepsilon = 0.002 \]
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Rationale

3-Timescale Bursting Model

\[ \varepsilon \to 0 \]
\[ \delta \neq 0 \]
\[ \varepsilon \neq 0 \]

1 Fast
3 Slow

3 Fast
1 Slow

1 Fast
2 Intermediate
1 Slow

\[ \varepsilon = 0 \]
\[ \delta \to 0 \]
\[ \varepsilon \to 0 \]

Bifurcation Theory
G.S.P.T

Origin & Properites of Bursting

Bifurcation Theory
G.S.P.T
**Motivation**

**MMO Model**

Bifurcations

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**Summary**

**Geometric Singular Perturbation Analysis**

**‘FAST’ SYSTEM**

\[
\begin{align*}
\epsilon \frac{dV}{dt_I} &= f(V, n, e, c) \\
\frac{dn}{dt_I} &= g_1(V, n) \\
\frac{de}{dt_I} &= g_2(V, e) \\
\frac{dc}{dt_I} &= \delta h(V, c)
\end{align*}
\]

\[\delta \downarrow 0\]

\[\delta \downarrow 0\]

**SLOW SYSTEM**

\[
\begin{align*}
\epsilon \delta \frac{dV}{dt_S} &= f(V, n, e, c) \\
\delta \frac{dn}{dt_S} &= g_1(V, n) \\
\delta \frac{de}{dt_S} &= g_2(V, e) \\
\frac{dc}{dt_S} &= h(V, c)
\end{align*}
\]

**3D LAYER PROBLEM**

\[
\begin{align*}
\epsilon \frac{dV}{dt_I} &= f(V, n, e, c) \\
\frac{dn}{dt_I} &= g_1(V, n) \\
\frac{de}{dt_I} &= g_2(V, e) \\
\frac{dc}{dt_I} &= 0
\end{align*}
\]

**1D REDUCED PROBLEM**

\[
\begin{align*}
0 &= f(V, n, e, c) \\
0 &= g_1(V, n) \\
0 &= g_2(V, e) \\
\frac{dc}{dt_S} &= h(V, c)
\end{align*}
\]
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**Motivation**

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**Summary**

Layer and Reduced Flows

\[ \varepsilon \frac{dV}{dt} = f(V, n, e, c) \]

\[ \frac{dn}{dt} = g_1(V, n) \]

\[ \frac{de}{dt} = g_2(V, e) \]

\[ \frac{dc}{dt} = 0 \]

\[ SS = \{(V, n, e, c) \in S : g_1(V, n) = g_2(V, e) = 0 \} \]

Fold points, \[ LL := \{(V, n, e, c) \in SS : \text{det } Df = 0 \} \]

Hopf Bifurcation, \[ SS_H := \{(V, n, e, c) \in SS : f_V = \mathcal{O}(\varepsilon) \} \]
Singular Orbits

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Canards

### 3-Fast/1-Slow

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### 3-Timescale

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### Summary

\[
\frac{dc}{dt} = \frac{1}{T(c)} \int_0^{T(c)} h(V(s, c), c) \, ds \equiv \bar{h}(c)
\]

![Graph of calcium-clamped MMOs](image)

- **SS**
- **SS_H**
- **Averaged**
- **\( h = 0 \)**

![Graph of averaged MMOs](image)

- **\( \Gamma(\epsilon, \delta) \)**
- **Averaged**
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3-Timescale Bursting Model

1 Fast
3 Slow

3 Fast
1 Slow

1 Fast
2 Intermediate
1 Slow

Bifurcation Theory
- G.S.P.T

Origin & Properites of Bursting

Bifurcation Theory
- G.S.P.T
The Double Limit

\[ \varepsilon = 0, \delta \neq 0 \]

1-Fast/3-Slow Layer
\[
\frac{dV}{dt_F} = f(V, n, e, c) \\
\frac{dn}{dt_F} = 0 \\
\frac{de}{dt_F} = 0 \\
\frac{dc}{dt_F} = 0
\]

1-Fast/3-Slow Reduced
\[ 0 = f(V, n, e, c) \]
\[
\frac{dn}{dt_i} = g_1(V, n) \\
\frac{de}{dt_i} = g_2(V, e) \\
\frac{dc}{dt_i} = \delta h(V, c)
\]

\[ \varepsilon \neq 0, \delta = 0 \]

3-Fast/1-Slow Layer
\[
\frac{dV}{dt_i} = f(V, n, e, c) \\
\frac{dn}{dt_i} = g_1(V, n) \\
\frac{de}{dt_i} = g_2(V, e) \\
\frac{dc}{dt_i} = 0
\]

3-Fast/1-Slow Reduced
\[ 0 = f(V, n, e, c) \]
\[ 0 = g_1(V, n) \]
\[ 0 = g_2(V, e) \]
\[
\frac{dc}{dt_s} = h(V, c)
\]
The Double Limit

$\varepsilon = 0, \delta = 0$

1D Fast Subsystem

\[
\frac{dV}{dt_F} = f(V, n, e, c)
\]
\[
\frac{dn}{dt_F} = 0
\]
\[
\frac{de}{dt_F} = 0
\]
\[
\frac{dc}{dt_F} = 0
\]

2D Intermediate Subsystem

\[
0 = f(V, n, e, c)
\]
\[
\frac{dn}{dt_i} = g_1(V, n)
\]
\[
\frac{de}{dt_i} = g_2(V, e)
\]
\[
\frac{dc}{dt_i} = 0
\]

2D Intermediate Subsystem

\[
0 = f(V, n, e, c)
\]
\[
\frac{dn}{dt_i} = g_1(V, n)
\]
\[
\frac{de}{dt_i} = g_2(V, e)
\]
\[
\frac{dc}{dt_i} = 0
\]

1D Slow Subsystem

\[
0 = f(V, n, e, c)
\]
\[
0 = g_1(V, n)
\]
\[
0 = g_2(V, e)
\]
\[
\frac{dc}{dt_S} = h(V, c)
\]
Geometric Structures Persist

2D INTERMEDIATE

\[ 0 = f(V, n, e, c) \]
\[ \frac{dn}{dt_l} = g_1(V, n) \]
\[ \frac{de}{dt_l} = g_2(V, e) \]
\[ \frac{dc}{dt_l} = 0 \]

Proj & Desing

DESINGULARIZED

\[ 0 = f(V, n, e, c) \]
\[ \frac{dV}{dt^*_l} = F_0(V, n, e, c) \]
\[ \frac{de}{dt^*_l} = -f_V g_2(V, e) \]
\[ \frac{dc}{dt^*_l} = 0 \]
Dynamic & Calcium-Clamped MMOs

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Calcium-clamped MMOs
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Summary

\((\varepsilon, \delta) = (0, 0)\)

\((\varepsilon, \delta) \neq (0, 0)\)

\[ g_A \quad (\text{nS}) \]

\[ g_K \quad (\text{nS}) \]

Dep

Bistability

Calcium-clamped

Dynamic MMO

\(E_{\text{SHB}}\)

Spiking

Hopf Bifurcation

Bursting

Period-Doubling

Spiking

\[ V \quad (\text{mV}) \]

\[ \text{Time (ms)} \]
Recapitulation

- Motivation: explain dynamics
- 1-Fast/3-Slow: canard theory
- 3-Fast/1-Slow: delay phenomena
- 3-Timescale: best of both worlds

It never hurts to look at your problem from multiple points of view!
Thank You!