Dynamics from Seconds to Hours in Hodgkin–Huxley Model

with Time–Dependent Ion Concentrations and Buffer Reservoirs

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Outline

Closed Models

- model review
- dynamics → bistability
- bifurcation analysis → insufficiency of ion pumps

Open Models with External Reservoirs

- dynamics → CSD
- time scales → slow–fast analysis

Oscillatory Dynamics

- seizure–like activity (SLA) and SD
- bifurcation analysis → assign specific bifurcations to SLA and SD

Introduction

Trying to find and analyze the **simplest possible model** of local ion dynamics that…

…can be **biophysically** interpreted.

…shows **spreading depression** dynamics.

What has been done?

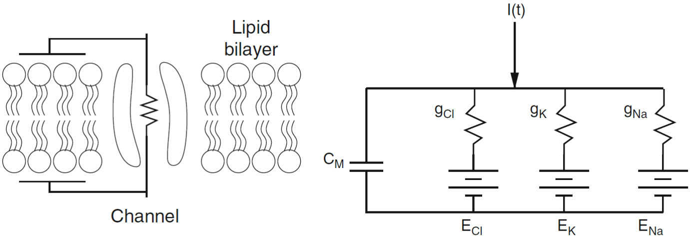
A lot! An incomplete list…

- Hodgkin–Huxley
- cardiac models (DiFrancesco, Noble, 1980s)
- cortical ion dynamics: Kager, Wadman, Somjen
- Barreto, Cressman
- Schiff, Ullah
- Bazhenov, Fröhlich
- Zandt

What do we do?

- investigate **entire repertoire** of ion dynamics in simple model
- bifurcation analysis **of ion dynamics**
- slow–fast interpretation **of ion dynamics** in SD
- **phase space** interpretation of ion dynamics

Hodgkin–Huxley Model (HH)



Developed for the description of **action potentials**.

equivalent electrical circuit

- lipid bilayer is a capacitor
- channel is a conductor in series with a battery
- energy from batteries not dissipated

Hodgkin–Huxley Model (HH)

Four rate equations of HH

$$\frac{dV}{dt} = -\frac{1}{C_m}(I_{Na} + I_K + I_{Cl} - I_{app})$$
$$\frac{dx}{dt} = \frac{x_\infty(V) - x}{\tau_x(V)} \quad \text{for } x \in \{n, m, h\}$$

Model parameters

- capitance C_m
- leak conductances g^l_{ion}
- max. gated conductances g^g_{ion}
- ion concentrations $ion_{i/e}$

Three ion currents

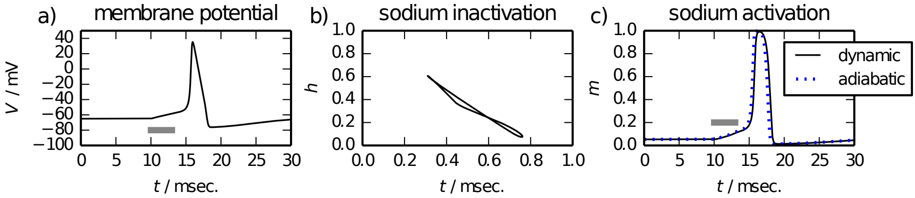
$$I_{Na} = (g^l_{Na} + g^g_{Na} m^3 h)(V - E_{Na})$$
$$I_K = (g^l_K + g^g_K n^4)(V - E_K)$$
$$I_{Cl} = g^l_{Cl}(V - E_{Cl})$$

Nernst potentials

$$E_{ion} = -\frac{26.6\text{mV}}{z}\ln(ion_i/ion_e)$$

for $ion \in \{Na^+, K^+, Cl^-\}$

HH Approximations



The action potential dynamics can be approximated by

- an adiabatic approximation for the sodium activation: $m = m_\infty(V)$
- assuming a functional dependence between sodium inactivation and potassium activation: $h = f(n)$

Two–dimensional HH model

rate eqations:

$$\dot{V} = -\frac{1}{C_m}\sum_{ion} I_{ion}$$

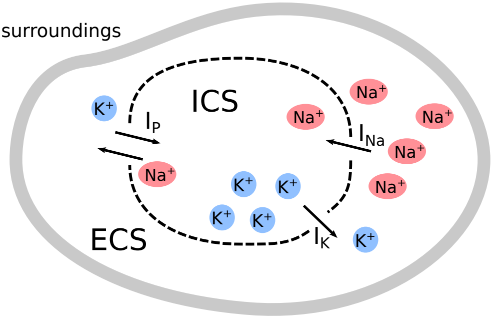
$$\dot{n} = \frac{n_\infty - n}{\tau_n}$$

gating constraints:

$$m = m_\infty(V)$$

$$h = -\frac{1}{1+\exp(-6.5(n-0.35))}$$

ION–BASED MODEL



The ion–based model contains

- intracellular space (ICS)
- extracellular space (ECS)

Note: The membrane separates ICS and ECS. Effects from surroundings are not included here $\longrightarrow$ *closed* system

Ion dynamics

The flux of ions across the membrane is induced by the *transmembrane* currents.

The novel effects include:

- Nernst potentials are dynamic:
  $E_{ion} = -\frac{26.6\text{mV}}{z} \ln\left(\frac{ion_i}{ion_e}\right)$
- Ion pumps are needed to maintain the resting state.

$$I_p = \rho\left(1+\exp\left(\frac{25-Na_i}{3}\right)\right)^{-1} \cdot \left(1+\exp\left(5.5-K_e\right)\right)^{-1}$$

Ion–Based Model

Rate equations

$$
\begin{aligned}
\dot{V} &= -\frac{1}{C_m}(I_{Na} + I_K + I_{Cl} - I_p) \\
\dot{n} &= \frac{n_\infty - n}{\tau_n} \\
\dot{Na}_i &= -\frac{\gamma}{\omega_i}(I_{Na} + 3I_p) \\
\dot{K}_i &= -\frac{\gamma}{\omega_i}(I_K - 2I_p) \\
\dot{Cl}_i &= +\frac{\gamma}{\omega_i} I_{Cl}
\end{aligned}
$$

Note: $\dot{Na}_i + \dot{K}_i - \dot{Cl}_i - \frac{C_m \gamma}{\omega_i}\dot{V} = 0$

$\Rightarrow$ conservation law

$\Rightarrow$ four–dimensional dynamics

Constraints

Gating constraints:

$$
\begin{aligned}
m &= m_\infty(V) \\
h &= h_{sig}(n)
\end{aligned}
$$

Mass conservation:

$$
\begin{aligned}
Na_e &= Na_e^0 + \frac{\omega_i}{\omega_e}(Na_i^0 - Na_i) \\
K_e &= K_e^0 + \frac{\omega_i}{\omega_e}(K_i^0 - K_i) \\
Cl_e &= Cl_e^0 + \frac{\omega_i}{\omega_e}(Cl_i^0 - Cl_i)
\end{aligned}
$$

Parameters:

- volumes $\omega_{i/e}$
- conversion factor γ

Donnan Equilibrium in Ion–Based Model

The conservation law implies electroneutrality:

$$
\begin{aligned}
0 &= \dot{Na}_i + \dot{K}_i - \dot{Cl}_i - \frac{C_m \gamma}{\omega_i} \dot{V} \\
\Rightarrow \Delta Q_i &= \Delta (Na_i + K_i - Cl_i) = \underbrace{\frac{C_m \gamma}{\omega_i}}_{\mathcal{O}(10^{-4} \frac{\text{mM}}{\text{mV}})} \Delta V
\end{aligned}
$$

ω_i	$2{,}160 \mu\text{m}^3$
ω_e	$720 \mu\text{m}^3$
F	$96485 \text{C}/\text{mol}$
A_m	$922 \mu\text{m}^2$
γ	$9.556\text{e–}3 \frac{\mu\text{m}^2\text{mol}}{\text{C}}$

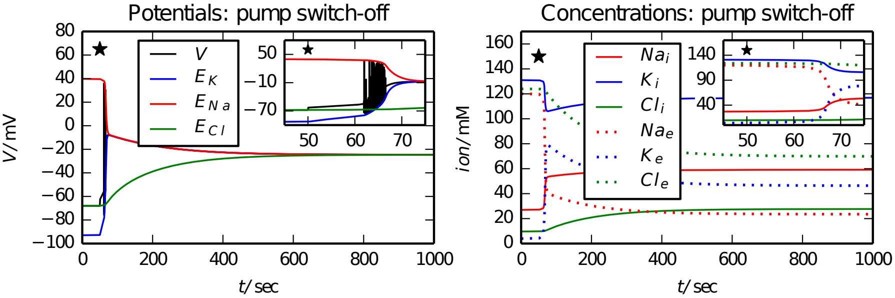
The equilibrium without pumps...

$$
0 = \frac{d ion_i}{dt} = \pm \frac{\gamma}{\omega_i} (g^l_{ion} + \ldots)(V - E_{ion}) \quad \Rightarrow \quad E_{Na} = E_K = E_{Cl}
$$

$$
\left. \begin{aligned} E_{Na} = E_K = E_{Cl} \\ \Delta Q_i \approx 0 \end{aligned} \right\} \quad \ldots \text{ is the Donnan equilibrium!}
$$

Note: No impermeant anions included!

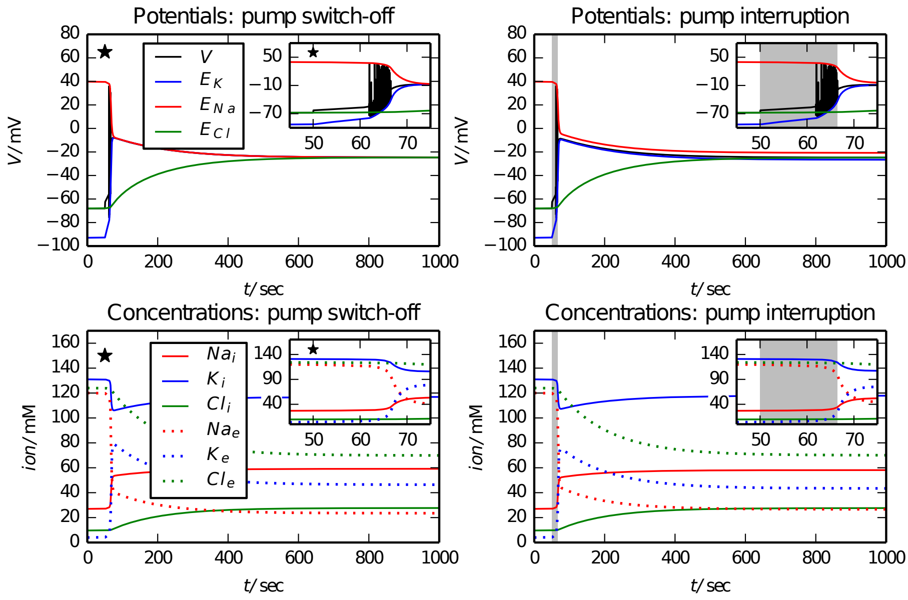
Donnan Equilibrium in Ion–Based Model



The pump is switched off after 50sec. The transition from the physiological resting state to the Donnan equilibrium follows.

- ion fluxes until spiking begin
- spiking until depolarization block is reached
- final asymptotic phase until Donnan equilibrium is attained

What if we turn the pumps on again?



⇒ **Another stable state shows up!**

Free Energy–Starvation (FES)

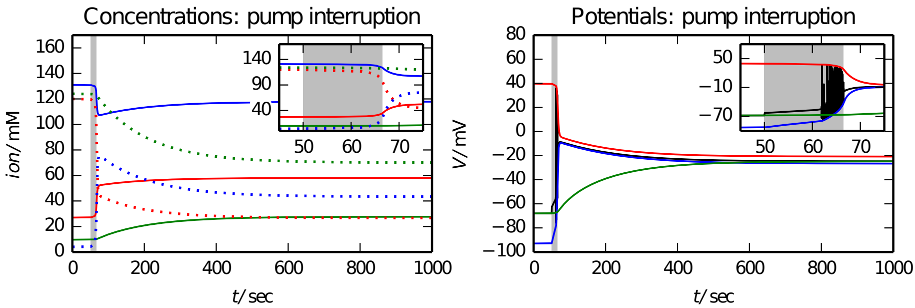
Symbol	Physiological	Donnan	FES	Units
V	−68	−24.6	−24.7	mV
n	0.065	0.611	0.609	1
Na_i	27	59.2	58.1	mM
Na_e	120	23.5	26.6	mM
K_i	131	116.9	117.9	mM
K_e	4	46.4	43.4	mM
Cl_i	9.7	27.7	27.7	mM
Cl_e	124	70.0	70.0	mM
E_{Na}	39.7	−24.6	−20.8	mV
E_K	−92.9	−24.6	−26.6	mV
E_{Cl}	−68	−24.6	−24.7	mV

Despite normal pump activity a stable state exists which...

... has largely reduced ion gradients (dissipated energy).

... is depolarized and cannot spike.

We frame the term **"free energy–starvation (FES)"** for this condition.



Phys. resting state

Pumps compensate for leak currents.

FES

Pumps compensate for gated currents. They **cannot re–establish** physiological conditions.

Symbol	phys.	FES	Units
I^l_{Na}	-1.89	-0.07	$\mu A/cm^2$
I^g_{Na}	-0.01	-15.68	$\mu A/cm^2$
I^l_K	1.25	0.09	$\mu A/cm^2$
I^g_K	0.02	10.41	$\mu A/cm^2$
I_p	0.63	5.25	$\mu A/cm^2$

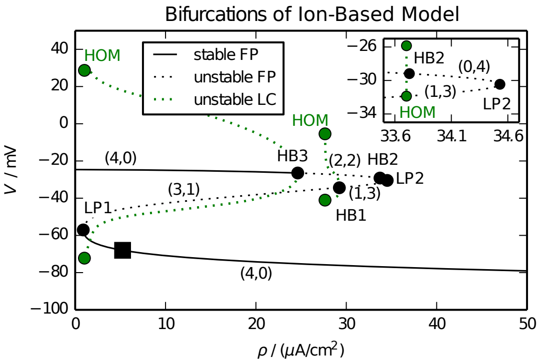
Note: This only holds for the closed model.

MINIMAL PHYSIOLOGICAL AND RECOVERY PUMP RATE

If we **increase the pump rate** ρ of

$$I_p = \rho \left(1 + \exp\left(\frac{25 - Na_i}{3}\right)\right)^{-1} \cdot \left(1 + \exp\left(5.5 - K_e\right)\right)^{-1}$$

drastically (normally $\rho = 5.25\mu A/cm^2$), recovery from FES after pump interruption is possible.



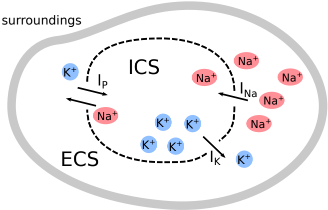
Two stable FP branches

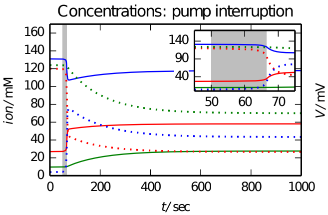
- physiological (lower)
- FES (upper)

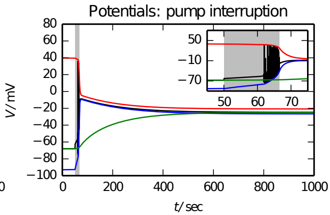
Two critical pump rates

- minimal phys. pump rate: $0.89\mu A/cm^2$ (LP1)
- recovery pump rate: $24.63\mu A/cm^2$ (HB3)

Summary







- The closed neuron system can be driven into FES by pump interruption and long/strong stimulation with applied currents (not shown).
- The transition is permanent. The ion pumps would have to be five times stronger to recover the physiological state.

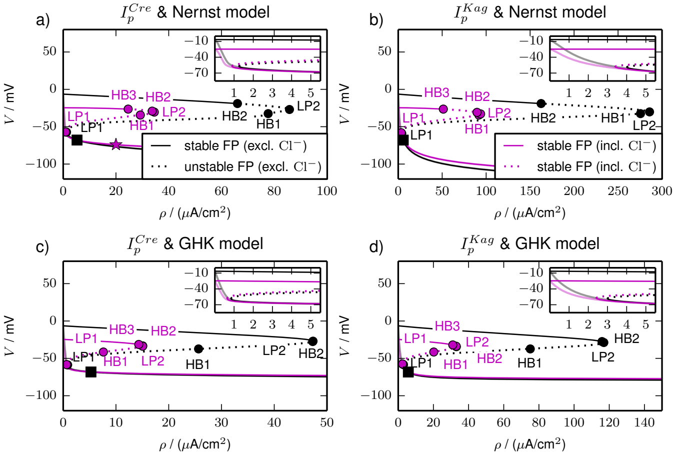
Robustness?

ROBUSTNESS?

Model variants

We tested the effect of:

- gating
- leak currents
- pump model
- GHK

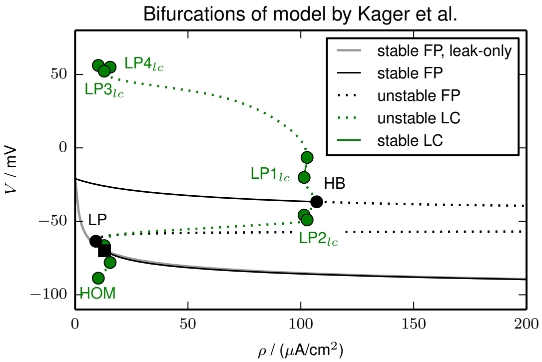


Result

- Model variants with voltage–gated ion channels are bistable.
- Variants without voltage–gated ion channels are not.

EVEN KAGER–WADMAN–SOMJEN

Also for the (single compartment) Kager–Wadman–Somjen model we find a **minimal physiological** pump rate $9.8\mu\text{A}/\text{cm}^2$ and a **recovery** pump rate $107\mu\text{A}/\text{cm}^2$ that is large compared to the normal value ($13\mu\text{A}/\text{cm}^2$).



⇒ Bistability of FES and physiological conditions apparently a **generic feature** of closed neuron models.

REMARK ON "FIXED LEAK CURRENTS"

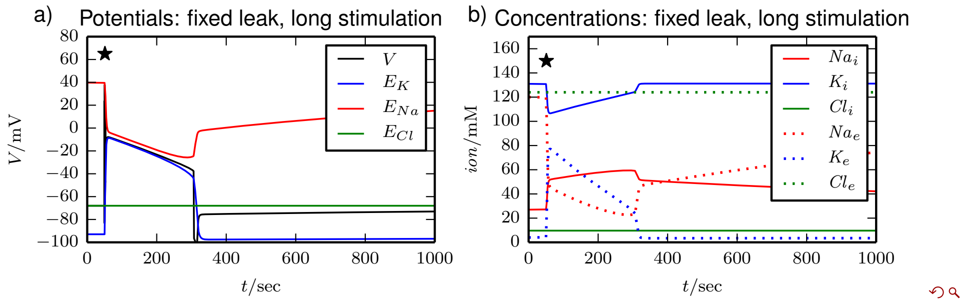
Many models contain "fixed leak currents":

$$\dot{V} = -\frac{1}{C_m}(I_{Na} + I_K + I_{Cl} - I_p)$$

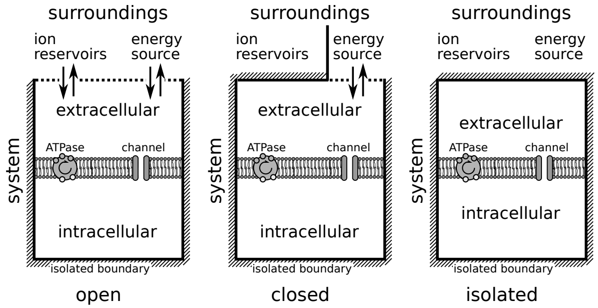
$$\vdots$$

$$\dot{Cl}_i = 0$$

Such a current with a fixed Nernst potential changes the dynamics dramatically!



Open Models



Coupling to a reservoir will resolve the bistability!

So far we have considered

- isolated $\longrightarrow$ Donnan
- closed $\longrightarrow$ bistability

Potassium exchange with a reservoir

Instead of potassium conservation we have:

$$K_e = K_e^0 + \frac{\omega_i}{\omega_e}(K_i^0 - K_i) + \tilde{K}_e$$

$\tilde{K}_e$ measures the potassium gain or loss.

Dynamics of $\tilde{K}_e$

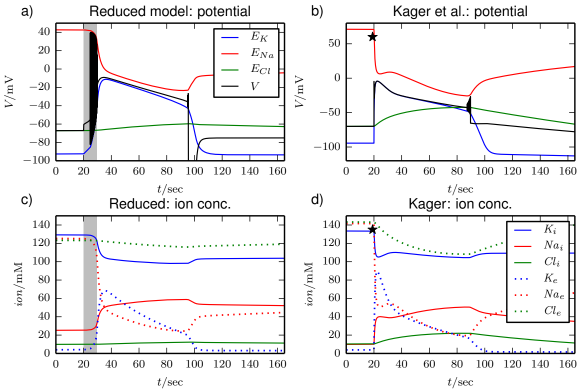
- diffusion to ECS bath or vasculature
- glial buffering

CSD in Buffered Models

Name	Value & unit
$\bar{k}_1$	5e–5/sec/mM
k_1	5e–5/sec
B^0	500mM

With buffering...

... bistability becomes **ionic excitability** in both KWS and reduced ion–base model! This is CSD!



$$K_e + B \underset{k_1}{\overset{k_2}{\rightleftharpoons}} K_b$$

$$k_2 = \frac{\bar{k}_1}{1+\exp(-(K_e-15)/1.09)}$$

$$B^0 = K_b + B$$

$$\frac{d\tilde{K}_e}{dt} = -k_2 K_e (B_0 - K_b) + k_1 K_b$$

Time Scales in Buffered Model

Time scale for **ion dynamics** from GHK equation with dimensionless potential ξ, permeability P_{ion}:

$$\frac{\mathrm{d}ion_i}{\mathrm{d}t} = \underbrace{\frac{A_m}{\omega_i} P_{ion} z}_{1/\tau_{ion}} \cdot \xi \cdot \frac{ion_e \exp(-\xi) - ion_i}{\exp(-\xi) - 1}$$

(with $m^p h^q \approx 0.1$ for gated channels $P_{ion} \approx 5\mu\text{m}/\text{sec}$, leak $P_{ion} \approx 0.5\mu\text{m}/\text{sec}$)

Forward and backward **buffering time scale**:

$$\tau_{buff}^{fw} = \frac{1}{\bar{k}_1 B^0}$$

$$\tau_{buff}^{bw} = \frac{1}{k_1}$$

Time scales

τ_V	0.05msec
τ_n	1msec
τ_{ion}	0.5sec
τ_{buff}^{fw}	50sec
τ_{buff}^{bw}	5h

For CSD dynamics in this model particle exchange with reservoirs is by far the slowest process!

$\rightarrow$ **slow–fast analysis**

Potassium Gain/Loss as Bifurcation Parameter

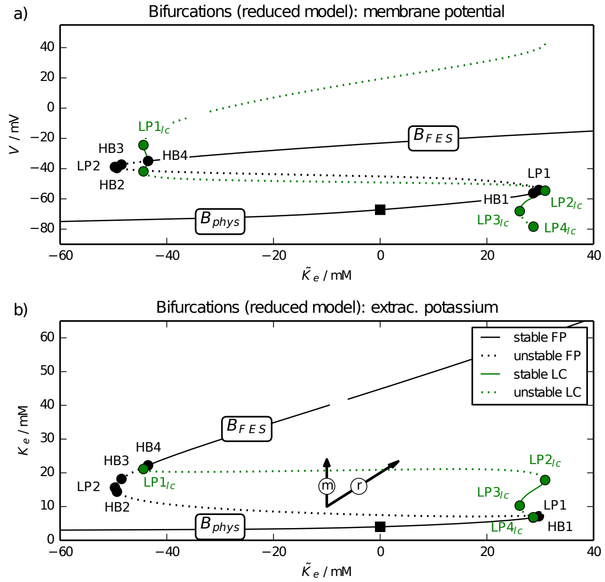
Slow–fast analysis

- use the slowest variable $\tilde{K}_e$ as a bifurcation parameter
- superimpose full dynamics on bifurcation diagram

→ Phase space explanation for observed dynamics?

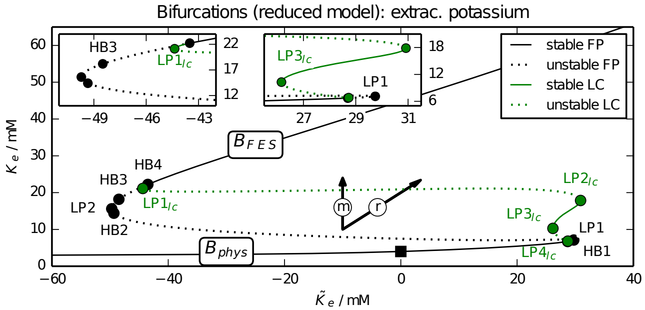
Two stable fixed points

physiological branch B_{phys}
free energy–starved B_{FES}



Implications of Bifurcation Diagram

Critical K_e values	
6.7mM	HB1
10.2mM	$LP3_{lc}$
17.8mM	$LP2_{lc}$
21.1mM	$LP1_{lc}$



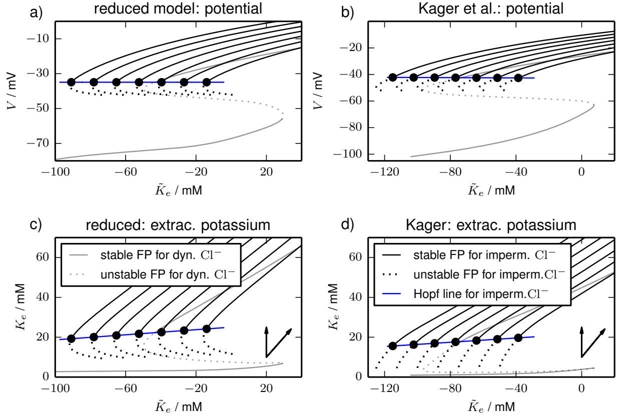
Implications

- maximal physiological potassium content (end of B_{phys} at 28.7mM)
- potassium reduction for recovery from FES (end of B_{FES} at −44mM)
- well–defined levels of stable ECS potassium concentration (limit cycle have almost constant ion concentrations)

Slow Chloride

Chloride is slower than sodium and potassium ($\tau_{Cl} \approx 50$sec)
$\rightarrow$ vary chloride as a prameter

Result: family of topologically equivalent FP curves



Recovery threshold

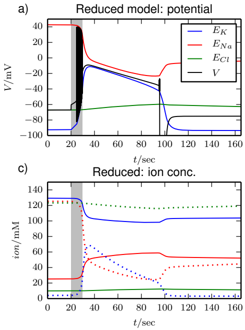
The recovery threshold is then the **line of Hopf bifurcations.**

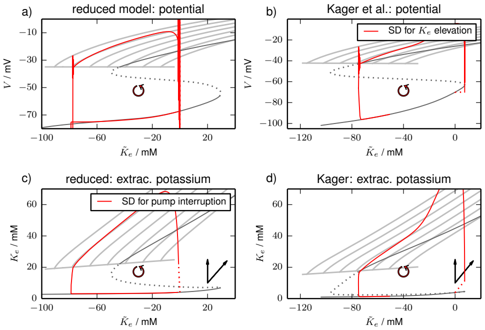
Arrows indicate K_e changes due to

(m) flux across membrane

(r) exchange with reservoir

CSD in Phase Space



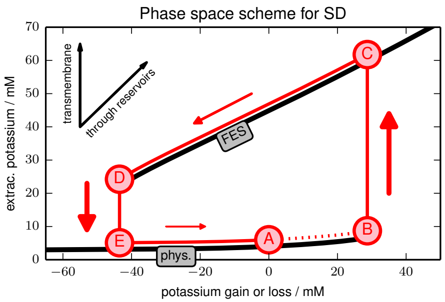


SD in reduced ion–based model and KWS. Ignition by potassium elevation and pump interruption.

Course of events after stimulation

1. vertical transition from B_{phys} to B_{FES}
2. diagonal transition along B_{FES} until threshold
3. abrupt vertical depolarization from B_{FES} to B_{phys}
4. slow asymptotic recovery

Schematic View on CSD



New insights concerning

- ignition threshold
- recovery mechanism
- recovery threshold
- SD duration

Note: Recovery is not due to the ion pumps!

SD phases and time scales

$\overline{\mathbf{AB}}$	stimulation	(instantaneous)
$\overline{\mathbf{BC}}$	ECS potassium accumulation, depolarization	$\tau_{ion} \approx 0.5$sec
$\overline{\mathbf{CD}}$	buffering, diffusion	$\tau_{buff}^{fw} \approx 50$sec
$\overline{\mathbf{DE}}$	abrupt repolarization	$\tau_{ion} \approx 0.5$sec
$\overline{\mathbf{EA}}$	final recovery	$\tau_{buff}^{bw} \approx 5$h

Oscillatory Dynamics

We investigate oscillatory dynamics for **bath coupling** with elevated potassium concentrations ($\lambda = 3e - 2/\text{sec}$).

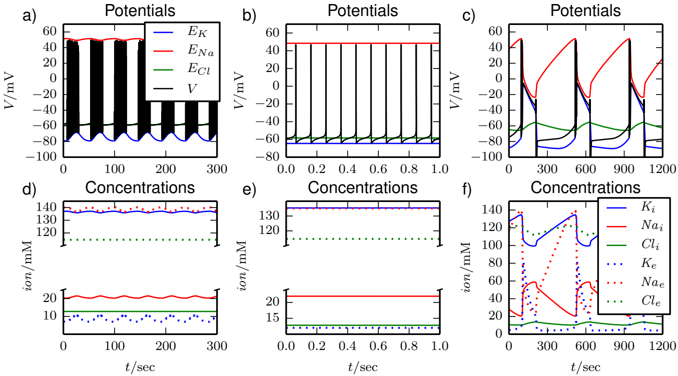
$$J_{diff} = \lambda(K_{bath} - K_e)$$
$$\frac{d\tilde{K}_e}{dt} = J_{diff}$$

Bifurcation analysis

Classify these pathologically important types of ion dynamics.

Oscillation Types

- seizures for 8.5mM
- tonic firing for 12mM
- periodic SD 15mM



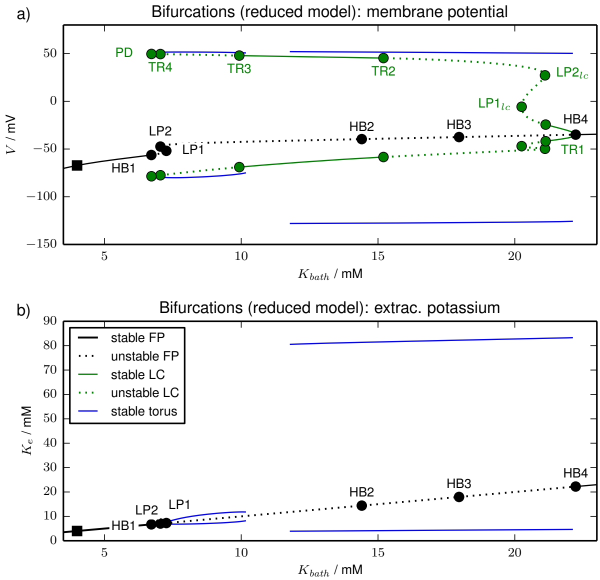
BIFURCATION DIAGRAM FOR K_{bath}

Result

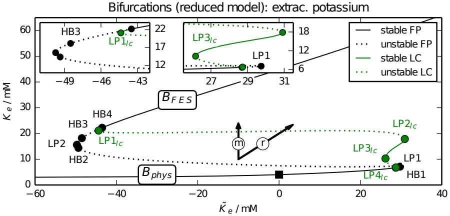
- seizure–like activity (SLA) via supercr. torus bif.
- T_{SLA} is 16–45sec
- periodic SD via subcrit. torus bif.
- T_{SD} is 350–550sec
- hysteresis

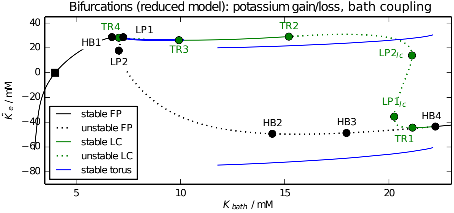
conclusion

→ SLA **graded**
→ SD **all–or–none**



Bifurcation Diagram for K_{bath} and for $\tilde{K}_e$





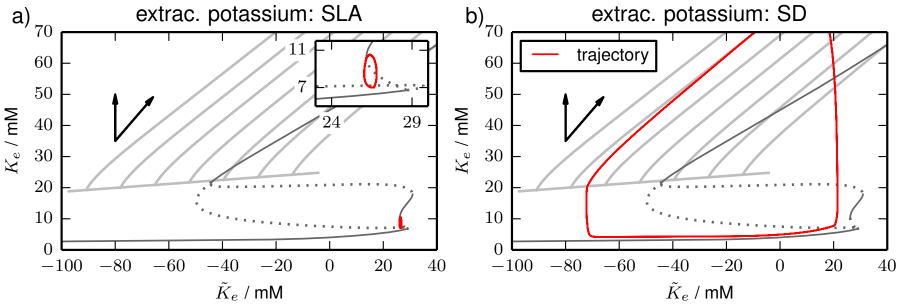
Bifurcations can be related:

$LP1_{lc} \leftrightarrow$ TR1
$LP2_{lc} \leftrightarrow$ TR2
$LP3_{lc} \leftrightarrow$ TR3
$LP4_{lc} \leftrightarrow$ TR4

Relevance of Close Model Phase Space

Many results for **parametrical** $\tilde{K}_e$ translate almost directly to the full system.

SLA vs SD in Phase Space

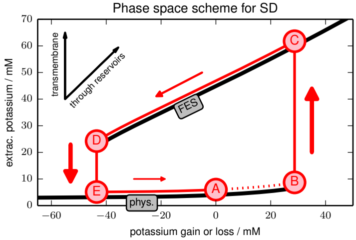


SLA is oscillation around physiological conditions and LCs at low ECS potassium.

SD is a large excursion to FES and subsequent return.

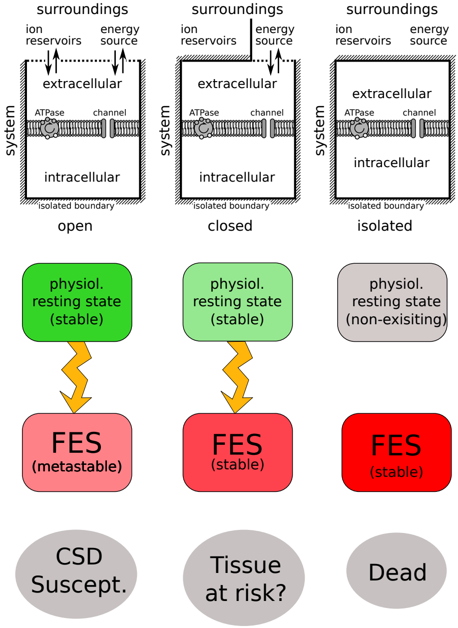
→ **SLA and SD are of fundamentally different nature!**

SUMMARY AND OVERVIEW: OPEN, CLOSED AND ISOLATED



Open vs Closed Model

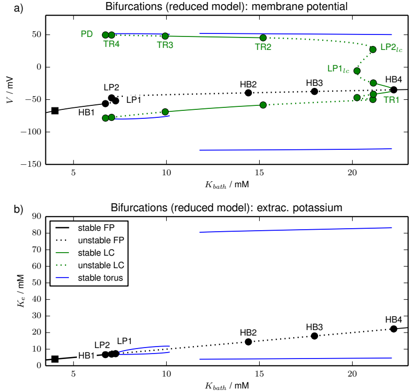
- Pumps cannot recover physiological conditions from FES.
- In ionic excitability ion exchange with surroundings leads to recovery.
- time scales, thresholds...

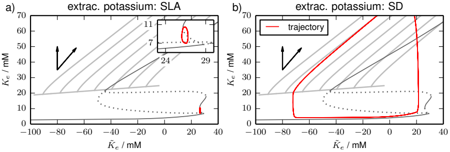


Summary: Oscillatory Dynamics

Key results

- SLA and SD related to different bifurcations
- SD and SLA of fundamentally different nature
- SD is all–or–none
- SLA is graded (probably model specific)
- approximative values of SD and SLA thresholds can be obtained from $\tilde{K}_e$ bifurcation diagram





Thank you and…

Markus Dahlem

Eckehard Schöll

Frederike Kneer

Steven Schiff

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