

Modelos Matemáticos en Epidemiología

Luis Claro

Sección Biofísica y Biología de Sistemas

Facultad de Ciencias

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Introducción

Epidemiología

- Estudio de la distribución, frecuencia y factores de riesgo de las enfermedades en una población definida.
- Particular interés en el tiempo y lugar donde ocurren los casos, en los grupos especialmente vulnerables, conductas y hábitos de riesgo.
- Puede tratarse de enfermedades transmisibles o no transmisibles. También, de enfermedades novedosas o establecidas en una población.

Epidemiología

- Aún el conocimiento refinado del desarrollo de una enfermedad transmisible no es suficiente para comprender cómo será la dinámica de la enfermedad en una población.
- Estas propiedades emergentes pueden ser estudiadas mediante la utilización de modelos matemáticos que aborden tal complejidad.

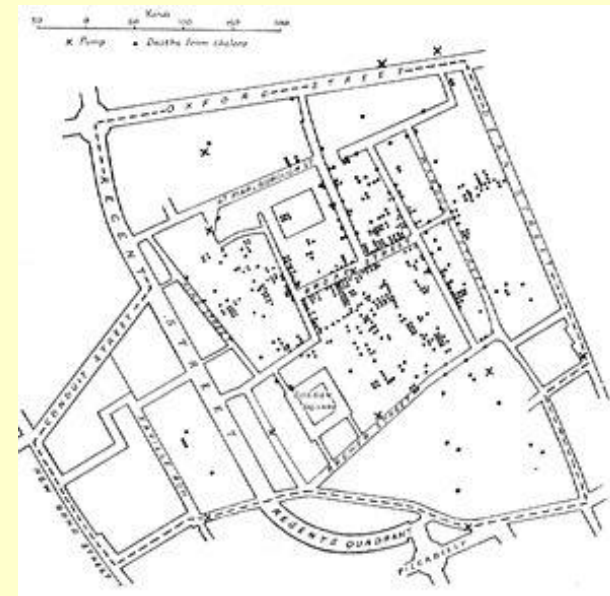
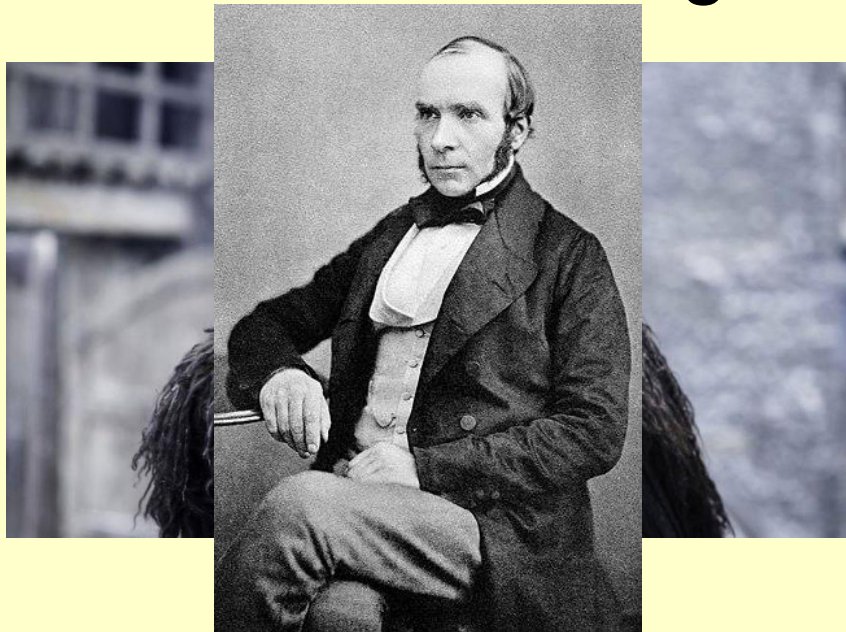
Antecedentes

- Daniel Bernoulli (1766) publicó un modelo matemático explícito donde abordaba el efecto de la variolización como método para la prevención de la viruela.



Antecedentes

- John Snow analizó geográficamente los casos de cólera en el distrito de Soho (Londres) durante la epidemia de 1854, asociando los casos a la contaminación con heces de una fuente de agua.



Antecedentes

- A fines del siglo XIX, Ronald Ross explicó el ciclo completo de la malaria humana, con la inclusión del mosquito como vector y el parásito *Plasmodium*, lo que le valió el Premio Nobel de Medicina en 1902.

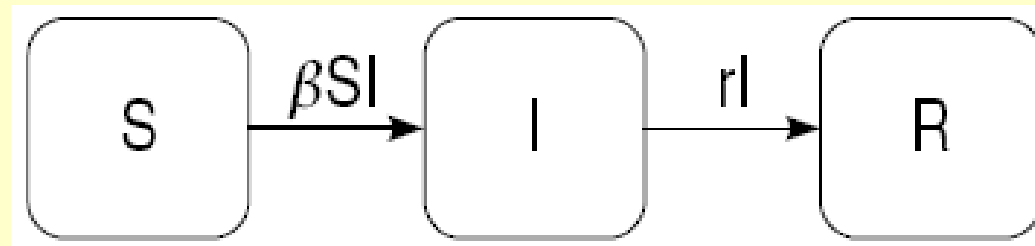


Antecedentes

- Trabajo matemático de Kermack y McKendrick, realizado durante el periodo de 1927 a 1939.
- A finales de la década de 1990, los investigadores comenzaron a interesarse por el estudio de las redes complejas al advertir que era vital esta perspectiva para entender la dinámica de las enfermedades como el VIH/SIDA.

Modelo de Kermack-McKendrick

- Modelo determinístico compartimental, en el cual los individuos de la población forman parte de uno y sólo uno de tres estados, referidos a una enfermedad infecciosa.



Los autores



Anderson Gray McKendrick (1876-1943) y William Ogilvy Kermack (1898-1970).

Artículo

A Contribution to the Mathematical Theory of Epidemics.

By W. O. KERMAK and A. G. MCKENDRICK.

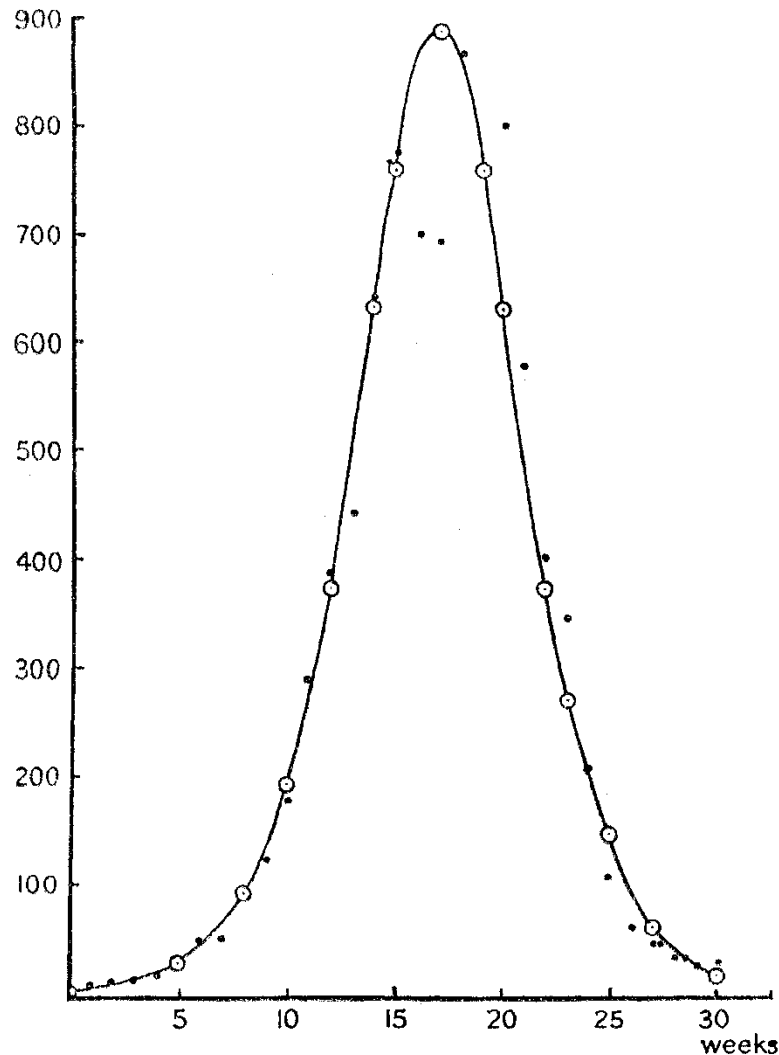
(Communicated by Sir Gilbert Walker, F.R.S.—Received May 13, 1927.)

(From the Laboratory of the Royal College of Physicians, Edinburgh.)

Introduction.

(1) One of the most striking features in the study of epidemics is the difficulty of finding a causal factor which appears to be adequate to account for the magnitude of the frequent epidemics of disease which visit almost every population. It was with a view to obtaining more insight regarding the effects of the various factors which govern the spread of contagious epidemics that the present investigation was undertaken. Reference may here be made to the work of Ross and Hudson (1915–17) in which the same problem is attacked. The problem is here carried to a further stage, and it is considered from a point of view which is in one sense more general. The problem may be summarised as follows: One (or more) infected person is introduced into a community of individuals, more or less susceptible to the disease in question. The disease spreads from

Algunos Resultados (I)



The accompanying chart is based upon figures of deaths from plague in the island of Bombay over the period December 17, 1905, to July 21, 1906. The ordinate represents the number of deaths per week, and the abscissa denotes the time in weeks. As at least 80 to 90 per cent of the cases reported terminate fatally, the ordinate may be taken as approximately representing dz/dt as a function of t . The calculated curve is drawn from the formula

$$dz/dt = 890 \operatorname{sech}^2(0,2t - 3,4)$$

(Kermack & McKendrick 1927)

Algunos resultados (II)

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EPIDEMIOLOGY

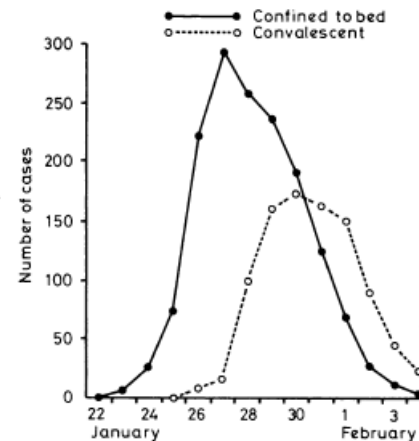
Influenza in a boarding school

The following notes are compiled by the Communicable Disease Surveillance Centre (Public Health Laboratory Service) and the Communicable Diseases (Scotland) Unit from reports submitted by 587 biological laboratories, community physicians, and environmental health officers.

During January an epidemic of influenza occurred in a boarding school in the north of England. A total of 763 boys between the ages of 10 and 18 were at risk, all except 30 being full boarders; the staff were from the surrounding villages. There were 113 boys between the ages of 10 and 13 in the junior house, while the rest were divided into 10 houses of about 60 boys each.

The Easter term began on 10 January, with boys returning from all over Britain and some from Europe and the Far East. One boy from Hong Kong had a transient febrile illness from 15 to 18 January. On Sunday 22 January three boys were in the college infirmary. The graph shows the daily total number confined to bed or convalescent during the epidemic: 512 boys (67%) spent between three and seven days away from class, and 83% of the boys in the junior house were affected. Of about 130 adults who had some contact with the boys, only one, a house matron, developed similar symptoms.

Most of the boys who became ill first complained of feeling very tired, with headache as fever developed, and sore throat and tracheitis being the rule. The temperature was usually 100°-102°F (38°-39°C) and often higher in the morning. Three boys with no other abnormal



signs had temperatures of 105°-106°F (40°-41°C). Many had mild reddening of the anterior pillars of the fauces, but the throat never looked as inflamed as symptoms suggested. In only five boys were there abnormal signs on chest examination. Symptoms subsided quickly once the boys were confined to bed. They were allowed up 36 hours after their temperatures had returned to normal and back to classes two to four days later, depending on the severity of the attack. The average time off sick was five to six days.

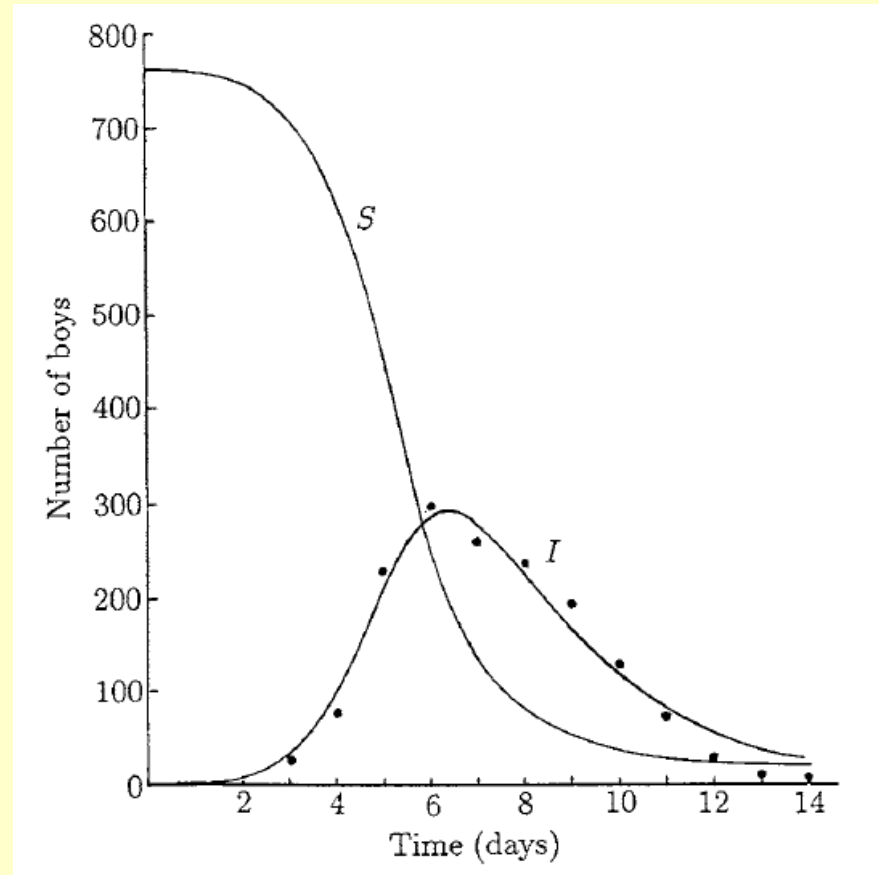
One boy of 13 was readmitted after two days with probable bacterial pneumonia, with a temperature of 104°F (40°C), pulse rate of 110/min, respiration rate of 22/min, and moist

sounds in his right lung. He was given ampicillin and by next morning his temperature was 99°F (37°C) and his chest clear. Five days later he went home to convalesce. Four boys developed wheezy bronchitis. Two received ampicillin and two tetracycline. All recovered quickly and were back at work in seven to eight days. Four boys with otitis media, with bulging red ear drums, responded to ampicillin within 48 hours and none had any aural discharge. One boy had sinusitis, which again responded to ampicillin. He was in bed for seven days and off work for ten days. In all, only 10 of the 512 boys who became ill received antibiotics.

Throat swabs were taken from eight boys, and influenza A viruses similar to A/USSR/90/77 (H1N1) were isolated from six. The spread of this virus through the school was much more rapid than in the outbreaks due to influenza B in November 1954 and to influenza A (Asian flu) H2N2 in October 1957. These two epidemics reached their peak in two weeks and lasted four weeks. This year's epidemic reached a peak in seven days and was over in 13 days. Influenza vaccine (Fluvirin) had been given to 630 boys in October 1977—as had been the practice for some years. The incidence of influenza among the boys had been low except in those years in which a definite antigenic shift occurred. The fact that this is the first major outbreak of influenza at the school since the Asian flu suggests that influenza vaccination has a useful role in a boarding school. Had it been possible to include the H1N1 strain in the vaccine a major outbreak might well have been avoided.

Algunos resultados (II)

Day	Number
1	3
2	8
3	28
4	75
5	221
6	291
7	255
8	235
9	190
10	125
11	70
12	28
13	12
14	5



$S(0)=762$; $I(0)=1$; $\beta=0,00218$; $r=0,4404$, $N=763$

Otros abordajes

- Es importante la utilización de modelos que incluyan estocasticidad.
- Dinámicas espaciales
- Teoría de redes
- Procesos de ramificación

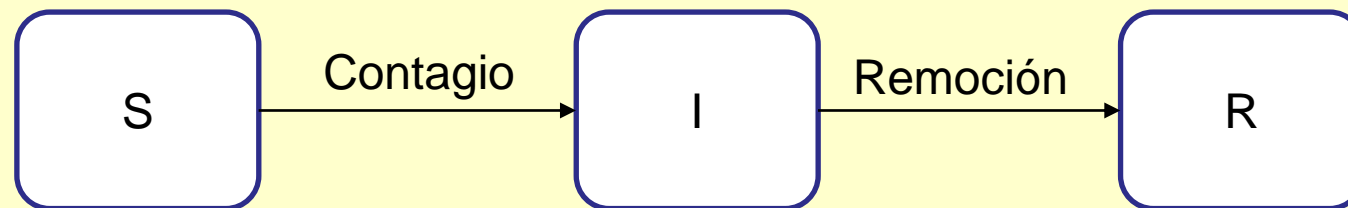
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- Kermack, W.O. and A.G. McKendrick, “A Contribution to the Mathematical Theory of Epidemics.” Proceedings of the Royal Society of London. Series A, 115:700-721, 1927.
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- Murray, J.D., “Mathematical Biology.” Springer-Verlag, 2007.
- Montesinos-López, O.A., Hernández-Suárez, C.M., “Modelos matemáticos para enfermedades infecciosas.” Salud Publica Mex, 49:218-226, 2007.
- Sulsky, D., “Using Real Data in an SIR Model”, 2012.

Modelo de Kermack-McKendrick o Modelo SIR

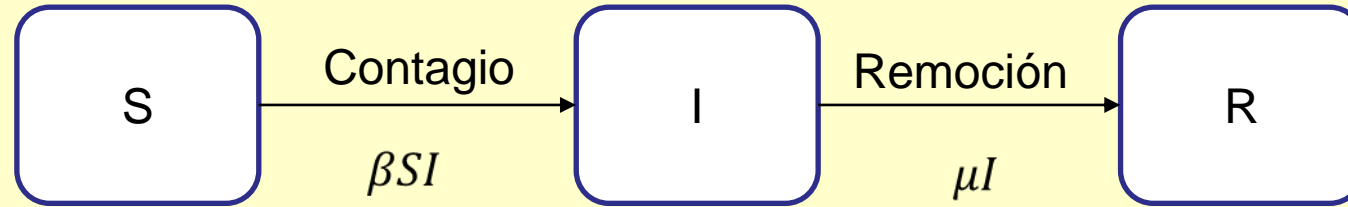
Modelo de Kermack-McKendrick o Modelo SIR

- Modelo determinístico compartimental, en el cual los individuos de la población forman parte de uno y sólo uno de tres estados, referidos a una enfermedad infecciosa.



- S: Susceptibles; I: Infecciosos; R: Removidos

Modelo de Kermack-McKendrick o Modelo SIR



$$\begin{aligned}\frac{dS}{dt} &= -\beta SI \\ \frac{dI}{dt} &= \beta SI - \mu I \\ \frac{dR}{dt} &= \mu I\end{aligned}$$

Sistema de ecuaciones diferenciales **no soluble**.

Procesos

Ocurren dos procesos independientes: contagio y recuperación.

¿Cómo modelamos el **proceso de contagio** y qué efecto tiene el mismo sobre las variables S e I?

Tasa de contagio = $\beta \cdot S \cdot I$; donde β es la contagiosidad (caracteriza a diferentes enfermedades en diferentes poblaciones).

β tiene unidades de individuo⁻¹ día⁻¹.

Procesos

¿De qué depende la tasa de recuperación?

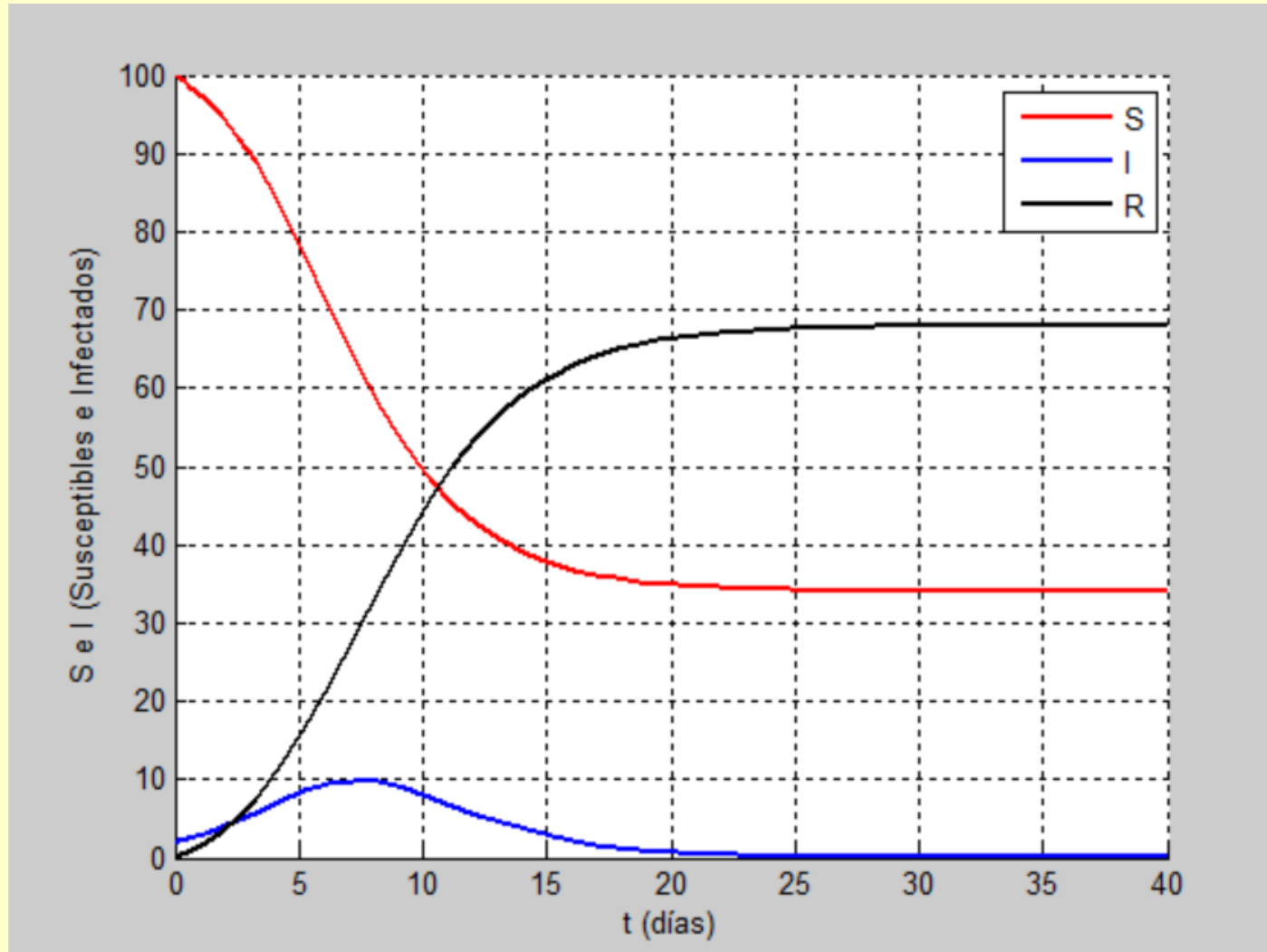
- Cantidad de infectados (I)
- El tiempo promedio que tardan los infectados en recuperarse (τ)

$$\textit{Tasa de recuperación} = \frac{I}{\tau} = \mu I$$

$$\mu = \frac{1}{\tau}$$

μ es la constante de recuperación y tiene unidades de tiempo⁻¹ o 1/tiempo, típicamente en días⁻¹.

Curso temporal de S, I y R



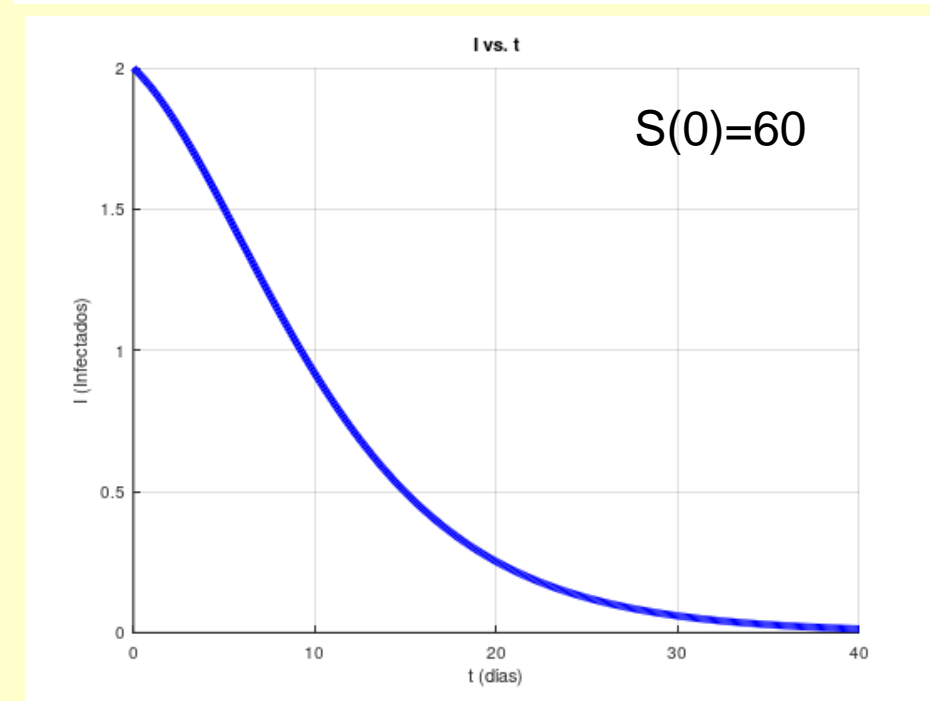
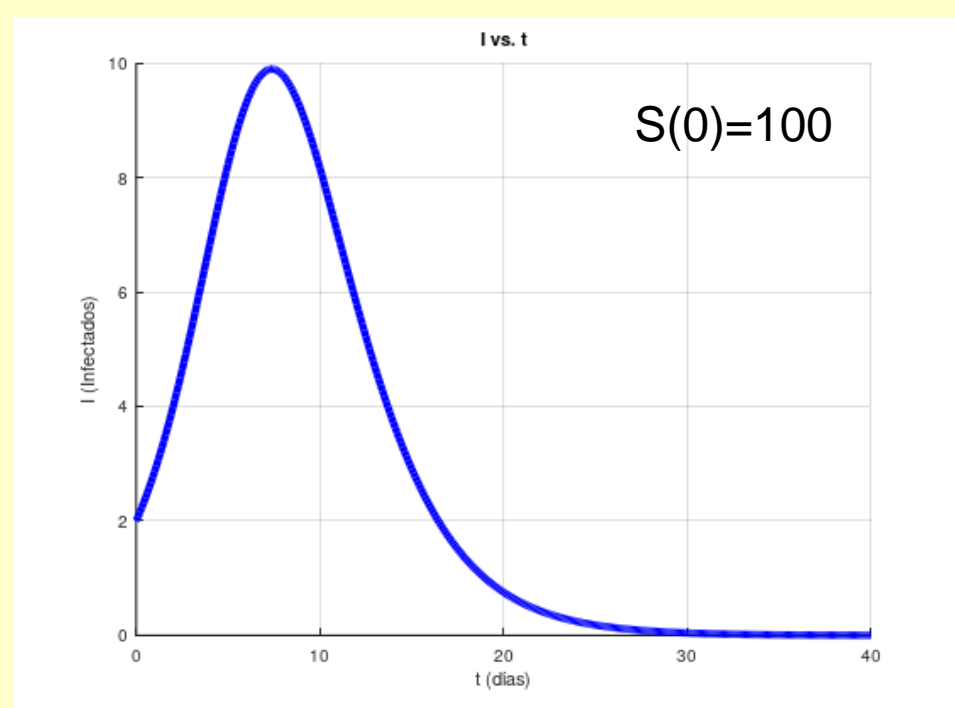
Algunas ideas importantes

- I muestra una fase de crecimiento exponencial al inicio (crecimiento o decrecimiento).
- El sistema deja de variar (alcanza el equilibrio), cuando $I = 0$.
- $S_{\infty} > 0$; $R_{\infty} < N$
(No toda la población atraviesa la enfermedad)

El sistema presenta un Umbral

Dos situaciones

- $\beta = 0,01 \text{ ind}^{-1} \text{ día}^{-1}$
- $\mu = 0,63 \text{ día}^{-1}$



Umbral

$$\frac{dI}{dt} = \beta SI - \mu I > 0$$

$$(\beta S - \mu)I > 0$$

$$\beta S - \mu > 0$$

$$\beta S > \mu$$

$$\frac{\beta S}{\mu} > 1$$

Definimos $\mathbb{R}_0 = \frac{\beta S}{\mu}$

$$\mathbb{R}_0 > 1$$

Fase exponencial

- Si en un cierto período de tiempo, S se mantiene aproximadamente constante, puede verse una fase exponencial.
- Supongamos que $S \approx cte$ (en un cierto intervalo de tiempo) \Rightarrow

$$\beta S - \mu = k \approx cte$$

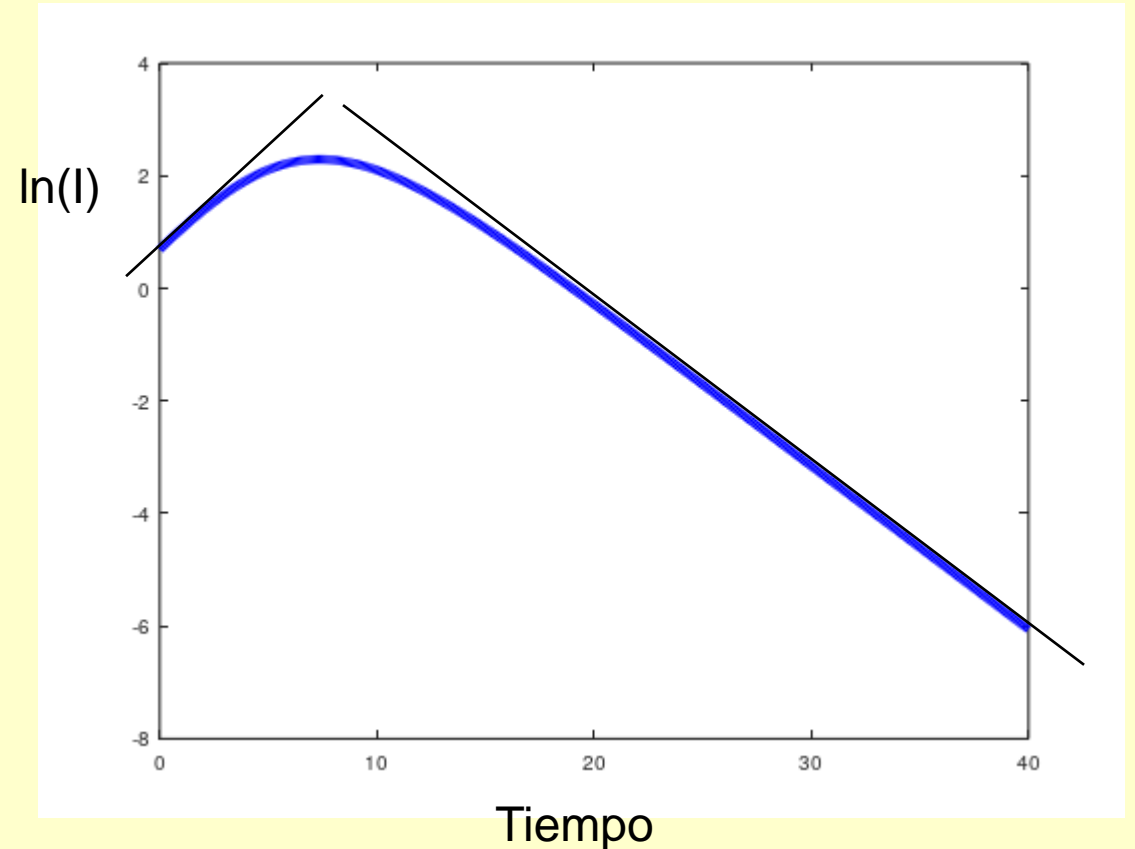
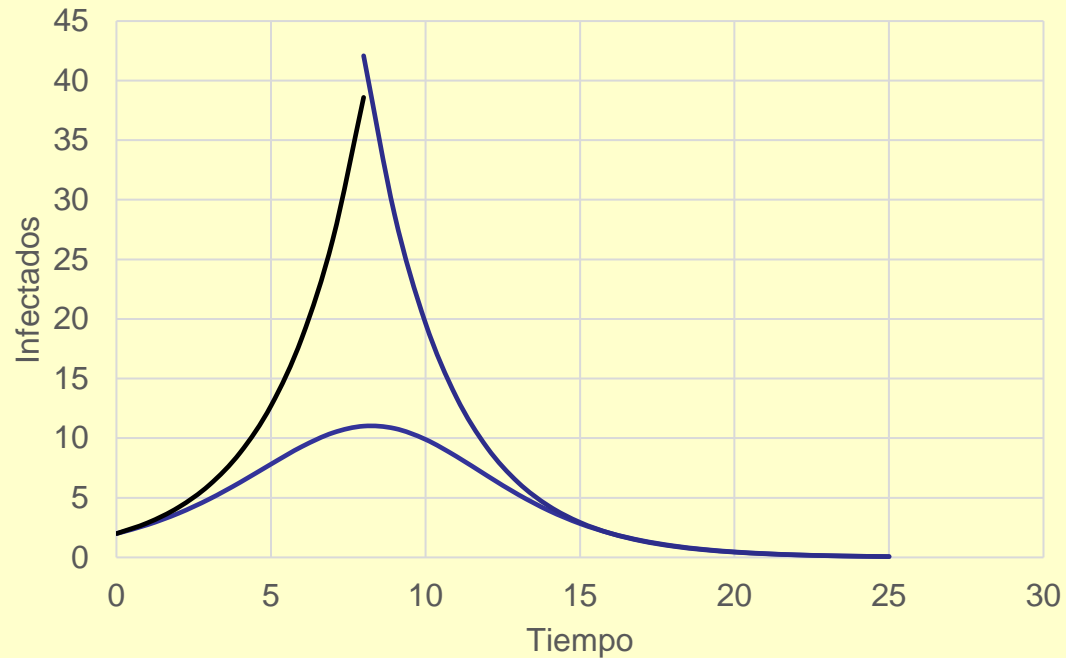
Esto implica que:

$$\frac{dI}{dt} = kI \Rightarrow I(t) \approx I_0 e^{kt}$$

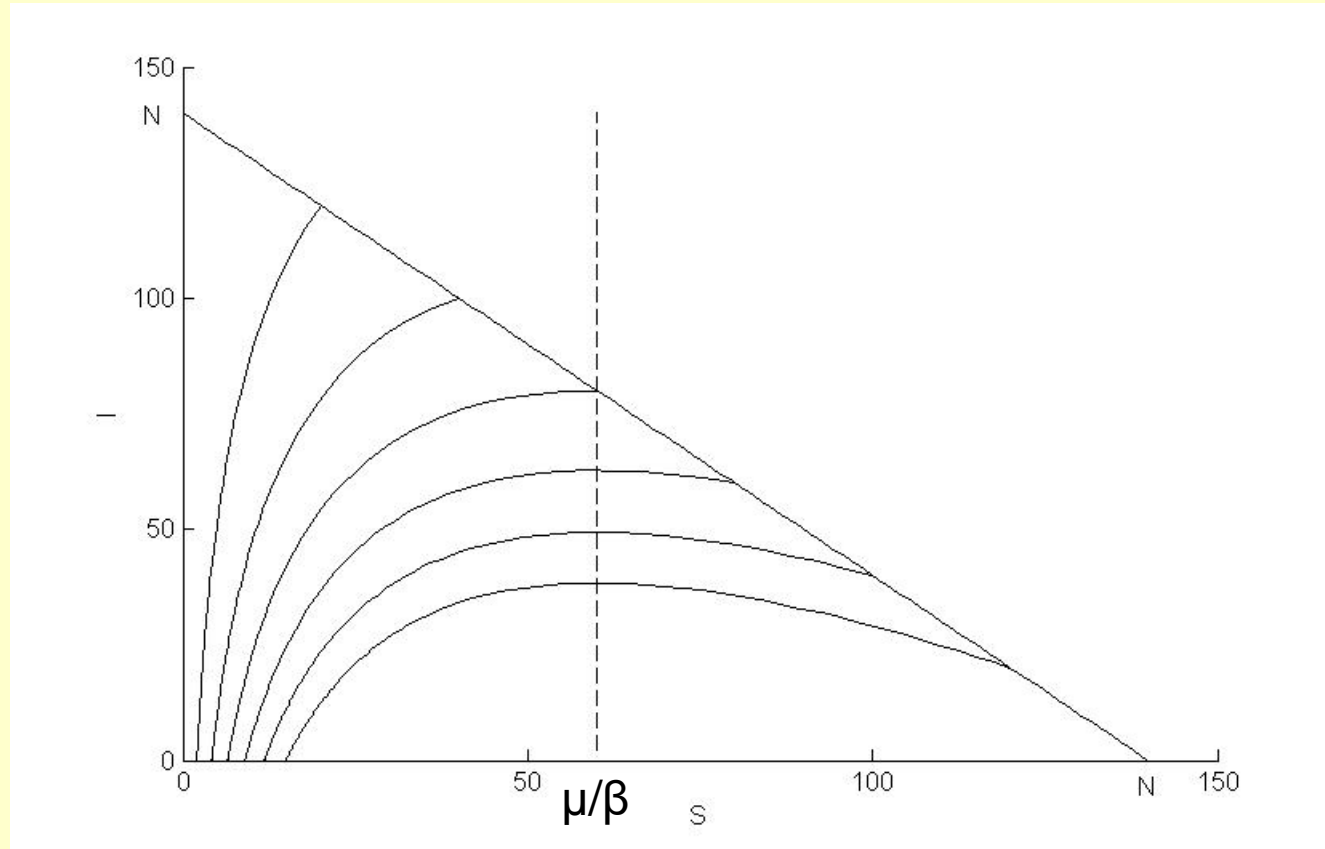
Fase exponencial

Típicamente habrán dos fases exponenciales

- $I(t) \approx I_0 e^{kt} \Rightarrow \ln(I) \approx \ln(I_0) + kt$



Plano de Fase



Diferentes simulaciones de una población de tamaño N , con distinta distribución inicial de susceptibles e infectados (puntos de la recta).

$$S_0 + I_0 = N$$

Nótese que solamente hay fase de crecimiento de I , cuando S_0 es menor a μ/β .

¿Podemos encontrar una relación entre I y S?

- Consideremos:

$$\frac{dI}{dt} \div \frac{dS}{dt} = \frac{dI}{dS} = \frac{\beta SI - \mu I}{-\beta SI} = -1 + \frac{\mu}{\beta} \frac{1}{S} \Rightarrow$$

$$dI = \left(-1 + \frac{\mu}{\beta} \frac{1}{S} \right) dS \Rightarrow \int_{I_0}^I dI = \int_{S_0}^S \left(-1 + \frac{\mu}{\beta} \frac{1}{S} \right) dS$$

$$\int_{I_0}^I dI = I - I_0 = - \int_{S_0}^S dS + \int_{S_0}^S \frac{\mu}{\beta} \frac{1}{S} dS = S_0 - S + \frac{\mu}{\beta} \ln \left(\frac{S}{S_0} \right)$$

$$I - I_0 = S_0 - S + \frac{\mu}{\beta} \ln \left(\frac{S}{S_0} \right)$$

$$I - I_0 = S_0 - S + \frac{\mu}{\beta} \ln \left(\frac{S}{S_0} \right) \Rightarrow I = I_0 + S_0 - S + \frac{\mu}{\beta} \ln \left(\frac{S}{S_0} \right)$$

Teniendo en cuenta que $S_0 + I_0 = N$, la expresión anterior queda:

$$I = N - S + \frac{\mu}{\beta} \ln \left(\frac{S}{S_0} \right)$$

Esta expresión describe exactamente la trayectoria que sigue el sistema en el plano S I (plano de fase).

Recordando que el sistema alcanza el equilibrio cuando $I=0$, podemos utilizar la expresión obtenida anteriormente para obtener la cantidad de susceptibles cuando se extingue el brote epidémico (S_∞). De esta forma tenemos:

$$N - S_\infty + \frac{\mu}{\beta} \ln \left(\frac{S_\infty}{S_0} \right) = 0$$

No se puede obtener analíticamente una expresión para S_∞ . Pero si se puede obtener una aproximación de su valor haciendo uso de ciertos métodos, como el método de Newton-Raphson (búsqueda recomendada).

S vs R

De manera similar a lo visto anteriormente, es posible encontrar una relación entre S y R.

Tomando:

$$\frac{dS}{dR} = \frac{dS}{dt} \div \frac{dR}{dt} = \frac{-\beta SI}{\mu I} = \frac{-\beta}{\mu} S \Rightarrow$$

$$\int_{S_0}^S \frac{1}{S} dS = \int_{R_0}^R \frac{-\beta}{\mu} dR$$

$$\ln(S) - \ln(S_0) = \frac{-\beta}{\mu} R - \left(\frac{-\beta}{\mu} R_0 \right)$$

Como normalmente $R_0=0$, tenemos:

$$\ln(S/S_0) = \frac{-\beta}{\mu} R \Rightarrow S = S_0 e^{-\frac{\beta}{\mu} R}$$

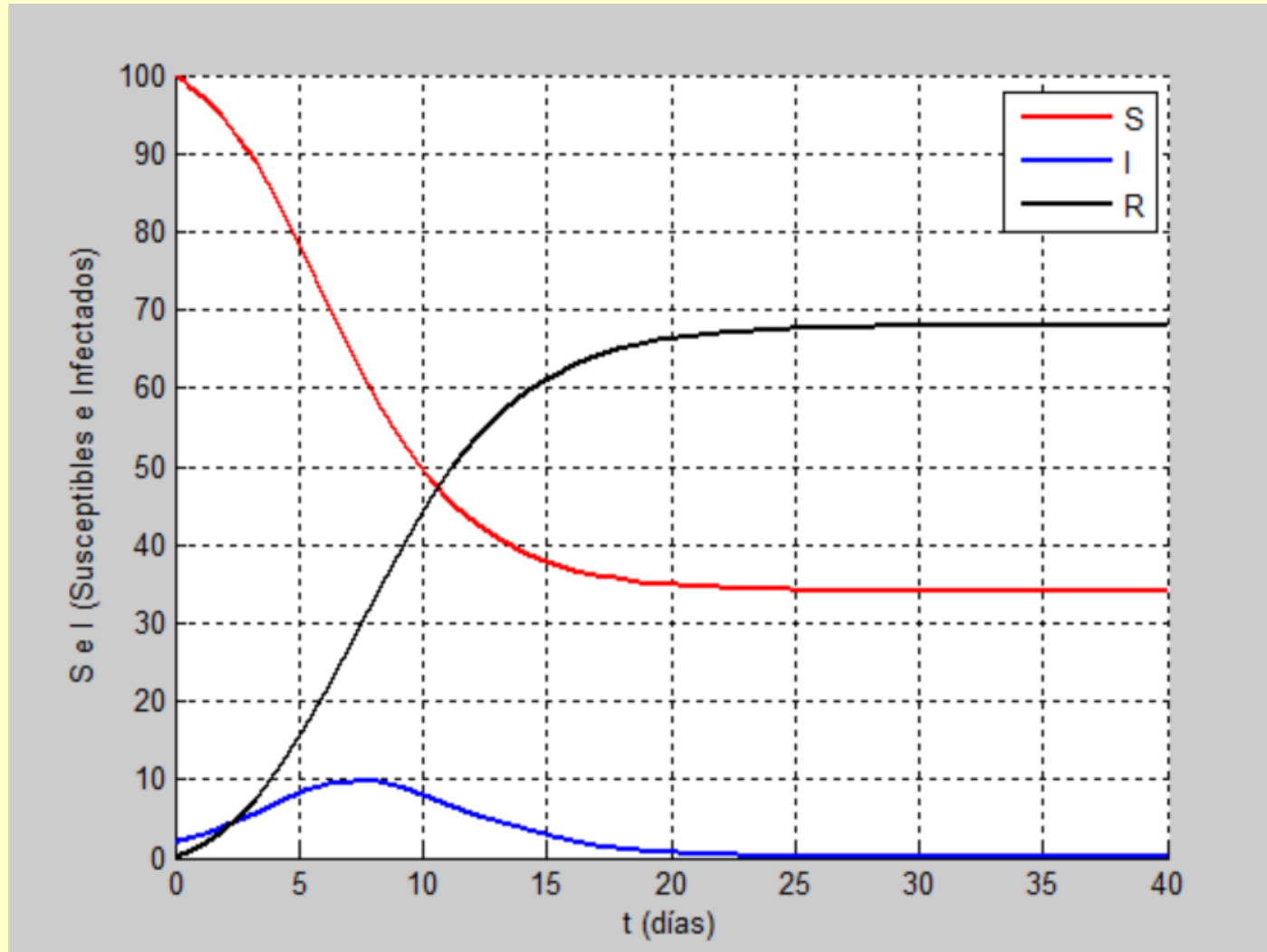
I vs S y S vs R

$$I(S) = N - S + \frac{\mu}{\beta} \ln \left(\frac{S}{S_0} \right)$$

$$S_\infty - N = \frac{\mu}{\beta} \ln \left(\frac{S_\infty}{S_0} \right)$$

$$S(R) = S_0 e^{-\frac{\beta}{\mu} R}$$

Curso temporal de S, I y R



¿En qué condiciones se alcanzan los puntos de inflexión?

- Ejercicio: Considerando las expresiones de las derivadas de S, I y R, y analizando sus derivadas segundas, encuentre las condiciones en las que estas variables tienen un punto de inflexión.

- Solución:

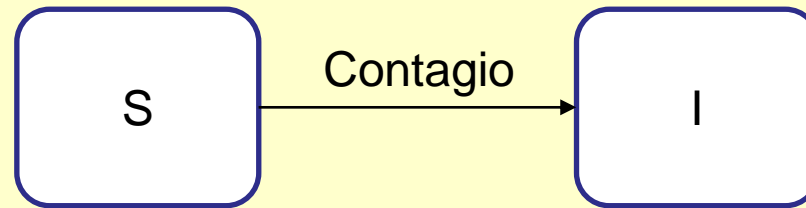
S(t) tiene un punto de inflexión cuando $S = \frac{\mu}{\beta} + I$

I(t) tiene un punto de inflexión cuando $I = \frac{(S - \frac{\mu}{\beta})^2}{S}$

R(t) tiene un punto de inflexión donde cuando $S = \frac{\mu}{\beta}$

Otros modelos epidemiológicos

Modelo SI

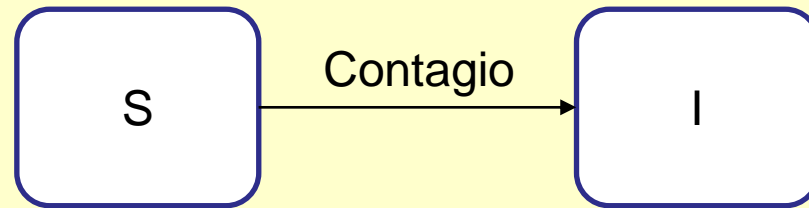


$$\frac{dS}{dt} = -\beta SI$$
$$\frac{dI}{dt} = \beta SI$$

$$N = S + I$$

Sistema de ecuaciones diferenciales: en este caso tenemos dos ecuaciones diferenciales con dos variables.

Modelo SI



$$\frac{dI}{dt} = \beta SI$$

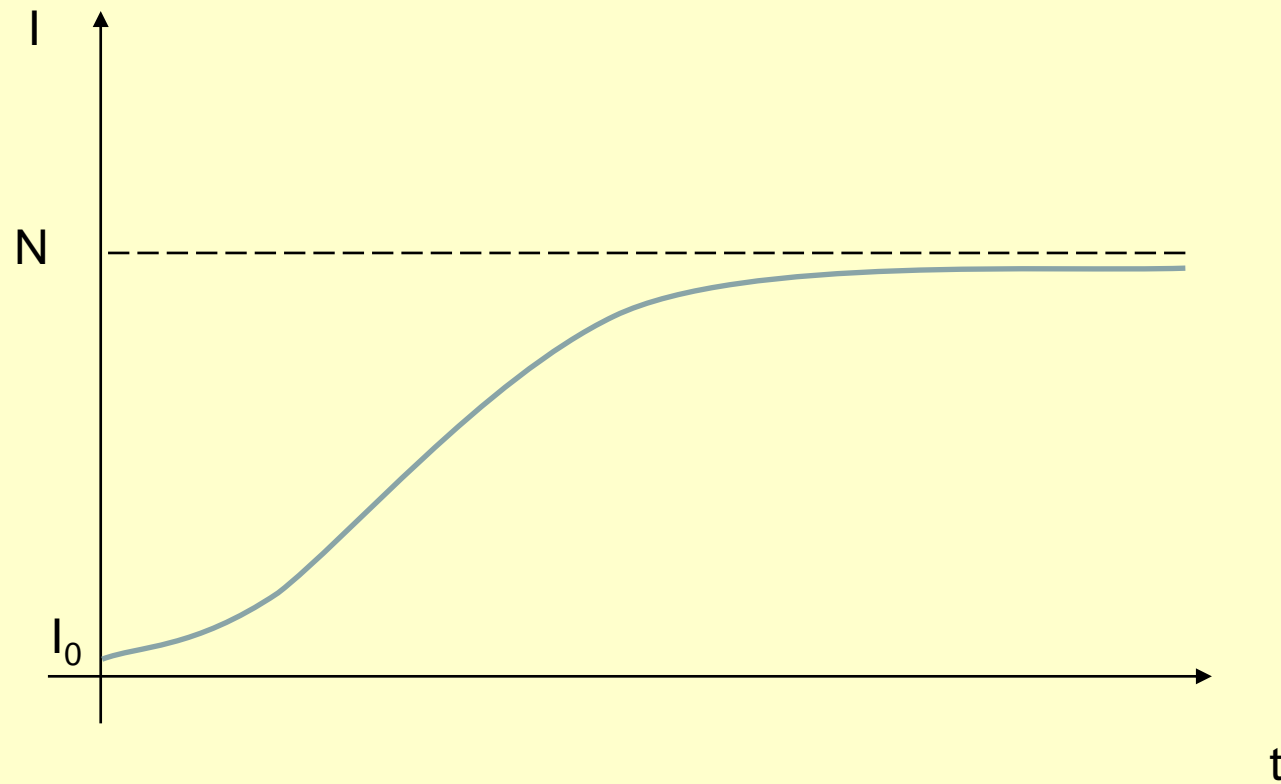
Recordando que $S+I=N \Rightarrow S=N-I$

Entonces:

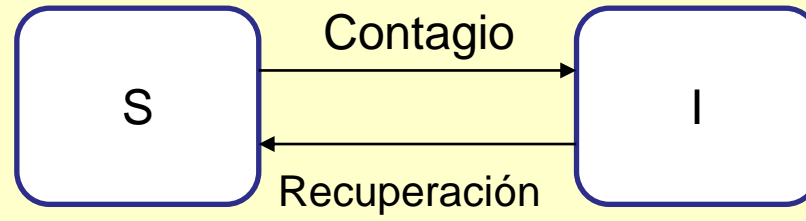
$$\frac{dI}{dt} = \beta I(N - I)$$

La ley de conservación nos permite obtener un sistema con una única variable.

Curso temporal de I



Modelo SIS



$$\frac{dS}{dt} = -\beta SI + \mu I$$
$$\frac{dI}{dt} = \beta SI - \mu I$$

$$N = S + I$$

El modelo SIS también es un modelo de tipo logístico

$$\frac{dI}{dt} = \beta SI - \mu I = I(\beta S - \mu)$$

Ahora usamos la ley de conservación $N=S+I$

$$\frac{dI}{dt} = I(\beta S - \mu) = I(\beta(N - I) - \mu)$$

$$\frac{dI}{dt} = I(\beta N - \beta I - \mu)$$

$$\frac{dI}{dt} = \beta I \left(N - \frac{\mu}{\beta} - I \right)$$

Curso temporal de I

