Mathematical Foundations of Neuroscience - Lecture 5. Two dimensional systems.

Filip Piękniewski

Faculty of Mathematics and Computer Science, Nicolaus Copernicus University, Toruń, Poland

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What it really means for the neuron to spike?

- By limiting ourselves to voltage changes we can't see the whole picture!
- Unfortunately the voltage is the only parameter we can measure directly...
- We can however infer what's going on, by looking at the equations. 2d systems are sufficient to figure out spiking mechanisms, yet still easy to visualize and understand.

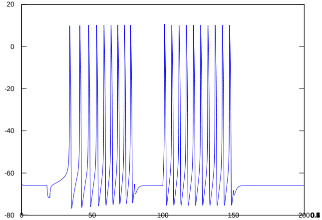
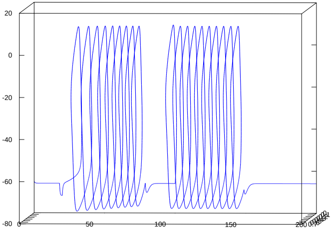


Figure: Spiking is a periodic solution of a 2d system!



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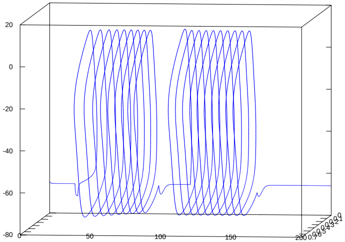

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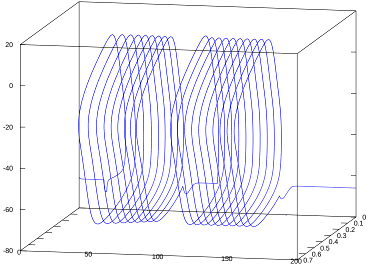

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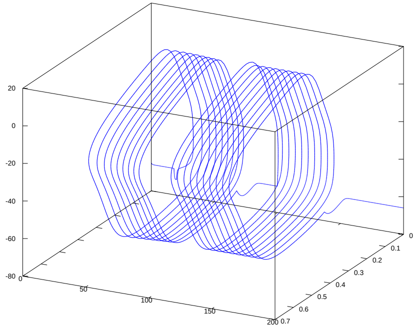


Figure: Spiking is a periodic solution of a 2d system!

Definitions

In general two dimensional systems are of the form:

$$\frac{dx(t)}{dt} = F(x, y, t)$$
$$\frac{dy(t)}{dt} = G(x, y, t)$$

Similarly to one dimensional systems, if functions F and G don't depend on time, we shall call such systems autonomous. The system can also be expressed in dense vector form:

$$\frac{d\overrightarrow{x}}{dt} = F(\overrightarrow{x}, t)$$

where $\overrightarrow{x} = [x_1(t), x_2(t)]^T$ is a vector. We will rather use the former definition for clarity.

Definitions

Any pair of functions $x(t)$ and $y(t)$ that satisfy initial condition $x(t_0) = x_0$, $y(t_0) = y_0$ and the differential equation we will call a solution or trajectory. Trajectories can be plotted on two dimensional phase plane as implicit functions (note were not plotting $y(x)$ but a pair $y(t), x(t)$).

Likewise with 1d systems, the trajectories can converge to an equilibrium, diverge to infinity. Unlike with first order autonomous 1d systems , in 2d case trajectories can be periodic. In fact any non-autonomous 1d system $\frac{dx}{dt} = F(x,t)$ can be expressed as autonomous 2d system[1]: $\frac{dx(t)}{dt} = F(x,y)$ and $\frac{dy(t)}{dt} = 1$.

[1] Similarly higher order 1d systems can be treated as higher dimensional first order ODE

Definitions

To understand a 2d system, one has to deal with a function

$$[F, G] : \mathbb{R}^2 \to \mathbb{R}^2$$

Such a function takes a point from 2d plain and returns another 2d point. It is better however to think a that it returns a vector. We then have a function that attaches a vector to any point in the x, y plain. We call such a assignment a *vector field*.

Much like the analysis of autonomous 1d systems relies on the plot of right hand side function F, the analysis of 2d systems relies on plotting a vector field.

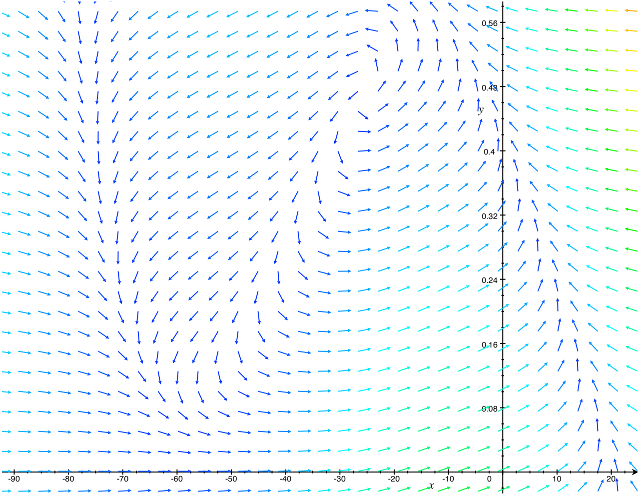


Figure: A vector field in 2d. The magnitude of a vector is marked with color.

Definitions

An important concept for the 2d phase plane analysis is the so called nullcline. Nullclines are the solutions:

$$F(x, y) = 0$$

and

$$G(x, y) = 0$$

Geometrically, nullcline is a locus of points in which the vector field changes direction with respect to x or y axis. In other words on the nullcline the vectors are always parallel to either x or y axis.

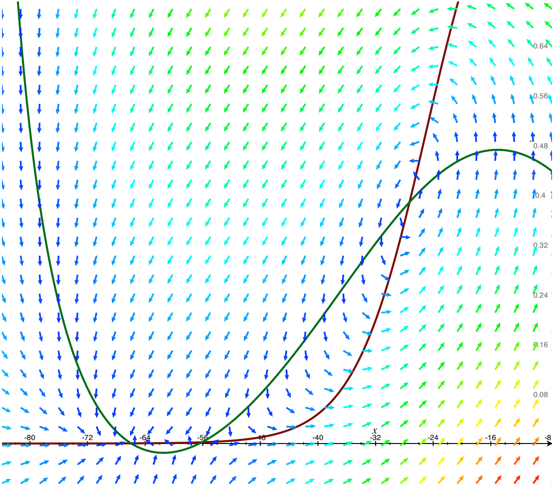


Figure: Nullclines. The X nullcline marked green, the Y nullcline is red.

Equilibria

- Similarly to 1d systems, 2d systems have equilibria whenever $F(x, y) = 0$ and $G(x, y) = 0$.
- It easy to see that both conditions are satisfied on the intersection of the nullclines.
- Moreover if F and G are continuous (which is the case for all our considerations) any equilibrium point must be on the intersection of nullclines.
- Equilibria can be either stable, unstable or neutral (neutrally stable), depending on the properties of the (total) derivative of function $[F, G]$. Things are a bit more complex than with 1d system though...

Total derivative

- Recall that a derivative of a function $F : U \subset \mathbb{R}^2 \to \mathbb{R}^2$ at some point (x_0, y_0) is a linear map $dF_{(x_0,y_0)} : \mathbb{R}^2 \to \mathbb{R}^2$ such that:

$$\lim_{(x,y)\to(x_0,y_0)} \frac{||F(x,y) - F(x_0,y_0) - dF_{(x_0,y_0)}(x-x_0, y-y_0)||}{||(x,y)-(x_0,y_0)||} = 0$$

- In other words, the function can be approximated in point (x_0, y_0) via a linear map $dF_{(x_0,y_0)}$.
- There is a weaker notion of partial derivative with respect to some variable $\frac{\partial F(x,y)}{\partial x}$. If the function F is continuous, the matrix of the total derivative coincides with matrix of partial derivatives (Jacobian matrix)

Linearization

- Much like the 1d Taylor expansion, we have

$$\begin{bmatrix} F(x,y) \\ G(x,y) \end{bmatrix} = \begin{bmatrix} F(x_0,y_0) \\ G(x_0,y_0) \end{bmatrix} + \begin{bmatrix} \partial F/\partial x & \partial F/\partial y \\ \partial G/\partial x & \partial G/\partial y \end{bmatrix} \cdot \begin{bmatrix} x - x_0 \\ y - y_0 \end{bmatrix} + \ldots$$

- Since at the equilibrium F and G are zero we have

$$\begin{bmatrix} F(x,y) \\ G(x,y) \end{bmatrix} = \begin{bmatrix} \partial F/\partial x & \partial F/\partial y \\ \partial G/\partial x & \partial G/\partial y \end{bmatrix} \cdot \begin{bmatrix} x - x_0 \\ y - y_0 \end{bmatrix} + \ldots \mathrm{HOT}$$

where HOT stands for higher order terms. If the linear part is "non zero", the behavior of the system near equilibrium can be fully derived from the properties of the matrix (particularly its eigenvalues).

Eigenvalues

- Recall that the eigenvalues are the roots of characteristic polynomial
$$\det(A - \lambda I)$$
where I is the identity matrix.
- Take λ_k satisfying
$$\det(A - \lambda_k I) = 0$$
Zero determinant means that $A - \lambda_k I$ is not invertible, that is it has non trivial kernel V_k. Take any vector $v_k \in V_k$, we have:
$$\begin{aligned}(A - \lambda_k I)v_k &= 0\\ Av_k &= \lambda_k I v_k\\ Av_k &= \lambda_k v_k\end{aligned}$$

Eigenvalues

- When the characteristic polynomial has roots $\lambda_1 \ldots \lambda_n$ and the matrix in non defective there exists a basis (eigenvector basis) in which matrix A can be expressed:

$$A \sim \begin{bmatrix} \lambda_1 & 0 & \ldots & 0 \\ 0 & \lambda_2 & \ldots & 0 \\ \vdots & \vdots & \ddots & 0 \\ 0 & 0 & 0 & \lambda_n \end{bmatrix}$$

- Such a diagonal matrix has a particularly simple geometrical interpretation - it stretches the space in the eigenvector directions by a factor proportional to the corresponding eigenvalue.

- In the general case, the matrix can be defective (it has less than n linearly independent eigenvectors). In this case the general representation is given by Jordan block form:

$$A \sim \begin{bmatrix} J_1 & 0 & \dots & 0 \\ 0 & J_2 & \dots & 0 \\ \vdots & \vdots & \ddots & 0 \\ 0 & 0 & 0 & J_k \end{bmatrix}$$

where each matrix J_k has the form

$$J_k = \begin{bmatrix} \lambda_{k,1} & 1 & \dots & 0 \\ 0 & \lambda_{k,2} & \dots & 0 \\ \vdots & \vdots & \ddots & 1 \\ 0 & 0 & 0 & \lambda_{k,i} \end{bmatrix}$$

Eigenvalues

- A defective matrix induces shear transformation (transvection) along certain axes.
- If the eigenvalues are complex conjugate (they have to be conjugate, since for real matrices the characteristic polynomial has real coefficients), the matrix induces a rotation.
- In general any non singular real matrix transformation is a combination of scaling, shear and rotation (these transformations can work on separate directions or be combined).
- Shear is something in between scaling and rotations - the vectors seem to rotate, but they never make the full π, instead they scale up to infinity...
- A matrix is called singular it has at least one zero eigenvalue.

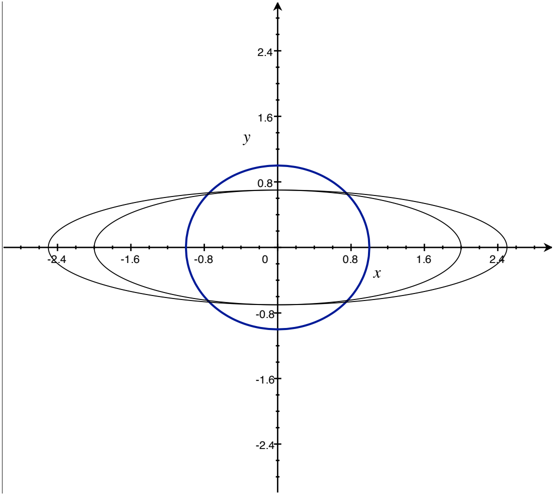


Figure: A non defective matrix with purely real eigenvalues scales the unit circle into ellipses.

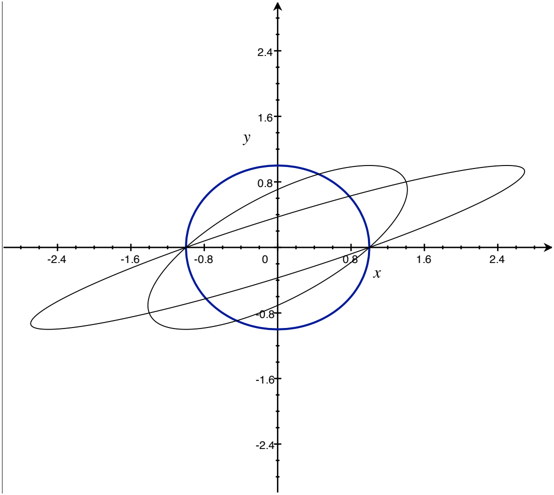


Figure: A defective matrix induces shear which smears the unit circle along one of the axis.

Hartman-Grobman theorem

An equilibrium point is called hyperbolic is the Jacobian matrix at that point is not singular (doesn't have zero eigenvalues)

Theorem (Hartman-Grobman)

Let $f : \mathbb{R}^n \to \mathbb{R}^n$ be a smooth map with a hyperbolic fixed point p. There exists a neighborhood U of p and a homeomorphism $h : U \to R^n$ such that

$$f = h^{-1} \circ df_p \circ h$$

that is, in a neighborhood U of p, f is topologically conjugate to its linearization.

In other words, the behavior of a dynamical system near a hyperbolic equilibrium is fully determined by its linearization.

For the 2d system at a fixed point we have:

$$F(x,y) = a\cdot(x-x_0) + b\cdot(y-y_0) + HOT$$
$$G(x,y) = c\cdot(x-x_0) + d\cdot(y-y_0) + HOT$$

where $a = \frac{\partial F}{\partial x}(x_0,y_0)$, $b = \frac{\partial F}{\partial y}(x_0,y_0)$, $c = \frac{\partial G}{\partial x}(x_0,y_0)$, $d = \frac{\partial G}{\partial y}(x_0,y_0)$. Let

$$A = \begin{bmatrix} a & b \\ c & d \end{bmatrix}$$

To determine stability, we have to find roots of the characteristic polynomial:

$$\det(A - I\lambda) = \det\begin{bmatrix} a-\lambda & b \\ c & d-\lambda \end{bmatrix} = (a-\lambda)(d-\lambda) - bc$$

We see that the characteristic polynomial:

$$\lambda^2 - (a+d)\lambda + ad - bc$$

can be written as

$$\lambda^2 - \tau\lambda + \Delta$$

where $\tau = \mathrm{tr} A = a + d$ (trace of the matrix A) and $\Delta = \det A = ad - bc$. The roots are then:

$$\lambda_1 = \frac{\tau + \sqrt{\tau^2 - 4\Delta}}{2}, \quad \lambda_2 = \frac{\tau - \sqrt{\tau^2 - 4\Delta}}{2}$$

They are real when $\tau^2 - 4\Delta > 0$, complex conjugate when $\tau^2 - 4\Delta < 0$ and real of multiplicity two when $\tau^2 - 4\Delta = 0$.

Having the eigenvalues we can fairly easily find eigenvectors. When there are two distinct eigenvalues λ_1 and *lambda*$_2$ we solve the equations $Ax_1 = \lambda_1 x_1$ and $Ax_2 = \lambda_2 x_2$. When the eigenvalue is a double (multiple) root the case is somewhat more difficult. There are two possibilities:

- We solve $Ax = \lambda x$. If the resulting kernel is two dimensional, were done, the vectors that span the kernel are the eigenvectors.
- If the kernel is one dimensional say $\{x_1\}$ (matrix A is defective), we have to find the generalized eigenvector x_g which satisfies $(A - I\lambda)^2 x_g = 0$. We can achieve that by solving $(A - I\lambda)x_g = x_1$. The resulting normal form matrix is the so called Jordan block.
- For the general n-dimensional matrix things are a bit more complex, for more information search for "Jordan normal form".

Once we have the eigenvectors v_1 and v_2, the solutions of a linear system are given by:

$$\begin{bmatrix} v(x) \\ w(y) \end{bmatrix} = c_1 e^{\lambda_1 t} v_1 + c_2 e^{\lambda_2 t} v_2$$

Where c_1 and c_2 are constants dependent on the initial condition. For the real eigenvalues we have exponential convergence (divergence) along the eigenvectors. For complex conjugate eigenvalues we have complex eigenvectors. Nevertheless we can obtain the real basis of solutions by taking $u = \frac{e^{\lambda t} + e^{\overline{\lambda} t}}{2} = e^{\Re(\lambda) t} \cos(\Im(\lambda) t)$ and $v = \frac{e^{\lambda t} - e^{\overline{\lambda} t}}{2i} = e^{\Re(\lambda) t} \sin(\Im(\lambda) t)$. In that case u and v will be cosines and sines[2] of t possibly multiplied by an exponential function (of t).

[2] If anyone smells rotation and vortices in this case, he is right.

Proof: We have

$$\frac{d}{dt}\left[\begin{array}{c} c_1 e^{\lambda_1 t} v_{1,1} + c_2 e^{\lambda_2 t} v_{2,1} \\ c_1 e^{\lambda_1 t} v_{1,2} + c_2 e^{\lambda_2 t} v_{2,2} \end{array}\right] = \left[\begin{array}{cc} a & b \\ c & d \end{array}\right]\left[\begin{array}{c} c_1 e^{\lambda_1 t} v_{1,1} + c_2 e^{\lambda_2 t} v_{2,1} \\ c_1 e^{\lambda_1 t} v_{1,2} + c_2 e^{\lambda_2 t} v_{2,2} \end{array}\right]$$

$$\left[\begin{array}{c} c_1 \lambda_1 e^{\lambda_1 t} v_{1,1} + c_2 \lambda_2 e^{\lambda_2 t} v_{2,1} \\ c_1 \lambda_1 e^{\lambda_1 t} v_{1,2} + c_2 \lambda_2 e^{\lambda_2 t} v_{2,2} \end{array}\right] = \left[\begin{array}{cc} a & b \\ c & d \end{array}\right]\left[\begin{array}{c} c_1 e^{\lambda_1 t} v_{1,1} + c_2 e^{\lambda_2 t} v_{2,1} \\ c_1 e^{\lambda_1 t} v_{1,2} + c_2 e^{\lambda_2 t} v_{2,2} \end{array}\right]$$

but since v_1 and v_2 are the eigenvectors, we know that $Av_1 = \lambda_1 v_1$ etc. So:

$$\left[\begin{array}{c} c_1 \lambda_1 e^{\lambda_1 t} v_{1,1} + c_2 \lambda_2 e^{\lambda_2 t} v_{2,1} \\ c_1 \lambda_1 e^{\lambda_1 t} v_{1,2} + c_2 \lambda_2 e^{\lambda_2 t} v_{2,2} \end{array}\right] = \left[\begin{array}{c} c_1 \lambda_1 e^{\lambda_1 t} v_{1,1} + c_2 \lambda_2 e^{\lambda_2 t} v_{2,1} \\ c_1 \lambda_1 e^{\lambda_1 t} v_{1,2} + c_2 \lambda_2 e^{\lambda_2 t} v_{2,2} \end{array}\right]$$

QED.

Equilibria

- What kind of equilibria we can have in a 2d system?
- Assuming hyperbolicity, we have the following choices:
  1. Eigenvalues are real and positive - this results in a repelling, unstable node
  2. Eigenvalues are real and negative - this results in a stable node
  3. Eigenvalues are real, one positive the other negative - this results in a saddle
  4. Eigenvalues are real and equal, but the matrix is defective - this gives either stable or unstable shear node
  5. Eigenvalues are complex conjugates with non zero real parts - this gives either stable or unstable focus
  6. Eigenvalues are purely imaginary - this gives neutrally stable node

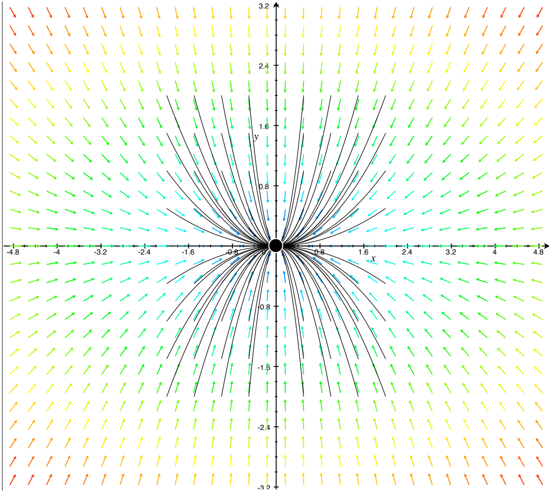


Figure: Stable node.

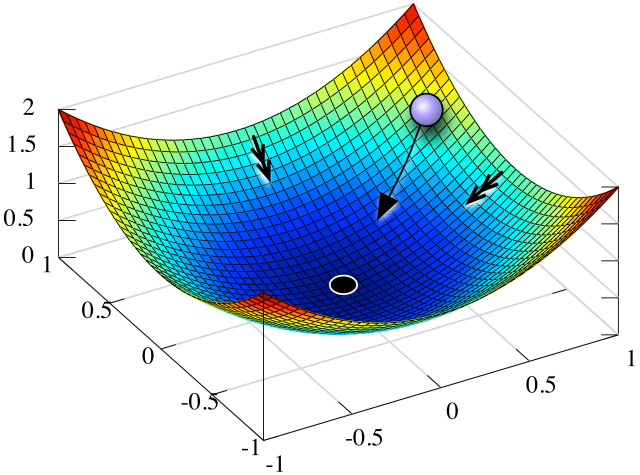


Figure: Stable node on a gradient (irrotational) field.

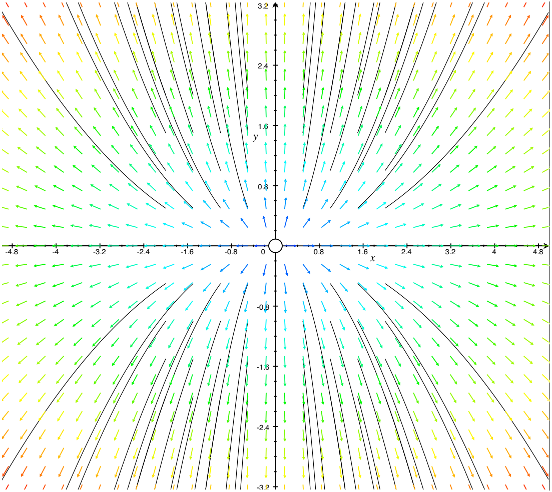


Figure: Unstable node.

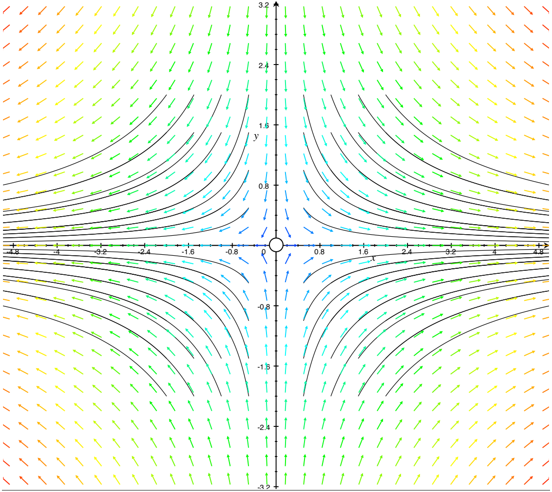


Figure: Saddle.

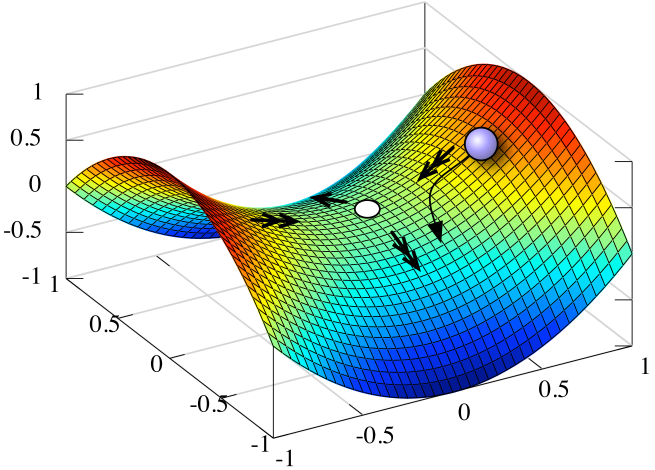


Figure: Saddle on a gradient (irrotational) field.

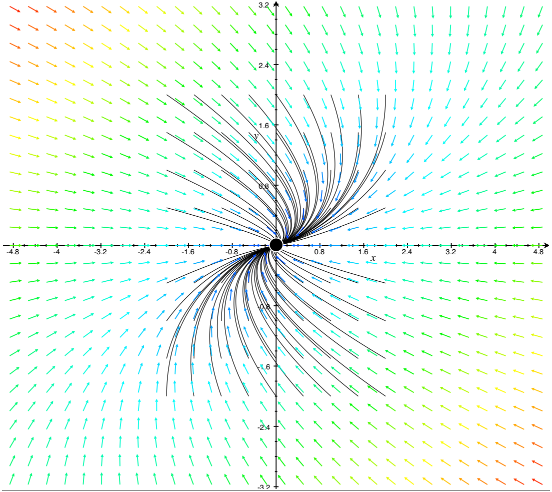
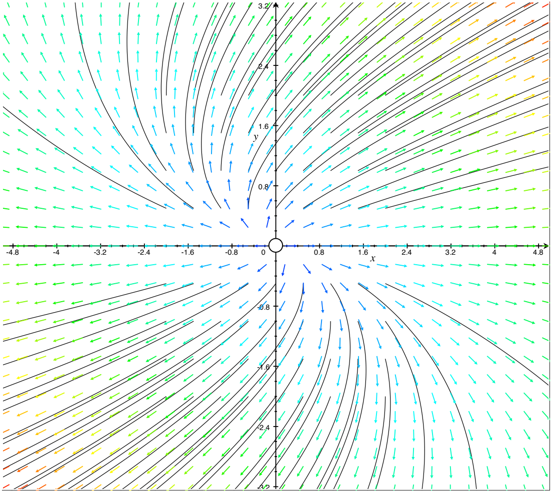


Figure: Stable shear node.



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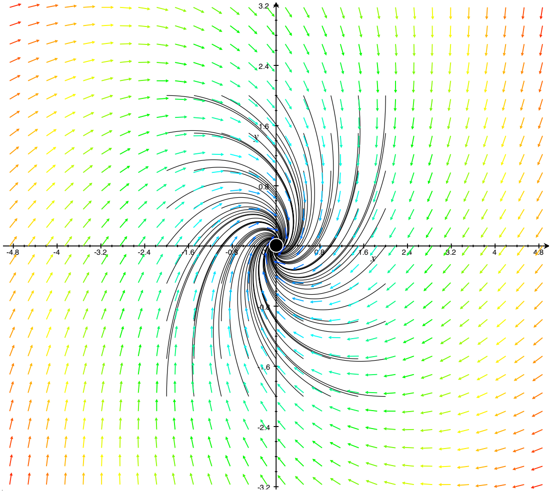


Figure: Stable focus.

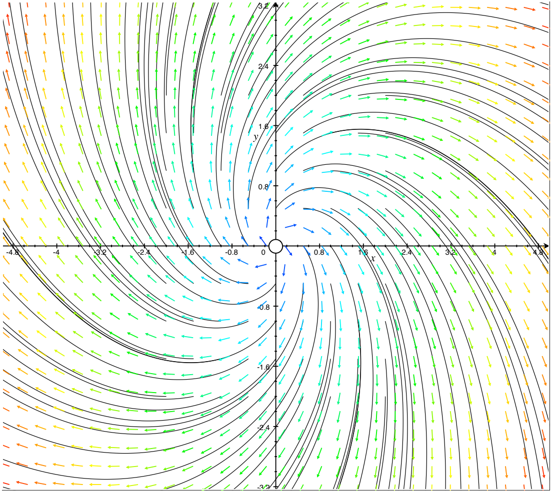


Figure: Unstable focus.

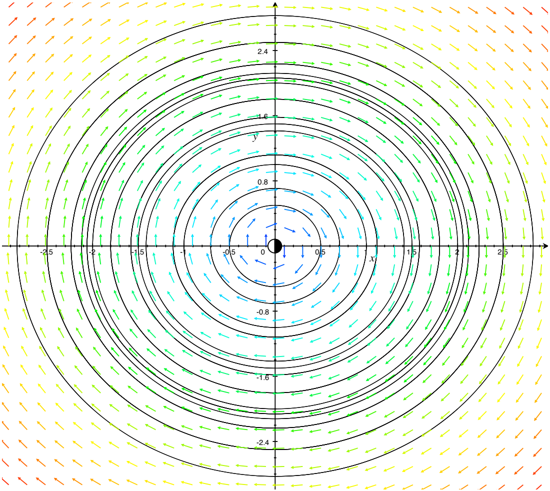


Figure: Neutral focus.

Phase portrait analysis

- Equilibria are not the only invariant sets with respect to 2d system. There are also invariant cycles, called limit cycles.
- The cycle is invariant, when any trajectory departing from a point on the cycle, will always stay on the cycle.
- Limit cycles like equilibria can be attracting, repelling or neutral.
- Like in the 1d case, the phase portrait can be divided into attraction domains, but in this case two attracting equilibria do not have to divided by a repelling equilibirum, but also by a special trajectory called a separatrix (which can be a cycle).

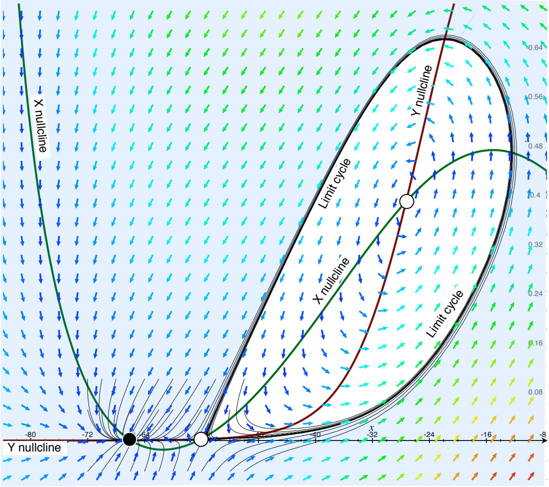


Figure: A phase portrait of a sample 2d system (in blue is the attraction domain of the stable node).

Trajectories and separatrices

A separatrix is a special kind of trajectory which divides two attraction domains. It can:

- Originate at the infinity
- End up in an unstable node or a saddle
- Form a closed curve (cycle)

A trajectory that originates in some equilibrium point may

- Get back to the origin after making a cycle (homoclinic trajectory)
- End up in another equilibrium or a cycle (heteroclinic trajectory)

Trajectories may never cross! (why?)

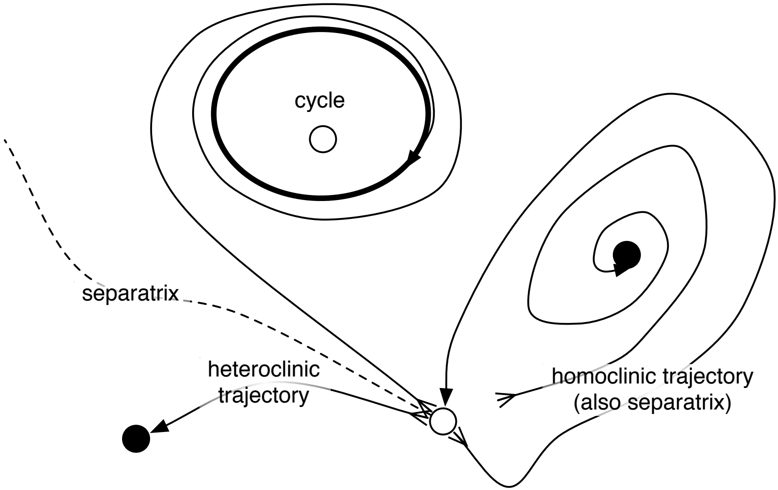


Figure: Homoclinic and hetoroclinic trajectories (orbits).

Let us get back our favourite Hodgkin-Huxley model:

$$C_m \frac{dV}{dt} = I - g_L(V - E_L) - g_{\mathrm{Na}} m^3 h(V - E_{\mathrm{Na}}) - g_{\mathrm{K}} n^4 (V - E_{\mathrm{K}})$$
$$\frac{dm}{dt} = (m_\infty(V) - m)/\tau_m(V)$$
$$\frac{dn}{dt} = (n_\infty(V) - n)/\tau_n(V)$$
$$\frac{dh}{dt} = (h_\infty(V) - h)/\tau_h(V)$$

We will now simplify it so that we end up with a two dimensional model. First of all lets assume, that sodium has only activation and that it is instantaneous.

W obtain:

$$C_m \frac{dV}{dt} = I - g_L(V - E_L) - g_{\mathrm{Na}} m_\infty(V)(V - E_{\mathrm{Na}}) - g_{\mathrm{K}} n^4 (V - E_{\mathrm{K}})$$
$$\frac{dn}{dt} = (n_\infty(V) - n)/\tau_n(V)$$

Let simplify the potassium activation, so that we get rid of fourth power. We end up with

$$C_m \frac{dV}{dt} = -g_L(V - E_L) - g_{\mathrm{Na}} m_\infty(V)(V - E_{\mathrm{Na}}) - g_{\mathrm{K}} n (V - E_{\mathrm{K}})$$
$$\frac{dn}{dt} = (n_\infty(V) - n)/\tau_n(V)$$

We will name the model *persistent instantaneous sodium plus potassium* ($I_{Na,p}$ - I_K model). Now for the parameters.

We will have: $C_m = 1$, $E_L = -80$, $g_L = 8$, $E_{Na} = 60$, $g_{Na} = 20$, $E_K = -90$, $g_K = 10$, $m_\infty(V) = \frac{1}{1+\exp\left(\frac{-20-V}{15}\right)}$, $n_\infty(V) = \frac{1}{1+\exp\left(\frac{-25-V}{5}\right)}$, $\tau_n(V) = 1$, $I = 0$. Later we shall study other variants of that model.

Now lets establish the nullclines of the model. We have

$$0 = I - g_L(V - E_L) - g_{Na} m_\infty(V)(V - E_{Na}) - g_K n(V - E_K)$$
$$n = \frac{I - g_L(V - E_L) - g_{Na} m_\infty(V)(V - E_{Na})}{g_K(V - E_K)}$$

(the V nullcline). The n nullcline:

$$0 = (n_\infty(V) - n)/\tau_n(V)$$
$$n = n_\infty(V)$$

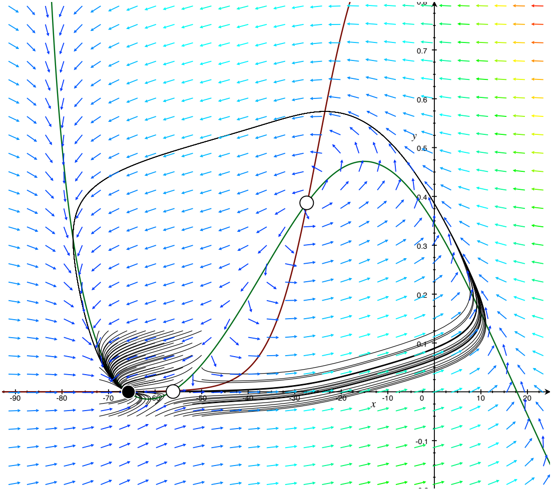


Figure: Phase plane of the $I_{Na,p}$ - I_K model with parameters as above.

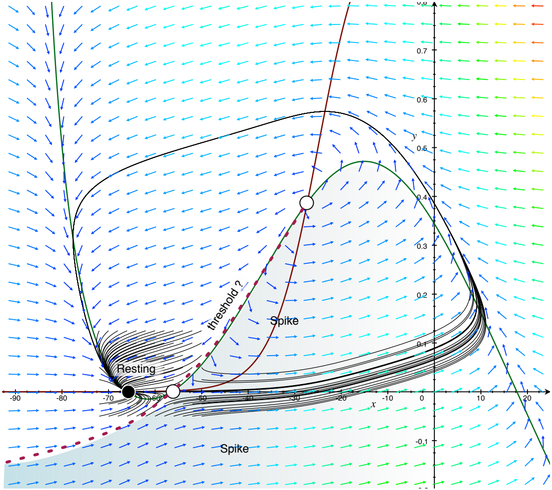


Figure: Phase plane of the $I_{Na,p}$ - I_K model with parameters as above.

Bifurcations

- Similarly to 1d systems, two phase portraits are equivalent, if there exists a continuous transformation from one to another, which preserves all the equilibria, attraction domains, separatrices, cycles etc.
- Whenever due to a change of some parameter the system changes qualitatively its phase portrait it is said to undergo a bifurcation.
- If a bifurcation occurs when a single parameter changes its value, it is called a codimension one bifurcation. Some bifurcations on 2d plane can only occur when two parameters are changing together. Such bifurcations or of codimension two.

Bifurcations

- There are many types of bifurcations in 2d. Surprisingly only four lead from a rest state to a limit cycle, therefore there are only four ways for neurons to get from resting to spiking
- The four dimensional Hodgkin-Huxley model may have a lot more bifurcations leading from resting to spiking. Nevertheless such bifurcations are rare, and don't seem to be very important from the qualitatively/computational point of view[3].
- We will study those bifurcations thoughtfully. Now lets see what happens to the $I_{Na,p}$ - I_K model when the current I increases.

[3] At least in the current state of the art.

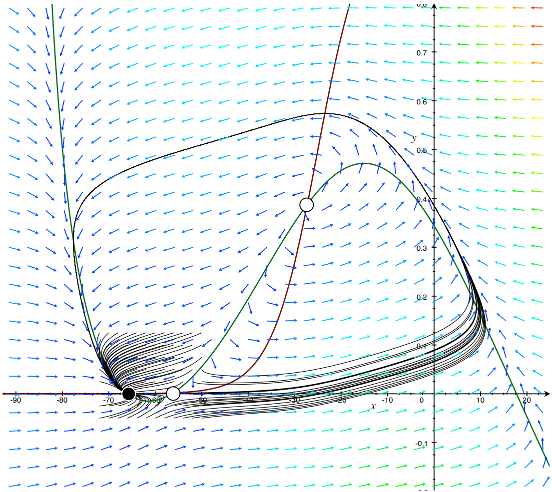
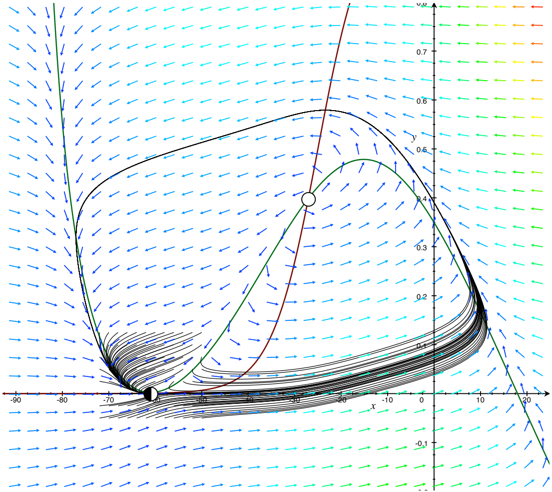


Figure: Phase plane of the $I_{Na,p}$ - I_K model I=0, I=5 and I=40.



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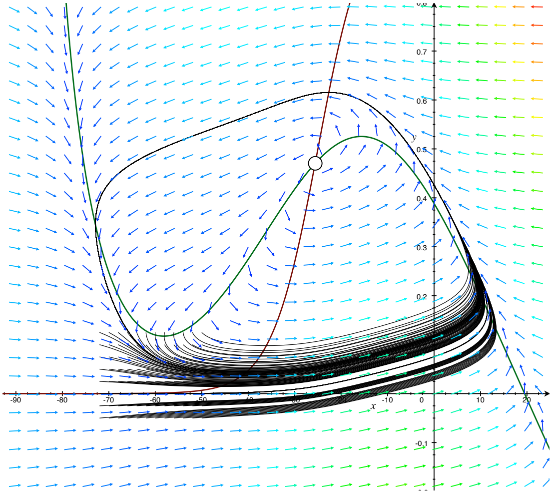

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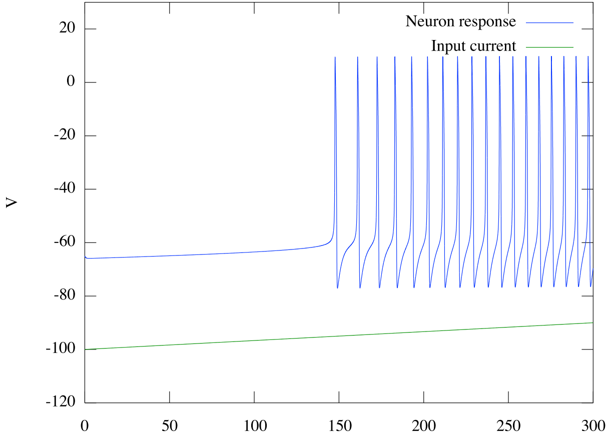

Figure: $I_{Na,p}$ - I_K in response to ramp current.

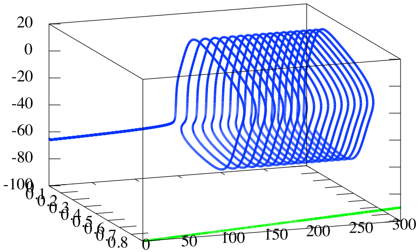

Figure: $I_{Na,p}$ - I_K in response to ramp current.

Bifurcations

- As the current increases, the stable node and saddle approach and coalesce.
- The sight is familiar, we see here the good old saddle-node bifurcation!!!
- When the stable node vanishes, the system looses stability (rest state no longer exists) and therefore all the trajectories must follow the limit cycle.
- Near the ruins of the attractor the trajectories slow down (slow transition) resulting in distances between the spikes...
- A short movie of how the phase plane changes can be found here http://www.mat.umk.pl/~philip/MFN2009/snic_web.mov.

- Spiking is in fact the byproduct of a system spending time on a limit cycle
- Two dimensional systems are the simplest possible in which limit cycles appear among other attractors
- The analysis and checking stability of two dimensional equilibria is much more complex than in 1d case. There are however profound analogies
- To fully understand what happens on the phase plane one has to know some linear algebra (eigenvalues and eigenvectors)
- We've met the $I_{Na,p}$ - I_K model, which we will see later on many occasions
- 2d systems can have various types of bifurcations but surprisingly only four of them lead from resting to spiking