Sept. 10. Math Oncology

(1.7) Review of Dynamical Systems for an Oncolytic Virus model.

a) $x(t)$: cancer density
$y(t)$: oncolytic virus

$$\left.\begin{aligned} \dot{x} &= Ax - Bxy \\ \dot{y} &= -Dy + Cxy \end{aligned}\right\} \quad (1)$$

Lotka-Volterra predator-prey model

1) Cancer only: $\dot{x} = Ax$, exponential growth with rate A.

2) virus only: $\dot{y} = -Dy$ exponential decay.

3) $-Bxy$ viral infection of cancer cells with rate B, mass-action term

4) $+Cxy$ $\quad \frac{C}{B}$: burst size per infection event

$= \frac{C}{B} Bxy$ mass-action

b) Equilibria (= steady states)

(existence is clear, since r.h.s. is Lipschitz cont., Picard-Lindelöf Theorem)

$$0 = x(A - By) \Rightarrow x = 0 \text{ or } y = \frac{A}{B}$$

$$0 = y(-D + Cx) \Rightarrow y = 0 \text{ or } x = \frac{D}{C}$$

Two equilibria $(0,0)$, $\left(\frac{D}{C}, \frac{A}{B}\right) = (\bar{x}, \bar{y})$

Stability : Linearization

$$f(x,y) = \begin{pmatrix} Ax - Bxy \\ -Dy + Cxy \end{pmatrix}$$

$$\text{Jacobian } Df(x,y) = \begin{pmatrix} A - By & -Bx \\ Cy & -D + Cx \end{pmatrix}$$

$$Df(0,0) = \begin{pmatrix} A & 0 \\ 0 & -D \end{pmatrix} \qquad \lambda_1 = A, \quad \lambda_2 = -D$$

$\Rightarrow$ saddle. $\qquad A, D > 0.$ $\quad B, C > 0.$

$$Df\left(\frac{D}{C}, \frac{A}{B}\right) = \begin{pmatrix} 0 & -\frac{BD}{C} \\ \frac{CA}{B} & 0 \end{pmatrix} = W$$

$$\operatorname{tr}(W) = 0 \qquad \det W = +\frac{BD}{C} \cdot \frac{CA}{B} = AD > 0$$

$$\lambda_{1/2} = \frac{\operatorname{tr}}{2} \pm \frac{1}{2}\sqrt{\operatorname{tr}^2 - 4\det} = \pm i\sqrt{AD}$$

purely imaginary. $\Rightarrow$ linear center.

Question : For the nonlinear system this can be a center, a stable spiral, a unstable spiral. Which is it?

Need a Hartman-Grobman Theorem.

<u>Def</u>: 1) An equil. point u^* of a smooth dynamical system is <u>hyperbolic</u> if all e-values have no-zero real part.

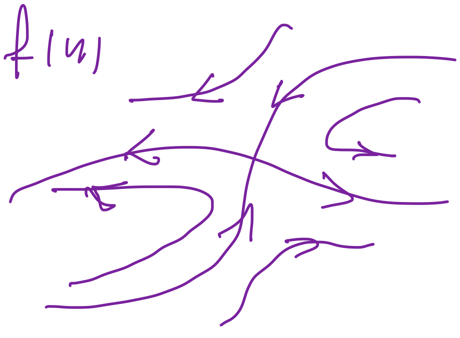
2) A <u>homeomorphism</u> is a continuous map with cont. inverse.

3) Two dyn. systems are <u>top. conjugate</u> $\dot{u} = f(u)$, $\dot{v} = g(v)$ if there exists a homeomorphism that maps orbits into orbits

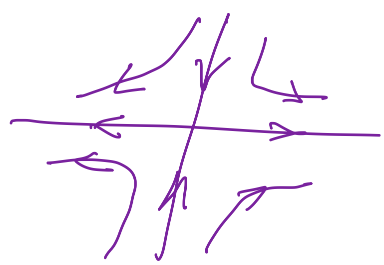
<u>Theorem Hartman + Grobman</u>:

Consider a smooth dyn. syst. $\dot{u} = f(u)$, If u^* is a hyperbolic equilibrium then there exists a neighborhood such $\dot{u} = f(u)$ is top. conj. to its linearization $\dot{u} = Df(u^*)u$.

e.g. $\dot{u} = f(u)$



$\dot{u} = Df(u^*)u$



<u>Def</u>. $\dot{u} = f(u)$ is <u>structurally stable</u> if for each ε small $\dot{y} = f(y) + \varepsilon g(y)$ is top. conjugate

- non-hyperbolic equilibria are not struct. stable.

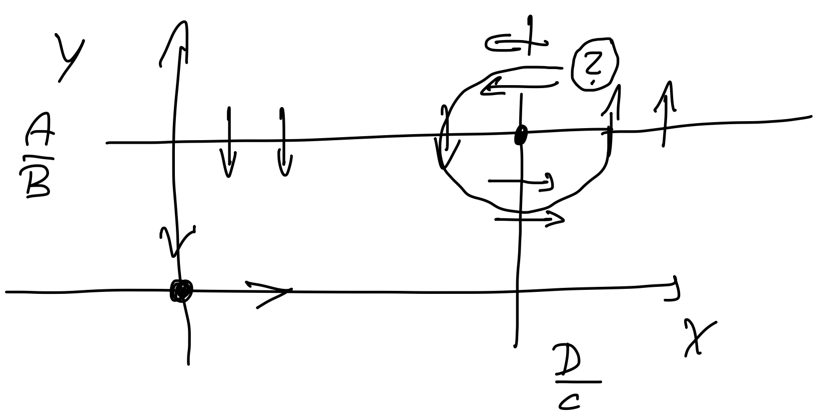
- If $\dot{u} = f(u,\mu)$ μ parameter
  if $\mu \neq \mu^*$ and $\dot{u} = f(u,\mu)$ is struct. stable
  but at μ^* it is not struct. stable. Then
  μ^* is a bifurcation value.

c) Back to model (1). nullclines

x-nullcline: $\dot{x} = 0 \Rightarrow 0 = x(A - By)$

$x = 0$ or $y = \frac{A}{B}$

y-nullcline: $\dot{y} = 0 \Rightarrow y = 0$ or $x = \frac{D}{C}$



Question: How can we decide stable, unstable spiral or center?

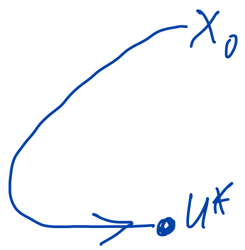
d) Find a Lyapunov function

Def: Let $\phi(t,x)$ denote the flow of a dyn. system $\dot{x} = f(x)$ x_0 initial cond.
$\phi(t, x_0)$ is the solution

The <u>ω-limit set</u> is

$$\omega(x_0) = \{ z \in \Omega : \exists \text{ montonic increasing sequence } t_n \nearrow \infty \text{ such that } \phi(t_n, x_0) = z \}$$

e.g.



$\omega(x_0) = \{u^*\}$

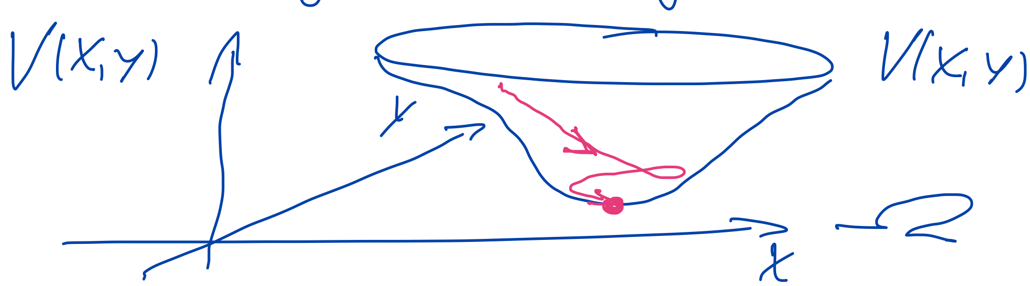
Let $V : \Omega \to \mathbb{R}$ be bounded below and differentiable. The derivative along orbits

$$\to \quad \dot{V} = \frac{d}{dt} V(\phi(t, x_0)) = \nabla V \cdot \dot{\phi}$$

$$= \nabla V \cdot f(\phi(t, x_0))$$

V is a (<u>weak) Lyapunov function</u> if $\dot{V} \leq 0$

and a strong Lyapunov function if $\dot{V} \leq 0$ and $\dot{V} = 0$ only at steady states.



Theorem of La Salle. $x_0 \in \Omega$

If V is a weak Lyap. fct. then

$$\omega(x_0) \subseteq \{x \in \Omega : \dot V(x) = 0\}$$

If V is a strong Lyap. fct.

$$\omega(x_0) \subseteq \{\text{equilibrium points}\}$$

e) Find a Lyapunov function for (1)

$$H(x,y) = F(x) + G(y) \qquad (\text{a naive try})$$

$H(x(t), y(t))$

$$\dot H = \frac{d}{dt} H(x(t), y(t)) = \frac{\partial H}{\partial x}\dot x + \frac{\partial H}{\partial y}\dot y$$

$$= F'\dot x + G'\dot y$$

$$= F'(x(A-By)) + G'(y(Cx-D))$$

Make $\dot H \equiv 0$ iff

$$\underbrace{\frac{F'x}{Cx-D}}_{\text{only depends on } x} = - \underbrace{\frac{G'y}{A-By}}_{\text{only depends on } y} \qquad (x,y) \neq (\bar x, \bar y)$$

Both terms must be constant! choose 1.

$$F' = C - \frac{D}{x} \qquad G' = -\frac{A}{y} + B$$

$$\underbrace{F(x) = Cx - D\ln x}_{} + C_1$$

$$\underbrace{G(y) = -A\ln y + By}_{} + C_2$$

choose: $C_1 = C_2 = 0$

define $\boxed{H(x,y) = Cx - D\ln x + By - A\ln y}$

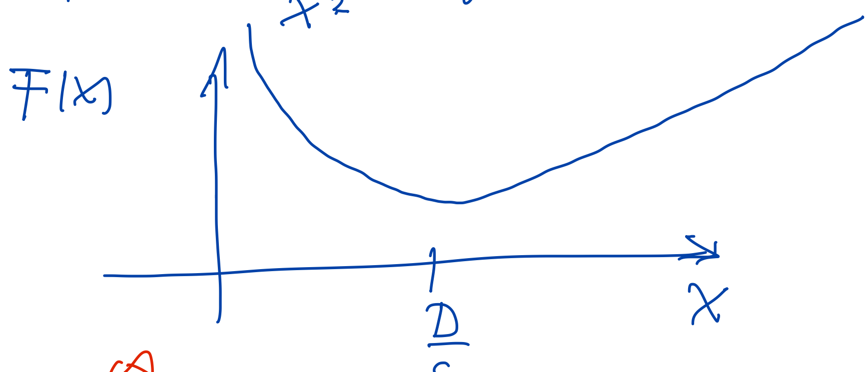
satisfies $\dot{H} \equiv 0$. i.e. weak Lyapunov function.

$H(x,y)$ is differentiable in $\Omega = (0,\infty)^2$

Minimum? $F(x) = Cx - D\ln x$

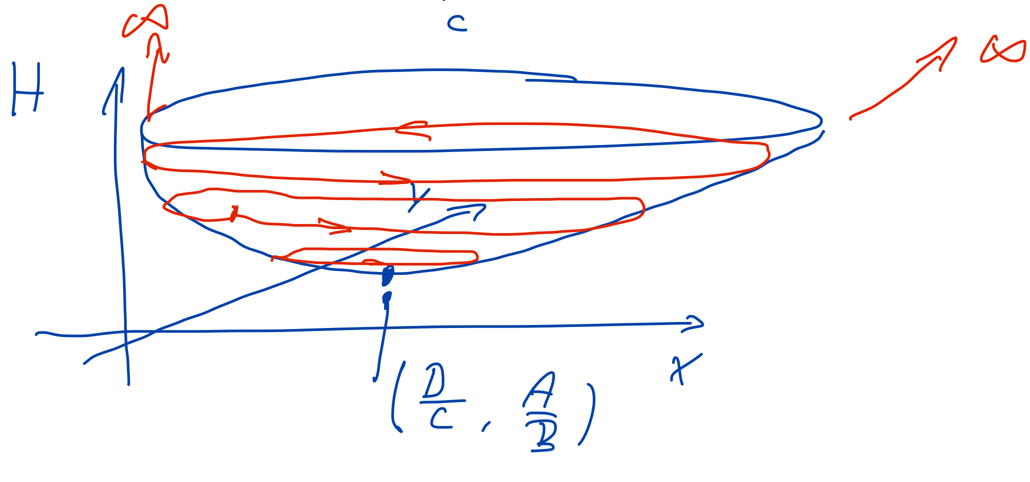
$F' = C - \frac{D}{x}$

$\left.\begin{array}{l} F' = 0 \text{ for } x = \frac{D}{C} \\ F'' = +\frac{D}{x^2} > 0 \end{array}\right\}$ local min.



$H(x,y)$

$\dot{H} = 0$



Each solution lies on level sets of $H(x,y)$

$$H(x(t), y(t)) = k.$$

This proofs that $\left(\frac{D}{C}, \frac{A}{B}\right)$ is a <u>nonlinear center</u>!

[$\rightarrow$ Refs: Perko

Strogatz

Keshet, Math Biol.

de Vries et al. SIAM]