

Math models in neurobiology

Ben Bolker

2021-02-24 ©BMB (except textbook material/other images)

Models of neuron excitation

This material will follow Edelstein-Keshet (2005) (E-K) closely: I was able to get the PDF from [here](#), let me know if you want it and don't have access to it. (Much more detail in Ermentrout and Terman (2010).)

Limit cycles

- non-point attractor of deterministic systems; repeated trajectory, periodic orbits
- “any simple oriented closed curve trajectory that does not contain singular points”

Properties

- stable or unstable
- hard to get limit cycles in epidemic systems
 - orbits via stochastic perturbation of weakly stable spirals
 - orbits via seasonal forcing, ditto
 - plenty of math models with limit cycles but **usually weird** (e.g. Wang and Ruan (2004))
- Lotka-Volterra predator-prey system has **neutrally stable** cycles
 - but **Rosenzweig-MacArthur** model = predator-prey + density-dependent prey limitation, nonlinearity in predation rate does have limit cycles: see E-K §8.7

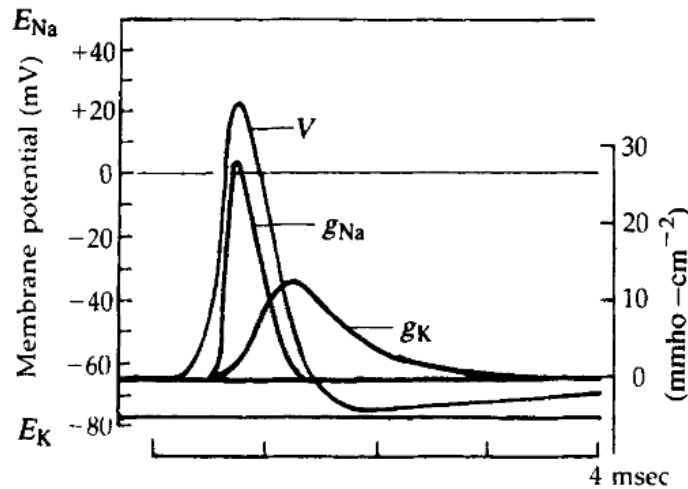
Limit cycles (part 2)

- can occur in any phase space $>1D$
- easiest to analyze in 2D (**Poincaré-Bendixson theorem**)

Neurons

- dendrites, soma, axon
- balance of ionic dynamics: Na^+ , K^+ , Cl^-
 - axon -50 mV below environment in resting state
 - maintained by active ion pumping, e.g.
 - * Na^+ : 30 vs 117 millimolar interior/exterior

- * K⁺: 90 vs 3 mmol
- * Cl⁻: 4 vs 120 mmol
- * A⁻ ("other"): 0 vs 116 mmol



- sequence:
 - voltage increases
 - Na⁺ channels open, Na⁺ in (further $\nearrow V$)
 - K⁺ channels open, K⁺ out ($V \searrow$)
 - Na⁺ channels close
 - changes in V trigger firing at neighbouring site, wave propagates
- experiments:
 - **voltage clamp**: apply/measure spatially homogeneous V dynamics
 - **patch clamp**: measure dynamics of individual pores
- electric circuit analog:
 - Voltage drop (\approx battery) + resistor + capacitor
 - Several **parallel** currents (Na⁺, K⁺, etc.)
 - * Ohm ($V = IR = I/g$, $g \equiv$ **conductance**)
 - * Faraday ($V = q/C$) where $q \equiv$ **charge**)
 - * $I = \sum Vg_i = q/C$ (typo in E-K eq 4bb??)
 - * $dV/dt = (dq/dt)/C = I/C = V/C \sum g_i$

Skipping a few steps:

$$\frac{dv}{dt} = -\frac{1}{C} \left(g_{\text{Na}}(v)(v - v_{\text{Na}}) + g_{\text{K}}(v)(v - v_{\text{K}}) + g_{\text{L}}(v - v_{\text{L}}) \right)$$

(L = "everything else"; only g_{Na} and g_{K} are concentration-dependent)

- g_{Na} and g_{K} are **strongly** nonlinear functions of v
- $g_{\text{Na}} = \bar{g}_{\text{Na}} m^3 h$; $g_{\text{K}} = \bar{g}_{\text{K}} n^4$

$$\begin{aligned}\frac{dn}{dt} &= \alpha_n(v)(1-n) - \beta_n(v)n \\ \frac{dm}{dt} &= \alpha_m(v)(1-m) - \beta_m(v)m \\ \frac{dh}{dt} &= \alpha_h(v)(1-h) - \beta_h(v)h\end{aligned}$$

Help from [here](#). (Didn't actually change much; found a typo.
Change in sign convention: $V \rightarrow -(V + 65)$)

```
parms0 <- c(g_bar_Na=120,g_bar_K=36,g_L=0.3, v_Na=-115, v_K=12, v_L=-10.5989,
           C=1,I=0)
alpha <- function(v,type) {
  switch(type,
    m=0.1*(v+25)/(exp((v+25)/10) -1),
    h=0.07*exp(v/20),
    n=0.01*(v+10)/(exp((v+10)/10) -1)
  )
}
beta <- function(v,type) {
  switch(type,
    m=4*exp(v/18),
    h=1/exp((v+30)/10 + 1),
    n=0.125*exp(v/80)
  )
}
HHgrad <- function(t,y,parms) {
  g <- with(as.list(c(y,parms)),
    c(v=-1/C*(-I + g_bar_Na*m^3*h*(v-v_Na) +
      g_bar_K*n^4*(v-v_K) +
      g_L*(v-v_L)),
    n=alpha(v,"n")*(1-n) - beta(v,"n")*n,
    m=alpha(v,"m")*(1-m) - beta(v,"m")*m,
    h=alpha(v,"h")*(1-h) - beta(v,"h")*h)
  )
  list(g)
}

y0 <- c(v=0,n=0.3,m=0.05,h=0.6)
HHgrad(0,y0,parms0)

## [[1]]
```

```
##          v          n          m          h
## -0.715470000  0.003238369  0.012385538  0.017010617

plot_hh <- function(h) {
  op <- par(mfrow=c(1,2), las=1, bty="l")
  plot(h[,1], h[,2], type="l", xlab="time", ylab="V")
  cvec <- c(1,2,4) ## colours
  matplot(h[,1], h[,3:5], type="l", lty=1, xlab="time", ylab="", col=cvec)
  legend("topright", legend=c("n", "m", "h"), lty=1, col=cvec)
}

library(deSolve)
res0 <- ode(y=y0, times=seq(0,60,by=0.05), func=HHgrad, parms=parms0)
plot_hh(res0)
```

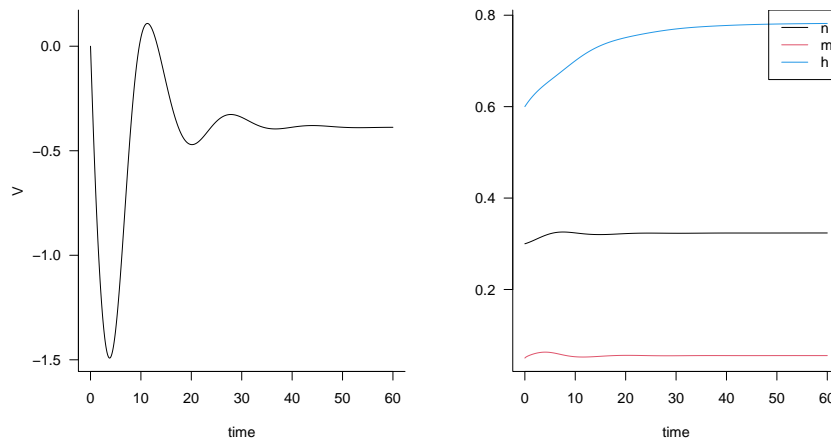


Figure 1: Hodgkin-Huxley (I=0)

```
parms_f <- function(I, parms=parms0) {
  parms[["I"]] <- I
  return(parms)
}

res2 <- ode(y=y0, times=seq(0,100,by=0.05), func=HHgrad, parms=parms_f(-7))
plot_hh(res2)
```

What about a **bifurcation diagram**?

```
get_maxmin <- function(I) {
  res <- ode(y=y0, times=c(0, seq(100,200,by=0.1)),
            func=HHgrad, parms=parms_f(I))
  res <- as.data.frame(res[-1,-1]) ## drop time and first row
  ans <- with(res,
              c(v_min=min(v), v_max=max(v)),
```

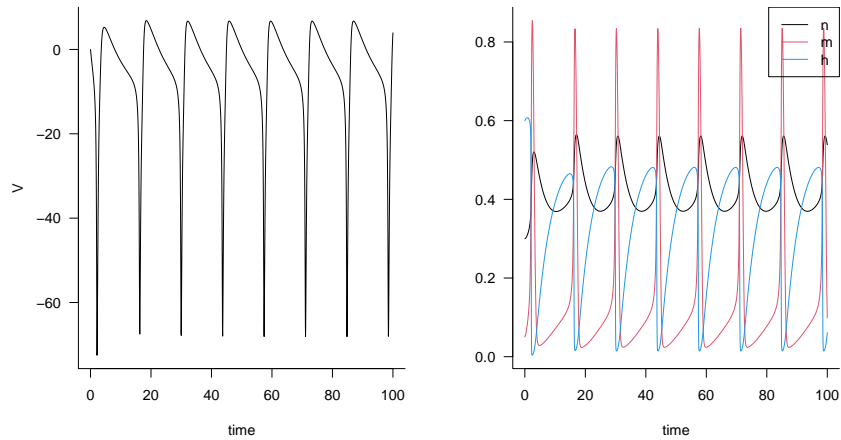


Figure 2: Hodgkin-Huxley (I=7)

```

      n_min=min(n),n_max=max(n),
      m_min=min(m),m_max=max(m),
      h_min=min(h),h_max=max(h))

  return(ans)
}
Ivec <- seq(-1, -4, by=-0.05)
res <- t(sapply(Ivec, get_maxmin))

```

what do we now?

- project into lower dimensions
- simplification: separate into **slow** and **fast** components
- (find small values?)
- map changes in nullclines (how?)

```
library(phaseR)
```

```

## -----
## phaseR: Phase plane analysis of one- and two-dimensional autonomous ODE systems
## -----
##
## v.2.1: For an overview of the package's functionality enter: ?phaseR
##
## For news on the latest updates enter: news(package = "phaseR")

HHeq <- res0[nrow(res0),c("v", "n", "m", "h")]
HHgrad2d <- function(t, y, parms) {
  full_y <- c(v=y[["v"]], m=y[["m"]], n=HHeq[["n"]], h=HHeq[["h"]])
  list(HHgrad(t, full_y, parms)[[1]][c("v", "m")])
}
HHgrad2d(0, y0[c("v", "m")], parms0)

```

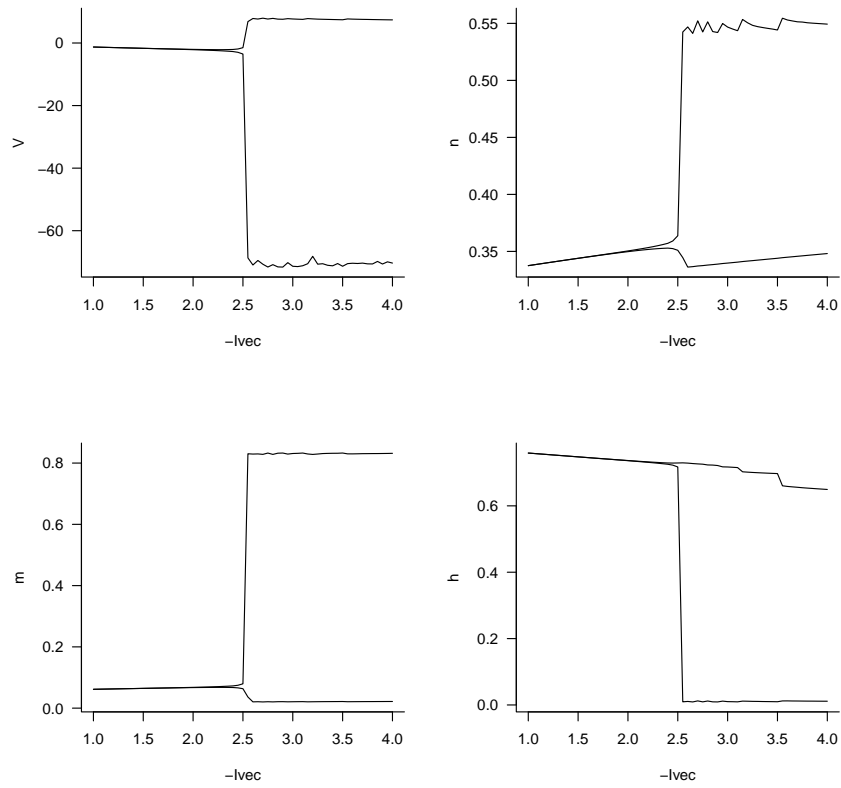


Figure 3: Hodgkin-Huxley bifurcation

```
## [[1]]
##          v          m
## 0.21059895 0.01238554

phasePlaneAnalysis(HHgrad2d,xlim=c(-120,10),
                   parameters=parms,
                   state.names=c("v","m"),
                   ylim=c(0,1))
```

Analysis: Poincaré-Bendixson

- bounded trajectories that don't approach a singular point are closed & periodic or approach a closed & periodic orbit
 - bounded region D that contains a single repelling (unstable) point, all flow inward
 - bounded annulus A containing no equilibria
- Bendixson: if D is simply connected, $\partial F/\partial x + \partial G/\partial y$ is not identically zero and doesn't change sign, then no closed orbits exist

Cubic nullclines

$$\begin{aligned}\frac{du}{dt} &= v - G(u) \\ \frac{dv}{dt} &= -u\end{aligned}$$

$$\text{and } G(u) = -(G(-u))$$

- nullclines $v = G(u), u = 0$

Fitzhugh-Nagumo model

$$\begin{aligned}\frac{dx}{dt} &= c(y + x - x^3/3 + z(t)) \approx \text{Voltage} \\ \frac{dy}{dt} &= -\frac{x - a + by}{c} \approx \text{recovery}\end{aligned}$$

Hopf bifurcations

References

Edelstein-Keshet, Leah. 2005. "8. Limit Cycles, Oscillations, and Excitable Systems." In *Mathematical Models in Biology*, 311–80. Classics in Applied Mathematics. Society for Industrial; Applied Mathematics. <https://doi.org/10.1137/1.9780898719147.ch8>.

- Ermentrout, G. Bard, and David H. Terman. 2010. *Mathematical Foundations of Neuroscience*. Vol. 35. Interdisciplinary Applied Mathematics. New York, NY: Springer New York. <https://doi.org/10.1007/978-0-387-87708-2>.
- Wang, Wendi, and Shigui Ruan. 2004. "Bifurcations in an Epidemic Model with Constant Removal Rate of the Infectives." *Journal of Mathematical Analysis and Applications* 291 (2): 775–93. <https://doi.org/10.1016/j.jmaa.2003.11.043>.