

具有免疫时滞和综合干预措施的流感模型研究

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摘要:考虑了接种流感疫苗的个体具有确定的免疫期,建立了具有免疫时滞的 SEIAR 流感模型以探究“媒体、疫苗接种和抗病毒治疗”这三类综合干预措施对流感传播的影响.通过构造 Lyapunov 函数并依据 Routh-Hurwitz 判据,分析了模型的无病平衡点和地方病平衡点的稳定性,并给出了模型存在 Hopf 分支的充分条件.

关键词:SEIAR 流感模型;Lyapunov 函数;免疫时滞;稳定性;Hopf 分支

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众所周知,流感对人类社会稳定 and 经济发展都带来了一些破坏性的影响.人们会采取各种措施来预防和控制流感疫情,比如隔离、媒体宣传、疫苗接种、抗病毒治疗等^[1-3].在当今信息时代下,媒体宣传会警示人们尽量减少与他人不必要的接触以防止潜在的感染^[4].据 WHO 评估,在 2013 年中国甲型禽流感 H7N9 疫情控制中,媒体宣传起到了重要的作用^[5].疫苗接种是主要控制流感策略之一,但流感疫苗并不能对人群产生完全的免疫保护^[6],这取决于接种者的免疫状态^[7].利用抗病毒药物对流感病人进行治疗^[8],尤其针对住院者和高风险人群,包括儿童、孕妇、免疫抑制病人,有助于缓解疾病严重性并减少死亡率^[9].尽管已有大量有关流感控制措施的研究文献,但是考虑“媒体+疫苗接种+抗病毒治疗”这三类综合干预措施的研究较少^[10].

在具有疫苗接种的传染病模型中,被接种者免疫力的丧失多以指数形式描述,且多为常微分系统.但事实上,疫苗的有效期是有限的,即在接种有限时间后,被接种者的免疫力就会衰退,所以引入一个时滞参数来表示免疫周期会更符合实际,它可能会影响系统的稳定性,从而引发各种振荡和周期性.文献[11]指出 2009 年甲型 H1N1 流感在全球范围内大规模流行,并在疫情暴发期间,有四分之三的感染者并没有呈现出任何症状.隐性感染者的出现可能导致如抗病毒药物预防和隔离等干预措施无法达到预期效果^[12],因此深入探究隐性感染者对流感传播的影响是有必要的.

1 模型的建立

在某一病毒毒株引发流感疫情期间,我们将总人口 N 分为 5 个不同的仓室:易感者(S),潜伏者(E),显性感染者(I),隐性感染者(A)和康复者(R).出于生物意义考虑,做如下假设:媒体报道未执行时,疾病传播率 $\beta > 0$ 为常数;广泛的媒体报道会使传播率减小,类似文献[13],假定媒体诱导的传播率为 $\beta(1-\mu_1)$ ($0 \leq \mu_1 \leq 1$),其中 μ_1 是常数.为了方便,仍将其记为 β .对于新出现的流感病毒菌株,人们需要时间去研发才能生产相应的预防疫苗,因此可获得的疫苗供给是有限的^[12].假设 τ 为疫苗接种的有效期,从而 $(t-\tau)$ 时刻被接种者在 t 时刻将会失去免疫力而再次进入易感类.假设康复者 R 会对该病株产生永久免疫而不会被再次感染;潜伏者 E 、显性感染者 I 和隐性感染者 A 具有不同的感染性,其传染率分别为 $\sigma\beta$, $\delta\beta$ 和 $\eta\beta$,显性感染者 I

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的抗病毒治疗率为 γ .

根据上面假设和文献[10]的研究基础,建立如下的时滞微分方程模型:

$$\begin{cases} \frac{dS}{dt} = \Lambda - \beta(\sigma E + \eta I + \delta A)S - (\mu + p)S + pS(t - \tau) e^{-\mu\tau}, \\ \frac{dE}{dt} = \beta(\sigma E + \eta I + \delta A)S - (\mu + \alpha)E, \\ \frac{dI}{dt} = \rho\alpha E - (\mu + d + \gamma_1 + \gamma)I, \\ \frac{dA}{dt} = (1 - \rho)\alpha E - (\mu + \gamma_2)A. \end{cases} \quad (1)$$

和

$$\frac{dR}{dt} = (\gamma_1 + \gamma)I + \gamma_2 A - \mu R + pS - pS(t - \tau) e^{-\mu\tau}. \quad (2)$$

表 1 模型(1)各参数说明及取值

Tab. 1 The descriptions and values of parameters in model(1)

参数	生物意义描述	参数值	来源	参数	生物意义描述	参数值	来源
β	传染率	0.000 15	[10]	μ	自然死亡率	$1/(70 \times 365)$ d	[12]
ρ	有症状感染者比例	0.6	估计	d	显性感染者因病死亡率	0.02/d	[12]
σ	潜伏者感染力减小因子	$0.2, \sigma \in (0, 1)$	[6]	γ_1	显性感染者自然康复率	0.244/d	[7]
η	显性感染者感染力减小因子	0.4	[6]	γ_2	隐性感染者自然康复率	0.244/d	[7]
α	潜伏者的转移率	0.526/d	[10]	γ	显性感染者抗病毒治疗率	0.05/d	[5]
p	有效接种率	0.25/d	[10]	Λ	易感者人口输入率	12/d	估计

由于 $N = S + E + I + A + R$, 则 $\frac{dN}{dt} = \Lambda - \alpha I - dI$. 根据模型所具有的生物学意义,假设模型(1)的初始条件如下:

$$\begin{cases} \phi_1(\theta) > 0, \phi_2(\theta) \geq 0, \phi_3(\theta) \geq 0, \phi_4(\theta) \geq 0, \phi_5(\theta) \geq 0, \theta \in [-\tau, 0], \\ \phi_1(0) > 0, \phi_2(0) > 0, \phi_3(0) > 0, \phi_4(0) > 0, \phi_5(0) > 0. \end{cases} \quad (3)$$

定理 1 在初始条件(3)下,模型(1)的全部解都为正的并且有界.

证明 假设存在 t_1 使得 $t_1 = \min\{t > 0 : S(t) \times E(t) \times I(t) \times A(t) \times R(t) = 0\}$.

首先,令 $S(t_1) = 0$,由模型(1)的第一个方程可得 $\frac{dS(t_1)}{dt} = \Lambda + pS(t_1 - \tau) e^{-\mu\tau} > 0$ 则对于任意小的 ϵ_1 ,

当 $t \in (t_1 - \epsilon_1, t_1)$ 时 $S(t)$ 为单调递增函数即有 $S(t) < 0$,与 $S(t) > 0, t \in [0, t_1)$ 矛盾.

然后,令 $E(t_1) = 0$,由模型(1)的第 2 个方程可得 $E(t_1) = e^{-(\mu+\alpha)t_1} E(0) + \int_0^{t_1} \beta(\eta I + \delta A)S e^{-(\mu+\alpha)(t_1-\xi)} d\xi > 0$,与 $E(t_1) = 0$ 矛盾.同理可证 $I(t_1) = 0, A(t_1) = 0$ 是不可能的.

最后,对于方程(2),定义 $R(0) = \int_{-\tau}^0 pS(u) e^{-\mu u} du$, 则方程(2)的等价积分方程为

$$R(t_1) = e^{-\mu t_1} R(0) + \int_{t-\mu}^t [(\gamma_1 + \gamma)I + \gamma_2 A + pS(u)] e^{-\mu u} du.$$

所以假设不成立,即当 $t > 0$ 时,模型的所有解都为正的.下面证模型解的有界性.

由 $\frac{dN}{dt} = \Lambda - \alpha N - dI < \Lambda - \alpha N$,根据比较原理可得 $N(t) < \epsilon + \frac{\Lambda}{\alpha}$ (ϵ 是任意小的正数),结合解的正性

可知模型中的每一项是最终有界的.

定理 1 得证.

2 控制再生数

模型(1)总有一个无病平衡点 $E_0(S_0, 0, 0, 0)$, 其中 $S_0 = \frac{\Lambda}{\mu + p(1 - e^{-\mu\tau})}$. 应用再生矩阵的方法^[14] 来计算模型

型(1)的控制再生数并检验 E_0 的局部稳定性. 矩阵 F 与 V 分别为

$$F = \begin{pmatrix} \sigma\beta S_0 & \eta\beta S_0 & \delta\beta S_0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}, V = \begin{pmatrix} \mu + \alpha & 0 & 0 \\ -\rho\alpha & \mu + d + \gamma_1 + \gamma & 0 \\ -(1 - \rho)\alpha & 0 & \mu + \gamma_2 \end{pmatrix}.$$

则可计算模型(1)的控制再生数为 $\mathcal{R}_c = \rho(FV^{-1}) = \frac{\beta S_0}{(\mu + \alpha)} (\sigma + \frac{\rho\eta\alpha}{\mu + d + \gamma_1 + \gamma} + \frac{\delta(1 - \rho)\alpha}{\mu + \gamma_2})$.

下证当 $\mathcal{R}_c > 1$ 时模型(1)有唯一的地方病平衡点. 设 $E_1(S^*, E^*, I^*, A^*)$ 是模型(1)的任意正平衡点. 由模型(1)的第 3、4 个方程得 $I^* = \frac{\rho\alpha E^*}{\mu + d + \gamma_1 + \gamma}, A^* = \frac{(1 - \rho)\alpha E^*}{\mu + \gamma_2}$, 并将其代入模型(1)的第 2 个方程中, 得

$$S^* = \frac{\Lambda}{\mu + p(1 - e^{-\mu\tau})} \times \frac{1}{\mathcal{R}_c} = \frac{S_0}{\mathcal{R}_c}.$$

再将 I^*, A^*, S^* 代入模型(1)的第 1 个方程中, 可得 $E^* = \frac{\Lambda}{\beta(\mu + \alpha)} (1 - \frac{1}{\mathcal{R}_c})$. 因此, 当 $\mathcal{R}_c > 1$ 时, S^*, E^*, I^*, A^* 均为正数, 且被唯一确定, 即模型(1)有唯一地方病平衡点 E_1 . 进一步将通过构造 Lyapunov 函数来判定平衡点的稳定性.

定理 2 当 $\mathcal{R}_c \leq 1$ 时, 模型(1)的无病平衡点 E_0 是全局渐近稳定的.

证明 首先将无病平衡点 E_0 平移到原点, 令 $x = S - S_0$, 于是模型(1)可化为:

$$\begin{cases} \frac{dx}{dt} = -(\mu + p)x(t) - \beta(\sigma E + \eta I + \delta A)[x(t) - S_0] + p e^{-\mu\tau} x(t - \tau), \\ \frac{dE}{dt} = \beta(\sigma E + \eta I + \delta A)x(t) + \beta(\sigma E + \eta I + \delta A)S_0 - (\mu + \alpha)E, \\ \frac{dI}{dt} = \rho\alpha E - (\mu + d + \gamma_1 + \gamma)I, \\ \frac{dA}{dt} = (1 - \rho)\alpha E - (\mu + \gamma_2)A. \end{cases} \tag{4}$$

构造如下的 Lyapunov 函数: $V_{11}(t) = \frac{x^2}{2} + S_0 E + \frac{\eta S_0 \pi}{(\mu + d + \gamma_1 + \gamma)} I + \frac{\delta S_0 \pi}{(\mu + \gamma_2)} A$, 其中 $\pi \triangleq (\mu + \alpha) \left[\sigma + \frac{\rho\eta\alpha}{\mu + d + \gamma_1 + \gamma} + \frac{\delta(1 - \rho)\alpha}{\mu + \gamma_2} \right]^{-1}$.

沿模型(4)的轨线求 $V_{11}(t)$ 对 t 的全导数, 可得:

$$\begin{aligned} \frac{dV_{11}(t)}{dt} &= x \frac{dx}{dt} + S_0 \frac{dE}{dt} + \frac{\eta S_0 \pi}{(\mu + d + \gamma_1 + \gamma)} \frac{dI}{dt} + \frac{\delta S_0 \pi}{(\mu + \gamma_2)} \frac{dA}{dt} = -(\mu + p)x^2 - \beta(\sigma E + \eta I + \delta A)x^2 + \\ & \quad \delta A)x^2 + p e^{-\mu\tau} x(t)x(t - \tau) - (\mu + \alpha)ES_0 + \beta(\sigma E + \eta I + \delta A)S_0^2 + \frac{\rho\alpha\eta S_0 \pi E}{(\mu + d + \gamma_1 + \gamma)} + \\ & \quad \frac{\delta(1 - \rho)\alpha\delta S_0 \pi E}{(\mu + \gamma_2)} - \eta\pi IS_0 - \delta\pi AS_0 + \sigma E\pi S_0 - \sigma E\pi S_0 = -(\mu + p)x^2 - \beta(\sigma E + \eta I + \delta A)x^2 + \\ & \quad p e^{-\mu\tau} x(t)x(t - \tau) - (\mu + \alpha)ES_0 + \beta(\sigma E + \eta I + \delta A)S_0^2 - \eta\pi IS_0 - \delta\pi AS_0 - \sigma E\pi S_0 + \\ & \quad \left[\sigma + \frac{\rho\eta\alpha}{\mu + d + \gamma_1 + \gamma} + \frac{\delta(1 - \rho)\alpha}{\mu + \gamma_2} \right] ES_0 \pi = -(\mu + p)x^2 - \beta(\sigma E + \eta I + \delta A)x^2 + \\ & \quad p e^{-\mu\tau} x(t)x(t - \tau) + \beta(\sigma E + \eta I + \delta A)S_0^2 - (\sigma E + \eta I + \delta A)\pi S_0 = -(\mu + p)x^2 - \end{aligned}$$

$$\beta(\sigma E + \eta I + \delta A)x^2 + p e^{-\mu\tau} x(t)x(t - \tau) + (\sigma E + \eta I + \delta A)S_0(\beta S - \pi) = -(\mu + p)x^2 - \beta(\sigma E + \eta I + \delta A)x^2 + p e^{-\mu\tau} x(t)x(t - \tau) + (\sigma E + \eta I + \delta A)\pi S_0(\mathcal{R}_c - 1).$$

要使 $\frac{dV_{11}(t)}{dt}$ 是负定的,取决于 $p e^{-\mu\tau} x(t)x(t - \tau)$ 项,故,将 $p e^{-\mu\tau} x(t)x(t - \tau)$ 适当放大.由于 $x(t)x(t - \tau) \leq \frac{x^2(t) + x^2(t - \tau)}{2}$, 从而 $\frac{dV_{11}(t)}{dt} \leq -(\mu - p)x^2 - \beta(\sigma E + \eta I + \delta A)x^2 + \frac{p e^{-\mu\tau}}{2}[x^2(t) + x^2(t - \tau)] + (\sigma E + \eta I + \delta A)\pi S_0(\mathcal{R}_c - 1)$.

不等式右端的项 $\frac{p e^{-\mu\tau}}{2}x^2(t)$ 可以并入右端第 1 项而保持负号,故只需消去 $\frac{p e^{-\mu\tau}}{2}x^2(t - \tau)$. 为此再构造

Lyapunov 泛函: $V_{12}(t) = \frac{p e^{-\mu\tau}}{2} \int_{t-\tau}^t x^2(u) du$, 而 $\frac{dV_{12}(t)}{dt} = \frac{p e^{-\mu\tau}}{2}[x^2(t) - x^2(t - \tau)]$.

取 $V_1 = V_{11} + V_{12}$, 则有 $\frac{dV_1(t)}{dt} \leq -[\mu + p(1 - e^{-\mu\tau})]x^2 - \beta(\sigma E + \eta I + \delta A)x^2 + (\sigma E + \eta I + \delta A)\pi S_0(\mathcal{R}_c - 1)$.

显然当 $\mathcal{R}_c < 1$ 时, $\frac{dV_1(t)}{dt}$ 除 $x = E = I = A = 0$ 外负定,故模型(1)的无病平衡点 E_0 是全局渐近稳定的; 当 $\mathcal{R}_c = 1$ 时, $\frac{dV_1(t)}{dt}$ 非负当且仅当 $x = 0$ 时为零.由模型(4)的第 1 个方程易见若 $x = 0$ 为其解,则必有 $E = I = A = 0$,故 $\frac{dV_1(t)}{dt} = 0$ 的集合内不含(4)式的非平凡轨线.由 Lyapunov-LaSalle 不变原理可知当 $\mathcal{R}_c \leq 1$ 时,模型(1)的无病平衡点 E_0 是全局渐近稳定的.

3 正平衡点的稳定性和 Hopf 分支的存在性

由上述证明可知:当 $\mathcal{R}_c > 1$ 时,模型(1)存在唯一的地方病平衡点 E_1 .

当 $\tau > 0$ 时,设模型(1)在该点处的线性化系统为

$$\frac{du}{dt} = F_1 u(t) + F_2 u(t - \tau), \tag{5}$$

其中,

$$F_1 = \begin{pmatrix} -x - (\mu + p) & -\beta\sigma S^* & -\beta\eta S^* & -\beta\delta S^* \\ x & \beta\sigma S^* - (\mu + \alpha) & \beta\eta S^* & \beta\delta S^* \\ 0 & \rho\alpha & -(\mu + d + \gamma_1 + \gamma) & 0 \\ 0 & (1 - \rho)\alpha & 0 & -(\mu + \gamma_2) \end{pmatrix}, F_2 = \begin{pmatrix} p e^{-\mu\tau} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix},$$

$$u(t) = [s(t) \quad e(t) \quad i(t) \quad a(t)]^T, x = \beta(\sigma E^* + \eta I^* + \delta A^*).$$

则对应的特征方程为:

$$\lambda^4 + q_1\lambda^3 + q_2\lambda^2 + q_3\lambda + q_4 + (p_1\lambda^3 + p_2\lambda^2 + p_3\lambda + p_4)e^{-\lambda\tau} = 0, \tag{6}$$

这里

$$\begin{aligned} q_1 &= 4\mu + d + \gamma_1 + \gamma + \gamma_2 + x + \alpha - \beta\sigma S^*, \\ q_2 &= (\mu + d + \gamma_1 + \gamma)(\mu + \gamma_2) + (x + 2\mu + p + \alpha - \beta\sigma S^*) + x\beta\sigma S^* + (x + \mu + p)(\mu + \alpha - \beta\sigma S^*) - \rho\alpha\beta\eta S^* - (1 - \rho)\alpha\beta\delta S^*, \\ q_3 &= (\mu + d + \gamma_1 + \gamma)(\mu + \gamma_2)(x + 2\mu + p + \alpha - \beta\sigma S^*) + (x + \mu + p)(\mu + \alpha - \beta\sigma S^*)(2\mu + d + \gamma_1 + \gamma + \gamma_2) + (2\mu + d + \gamma_1 + \gamma + \gamma_2)x\beta\sigma S^* + x\rho\alpha\beta\eta S^* + (1 - \rho)x\alpha\beta\delta S^* - \rho\alpha\beta\eta S^*(x + 2\mu + p + \gamma_2) - (1 - \rho)\alpha\beta\delta S^*(x + 2\mu + p + d + \gamma_1 + \gamma), \\ q_4 &= (x + \mu + p)(\mu + \alpha - \beta\sigma S^*)(\mu + d + \gamma_1 + \gamma)(\mu + \gamma_2) + (\mu + \gamma_2)x\rho\alpha\beta\eta S^* + (\mu + d + \end{aligned}$$

$$\begin{aligned} & \gamma_1 + \gamma)(\mu + \gamma_2)x\beta\sigma S^* + (\mu + d + \gamma_1 + \gamma)(1 - \rho)x\alpha\beta\delta S^* - \rho\alpha\beta\eta S^*(x + \mu + \\ & p)(\mu + \gamma_2) - (1 - \rho)\alpha\beta\delta S^*(x + \mu + p)(\mu + d + \gamma_1 + \gamma), \\ p_1 = & -pe^{-\mu\tau}, p_2 = -[(2\mu + d + \gamma_1 + \gamma + \gamma_2) + (\mu + \alpha - \beta\sigma S^*)]pe^{-\mu\tau}, \\ p_3 = & -[(\mu + d + \gamma_1 + \gamma)(\mu + \gamma_2) + (\mu + \alpha - \beta\sigma S^*)(2\mu + d + \gamma_1 + \gamma + \gamma_2) - \\ & \rho\alpha\beta\eta S^* - (1 - \rho)\alpha\beta\delta S^*]pe^{-\mu\tau}, \\ p_4 = & -[(\mu + \alpha - \beta\sigma S^*)(\mu + d + \gamma_1 + \gamma)(\mu + \gamma_2) - \rho\alpha\beta\eta S^*(x + \mu + p)(\mu + \gamma_2) - \\ & (1 - \rho)\alpha\beta\delta S^*(x + \mu + p)(\mu + d + \gamma_1 + \gamma)]pe^{-\mu\tau}. \end{aligned}$$

当 $\tau=0$ 时,方程(6)可化为

$$\lambda^4 + (q_1 + p_1)\lambda^3 + (q_2 + p_2)\lambda^2 + (q_3 + p_3)\lambda + (q_4 + p_4) = 0, \quad (7)$$

因此,根据 Routh-Hurwitz 判别法,若方程(7)的系数满足如下条件

$$\begin{aligned} H_1: & \quad q_1 + p_1 > 0, (q_1 + p_1)(q_2 + p_2) - (q_3 + p_3) > 0, \\ & \quad (q_4 + p_4) \begin{vmatrix} q_1 + p_1 & q_3 + p_3 & 0 \\ 1 & q_2 + p_2 & q_4 + p_4 \\ 0 & q_1 + p_1 & q_3 + p_3 \end{vmatrix} > 0, \end{aligned}$$

则方程(7)所有的根均有负实部.于是得到引理 1.

引理 1 当 H_1 成立且 $\tau=0$ 时,模型(4)的地方病平衡点 E_1 是局部渐近稳定的.

当 $\tau \neq 0$ 时,假设 $\lambda = i\omega$ 是方程(6)的一个纯虚根,则有

$$\omega^4 - iq_1\omega^3 - q_2\omega^2 + iq_3\omega + q_4 + [\cos(\omega\tau) - i\sin(\omega\tau)](-ip_1\omega^3 - p_2\omega^2 + ip_3\omega + p_4) = 0.$$

分离上式的实部与虚部,可得

$$\omega^4 - q_2\omega^2 + q_4 = \sin(\omega\tau)(p_1\omega^3 - p_3\omega) - \cos(\omega\tau)(-p_2\omega^2 + p_4), \quad (8)$$

$$-q_1\omega^3 + q_3\omega = \cos(\omega\tau)(p_1\omega^3 - p_3\omega) + \sin(\omega\tau)(-p_2\omega^2 + p_4). \quad (9)$$

将方程(8)与(9)左右分别平方并相加,得

$$\omega^8 + l_1\omega^6 + l_2\omega^4 + l_3\omega^2 + l_4 = 0. \quad (10)$$

其中

$$\begin{aligned} l_1 = & q_1^2 - 2q_2 - p_1^2, l_2 = q_2^2 + 2q_4 - 2q_1q_3 - p_2^2 + 2p_1p_3, \\ l_3 = & q_3^2 - 2q_2q_4 - p_3^2 + 2p_2p_4, l_4 = q_4^2 - p_4^2. \end{aligned}$$

令 $\omega^2 = \bar{\omega}$, 则

$$G(\bar{\omega}) = \bar{\omega}^4 + l_1\bar{\omega}^3 + l_2\bar{\omega}^2 + l_3\bar{\omega} + l_4 = 0. \quad (11)$$

如果满足条件 $H_2: l_4 = q_4^2 - p_4^2 = (q_4 + p_4)(q_4 - p_4) < 0$, 则方程(11)至少存在一个正根.

假设(11)式存在 $n(1 \leq n \leq 4)$ 个 $\bar{\omega}_n$. 则方程(10)有 n 个正实根且分别为

$$\omega_2 = \sqrt{\bar{\omega}_1}, \omega_2 = \sqrt{\bar{\omega}_2}, \dots, \omega_n = \sqrt{\bar{\omega}_n} (1 \leq n \leq 4).$$

由方程(8)和(9)可得

$$\begin{aligned} \sin(\omega\tau) = F_n = & \frac{(p_1\omega^3 - p_3\omega)(\omega^4 - q_2\omega^2 + q_4) + (-p_2\omega^2 + p_4)(-q_1\omega^3 + q_3\omega)}{(p_1\omega^3 - p_3\omega)^2 + (-p_2\omega^2 + p_4)^2}, \\ \cos(\omega\tau) = J_n = & \frac{(p_1\omega^3 - p_3\omega)(-q_1\omega^3 + q_3\omega) - (-p_2\omega^2 + p_4)(\omega^4 - q_2\omega^2 + q_4)}{(p_1\omega^3 - p_3\omega)^2 + (-p_2\omega^2 + p_4)^2}. \end{aligned}$$

$$\text{定义: } \tau_n^{(j)} = \frac{1}{\omega_n} \cos^{-1}(J_n) + \frac{2\pi j}{\omega_n} (1 \leq n \leq 4, j = 0, 1, 2, 3, \dots). \quad (12)$$

易知当 $\tau = \tau_n^{(j)}$ 时, $\pm i\omega_n$ 是方程(6)的一对纯虚根.

设 $\lambda_n^{(j)}(\tau) = \alpha_n^{(j)}(\tau) + i\omega_n^{(j)}(\tau)$ 是方程(6)在 $\tau = \tau_n^{(j)}$ 附近的根, 并满足 $\alpha_n^{(j)}(\tau) = 0, \omega_n^{(j)}(\tau) = \omega_n$. 那么, 将 $\lambda_n^{(j)}(\tau)$ 代入方程(7)则有

$$p(\lambda) + f(\lambda)e^{-\lambda\tau} = 0. \quad (13)$$

其中, $p(\lambda) = \lambda^4 + q_1\lambda^3 + q_2\lambda^2 + q_3\lambda + q_4, f(\lambda) = (p_1\lambda^3 + p_2\lambda^2 + p_3\lambda + p_4)$.

在方程(13)两边关于 τ 求得

$$p'(\lambda) \frac{d\lambda}{d\tau} + f'(\lambda) \frac{d\lambda}{d\tau} e^{-\lambda\tau} - \left(\lambda + \tau \frac{d\lambda}{d\tau}\right) f(\lambda) e^{-\lambda\tau} = 0, \left[\frac{d\lambda}{d\tau}\right]^{-1} = \frac{p'(\lambda) + f'(\lambda)e^{-\lambda\tau}}{\lambda f(\lambda)e^{-\lambda\tau}} - \frac{\tau}{\lambda}.$$

由 $p(i\omega_n) + f(i\omega_n)e^{-i\omega_n\tau_n^{(j)}} = 0$ 可得

$$\begin{aligned} \operatorname{Re}\left[\frac{d\lambda}{d\tau}\right]_{\tau=\tau_n}^{-1} &= \operatorname{Re}\left[\frac{p'(i\omega_n) + f'(i\omega_n)e^{-i\omega_n\tau_n^{(j)}}}{i\omega_n f(i\omega_n)e^{-i\omega_n\tau_n^{(j)}}}\right] = \operatorname{Re}\left[\frac{-f'(i\omega_n)}{\omega_n f(i\omega_n)}i\right] + \\ &\operatorname{Re}\left[\frac{p'(i\omega_n)}{\omega_n p(i\omega_n)}i\right] = \operatorname{Im}\left[\frac{f'(i\omega_n)}{\omega_n f(i\omega_n)} - \frac{p'(i\omega_n)}{\omega_n p(i\omega_n)}\right]. \end{aligned}$$

设 $\varphi(\omega) = |f(i\omega)|^2 - |p(i\omega)|^2$, 则有 $\varphi(\omega) = G(\omega^2)$. 对 $|f(i\omega)|^2$ 求导, 得

$$\begin{aligned} \frac{d}{d\omega}(|f(i\omega)|^2) &= \frac{d}{d\omega}\{[\operatorname{Re} f(i\omega)]^2 + [\operatorname{Im} f(i\omega)]^2\} = 2\operatorname{Re} f(i\omega) \cdot \operatorname{Re}[f'(i\omega)i] + \\ &2\operatorname{Im} f(i\omega) \cdot \operatorname{Im}[f'(i\omega)i] = 2\operatorname{Re}[f(i\omega)f'(i\omega)i]. \end{aligned}$$

所以

$$\begin{aligned} \frac{1}{2\omega} \cdot \frac{d\varphi}{d\omega} &= \frac{1}{2\omega} \cdot \frac{d}{d\omega}(|f(i\omega)|^2 - |p(i\omega)|^2) = \frac{1}{2\omega} \operatorname{Im}[\overline{p(i\omega)}p'(i\omega) - \overline{f(i\omega)}F'(i\omega)] = \\ &\operatorname{Im}\left[|f(i\omega)|^2 \frac{p'(i\omega)}{\omega p(i\omega)} - |p(i\omega)|^2 \frac{p'(i\omega)}{\omega p(i\omega)}\right]. \end{aligned}$$

由于 $|p(i\omega)|^2 = |f(i\omega)|^2$ 可知 $\left(\frac{1}{2\omega} \cdot \frac{d\varphi}{d\omega}\right)\Big|_{\omega=\omega_n} = |f(i\omega_n)|^2 \operatorname{Im}\left[\frac{p'(i\omega_n)}{\omega p(i\omega_n)} - \frac{p'(i\omega_n)}{\omega p(i\omega_n)}\right]$.

综上所述, 可得 $\operatorname{sign} \operatorname{Re}\left[\frac{d\lambda}{d\tau}\right]_{\tau=\tau_n^{(j)}}^{-1} = \operatorname{sign}\left[\left(\frac{1}{2\omega} \cdot \frac{d\varphi}{d\omega}\right)\Big|_{\omega=\omega_n}\right]$.

又因为 $\operatorname{sign}\left[\frac{d\operatorname{Re}(\lambda)}{d\tau}\right]_{\tau=\tau_n^{(j)}} = \operatorname{sign} \operatorname{Re}\left[\frac{d\lambda}{d\tau}\right]_{\tau=\tau_n^{(j)}} = \operatorname{sign} \operatorname{Re}\left[\frac{d\lambda}{d\tau}\right]_{\tau=\tau_n^{(j)}}^{-1} \cdot \operatorname{sign}[G'(\omega_n^2)] =$
 $\operatorname{sign}\left[\left(\frac{1}{2\omega} \cdot \frac{d\varphi}{d\omega}\right)\Big|_{\omega=\omega_n}\right]$, 所以 $\operatorname{sign}\left[\frac{d\operatorname{Re}(\lambda)}{d\tau}\right]_{\tau=\tau_n^{(j)}} = \operatorname{sign}[G'(\omega_n^2)]$.

显然, 如果满足条件 $H_3: G'(\omega_n^2) \neq 0$, 则 $\left[\frac{d\operatorname{Re}(\lambda)}{d\tau}\right]_{\tau=\tau_n^{(j)}} \neq 0$.

令 $\tau_0 = \tau_{n_0}^{(0)} = \min\{\tau_n^j \mid 1 \leq n \leq 4, j = 0, 1, 2, 3, \dots\}, \omega_0 = \omega_{n_0}$. 由上述分析可以得到定理 3.

定理 3 当 $\mathcal{R}_c > 1$, 且条件 H_1, H_2 和 H_3 均成立时, 则有

- (1) 当 $0 \leq \tau < \tau_0$ 时, 模型(1) 在地方病平衡点 E_1 处是局部渐近稳定的;
- (2) 当 $\tau > \tau_0$ 时, 模型(1) 在地方病平衡点 E_1 处是不稳定的;
- (3) 当 $\tau = \tau_0$ 时, 模型(1) 在地方病平衡点 E_1 处产生 Hopf 分支.

4 结 论

依据流感的传播机理, 构建了一类具有免疫时滞和“媒体、疫苗接种和抗病毒治疗”三类综合干预措施的 SEIAR 模型. 首先, 利用了再生矩阵方法给出了模型的控制再生数 \mathcal{R}_c . 然后通过构造 Lyapunov 函数并运用 Lyapunov-LaSalle 不变原理证明了当 $\mathcal{R}_c < 1$ 时, 模型(1) 的无病平衡点是全局稳定的; 并利用 Routh-Hurwitz 判别, 给出了地方病平衡点 E_1 的局部稳定性, 得到了在一定条件下 Hopf 分支的存在性, 揭示了免疫时滞会影响流感疫情的传播.

参 考 文 献

[1] PATEL R, JR I M L, HALLORAN M E. Finding optimal vaccination strategies for pandemic influenza using genetic algorithms[J]. Jour-

- nal of Theoretical Biology, 2005, 234(2): 201-212.
- [2] KELSO J K, MILNE G J, KELLY H. Simulation suggests that rapid activation of social distancing can arrest epidemic development due to a novel strain of influenza[J]. BMC Public Health, 2009, 9: 117. DOI: 10.1186/1471-2458-9-117.
- [3] LEE B Y, BROWN S T, COOLEY P C, et al. A computer simulation of employee vaccination to mitigate an influenza epidemic[J]. American Journal of Preventive Medicine, 2010, 38(3): 247-257.
- [4] WANG L W, LIU Z J, ZHANG X A. Global dynamics of an SVEIR epidemic model with distributed delay and nonlinear incidence[J]. Applied Mathematics and Computation, 2016, 284(5): 47-65.
- [5] TANG R B, CHEN H L. An overview of the recent outbreaks of the avian-origin influenza A(H7N9) virus in the human[J]. Journal of the Chinese Medical Association, 2013, 76(5): 245-248.
- [6] GULBUDAK H, MARYCHEVA M. A structured avian influenza model with imperfect vaccination and vaccine-induced asymptomatic infection[J]. Bulletin of Mathematical Biology, 2014, 76(10): 2389-2425.
- [7] 陈田木, 陈水连, 谢知, 等. 不同隐性感染和传播能力条件下的流感暴发防控措施效果模拟[J]. 中国热带医学, 2017, 17(5): 470-476.
CHEN T M, CHEN S L, XIE Z, et al. Simulated effectiveness of control countermeasures for influenza outbreaks based on different asymptomatic infections and transmissibility[J]. China Tropical Medicine, 2017, 17(5): 470-476.
- [8] WEBBY R J, WEBSTER R G. Are we ready for pandemic Influenza?[J]. Science, 2003, 302(5650): 1519-1522.
- [9] DOYLE T J, GOODIN K, HAMILTON J J. Maternal and neonatal outcomes among pregnant women with 2009 pandemic Influenza A (H1N1) illness in Florida, 2009-2010: A population-based cohort study[J]. Plos One, 2013, 8(10): e79040-e79040.
- [10] 陈田木, 刘如春, 张锡兴, 等. 长沙市甲型 H1N1 流感流行干预措施效果的数学模拟[J]. 中国卫生统计, 2015, 32(2): 205-210.
CHEN T M, LIU R C, ZHANG X X, et al. Simulating the effects of intervention strategies on the epidemic of Influenza A(H1N1) using dynamic model in Changsha city[J]. Chinese Journal of Health Statistics, 2015, 32(2): 205-210.
- [11] HAYWARD A C, FRAGASZY E B, BERMINGHAM A, et al. Comparative community burden and severity of seasonal and pandemic influenza: results of the Flu Watch cohort study[J]. The Lancet Respiratory Medicine, 2014, 2(6): 445-454.
- [12] ZHANG Q X, WANG D C. Antiviral Prophylaxis and Isolation for the Control of Pandemic Influenza[J]. International Journal of Environmental Research and Public Health, 2014, 11(8): 7690-7712.
- [13] XIAO Y N, XU X X, TANG S Y. Sliding mode control of outbreaks of emerging infectious diseases[J]. Bulletin of Mathematical Biology, 2012, 74(10): 2403-2422.
- [14] HASSARD B D, KAZARINOFF N D, WAN Y-H. Theory and applications of Hopf bifurcation[M]. Cambridge, Cambridge University Press, 1981.

An influenza transmission model with immune delay and comprehensive interventions

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Abstract: In this paper, we consider that an individual with influenza vaccination has a defined immune period, so we establish an SEIAR influenza model with immune delay and three types of comprehensive interventions including "media, vaccination and antiviral therapy". By constructing the Lyapunov function and the Routh-Hurwitz criterion, the stability of the disease-free equilibrium and the endemic disease equilibrium of the model are analyzed. Furthermore, the sufficient condition for the existence of Hopf bifurcation near the endemic equilibrium is given out.

Keywords: SEIAR influenza model; Lyapunov function; immune delay; stability; Hopf bifurcation

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