Dynamique et Evolution des Pathogènes :
Epidémiologie évolutive

Minus van Baalen

Equipe Mathématique Eco-Evolutive
IBENS, Paris

IHÉS, Bures-sur-Yvette

Maladies transmissibles

- Cause majeure de mortalité
  - paludisme, tuberculose, VIH
- Autres coûts
  - « morbidité »
  - reduction de la fértilité
- Epidémiologie : comprendre & prédire

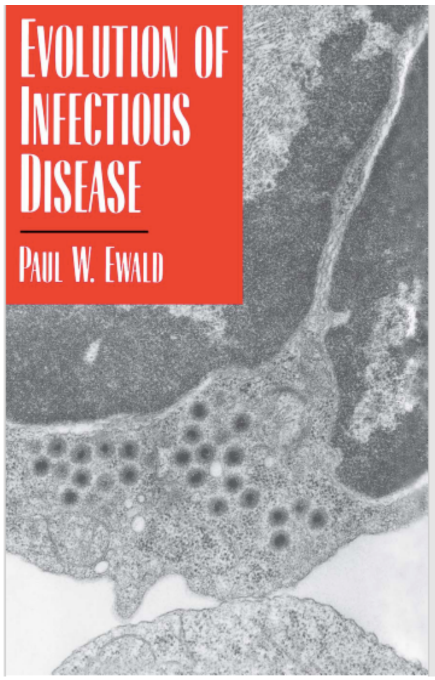
Epidémiologie

- Quelles maladies peuvent envahir ?
- Quel type de dynamique ?
  - maladies épidémiques
  - maladies endémiques
- Qu'est-ce que on peut faire contre ?
  - établir aspects clés
  - vaccination, quarantaine, *etc.*

(Anderson & May 1991)

Evolution

- Les parasites évoluent !
- Déjà adaptés aux défences naturelles de l'hôte
  – Resistance
  – Immunité
- Intervention humaine qu'une facteur de plus
- Conséquences évolutives ?
  – Ewald 1994



Virulent TB in South Africa May Imperil Millions
By MICHAEL WINES
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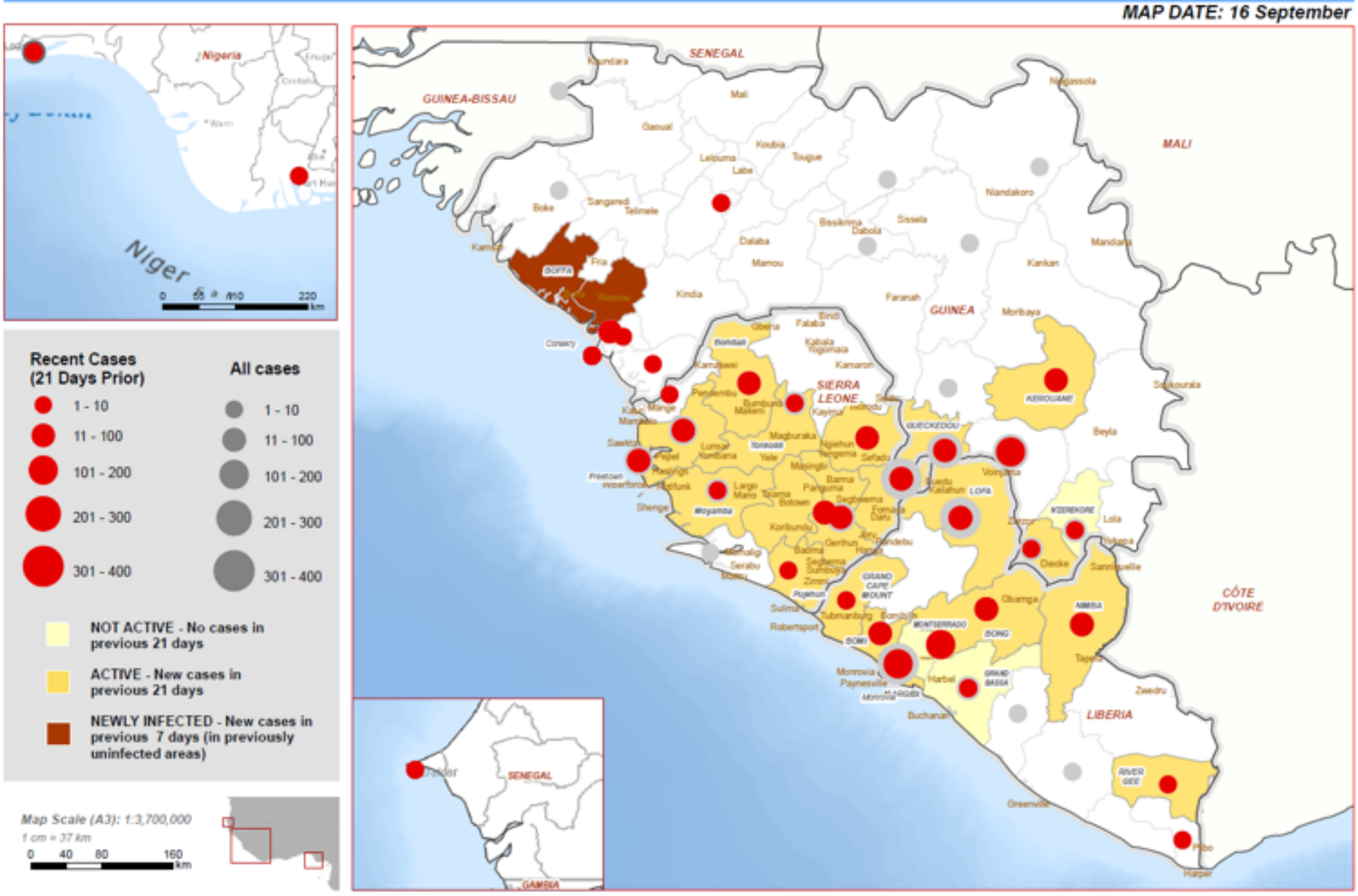
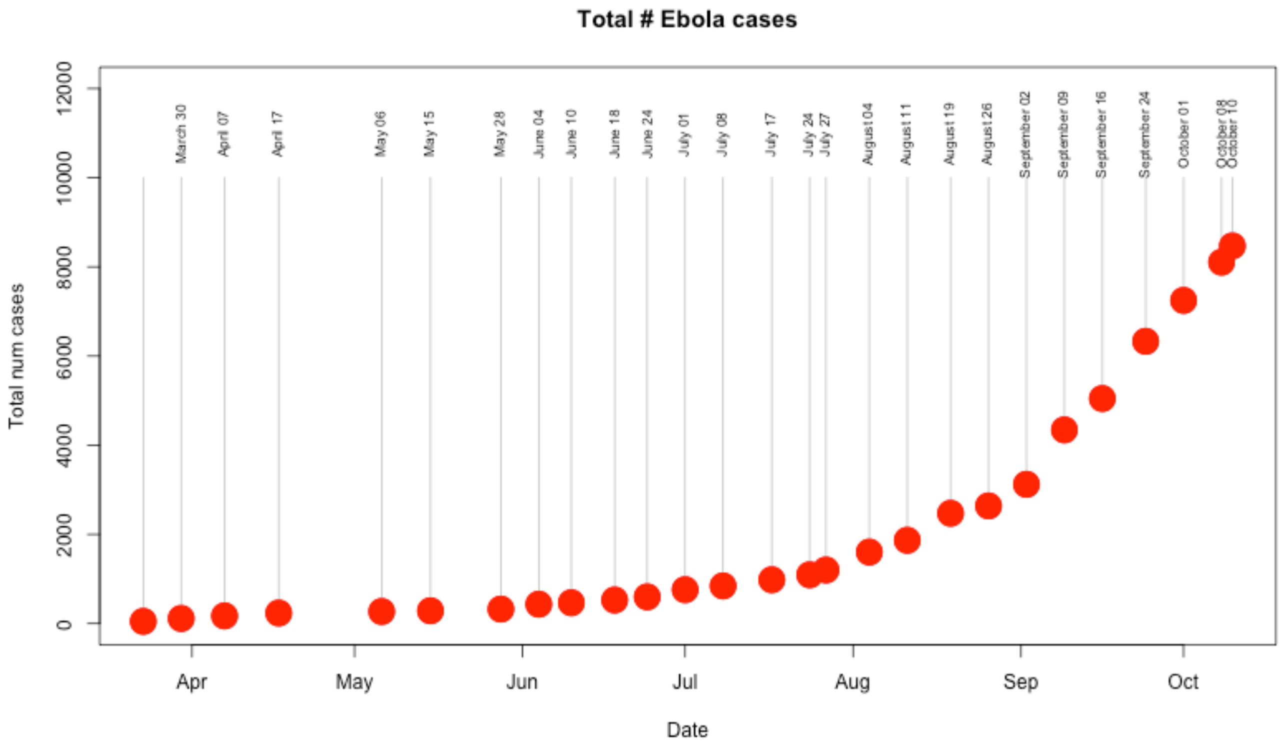
EBOLA OUTBREAK RESPONSE: REGIONAL CONFIRMED AND PROBABLE CASES

World Health Organization

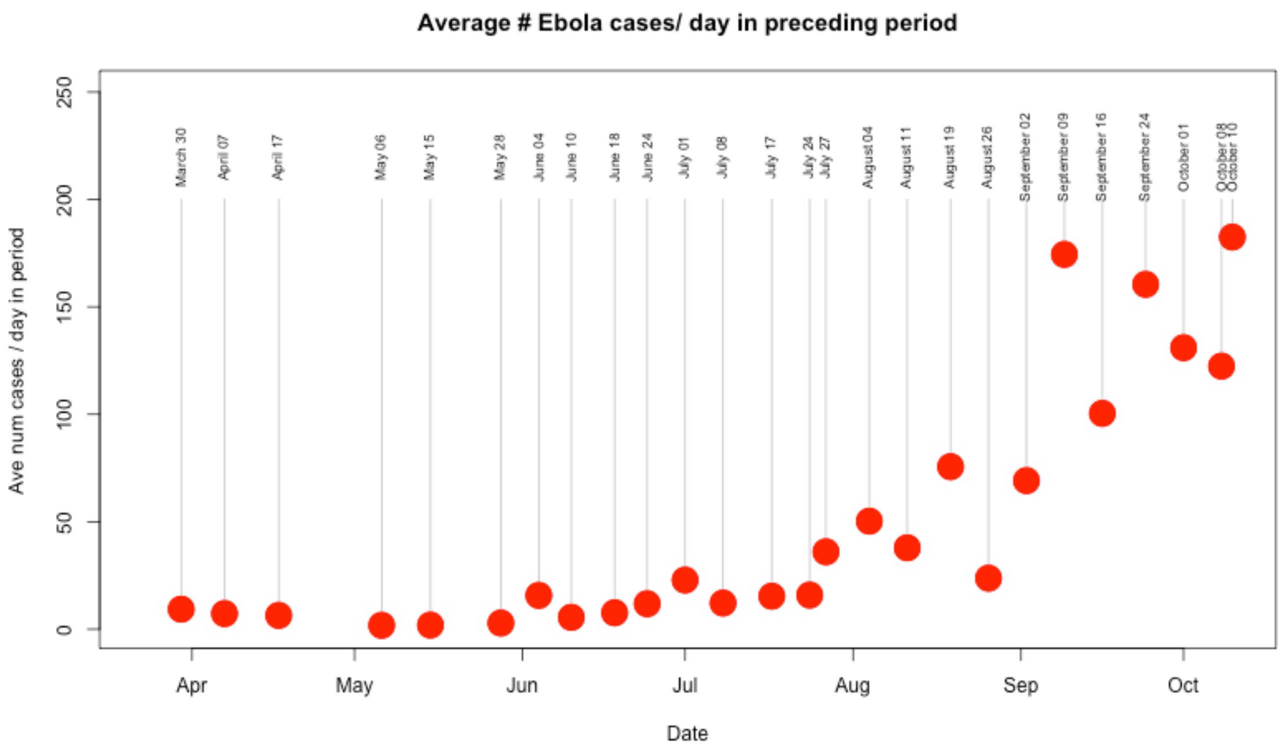
MAP DATE: 16 September



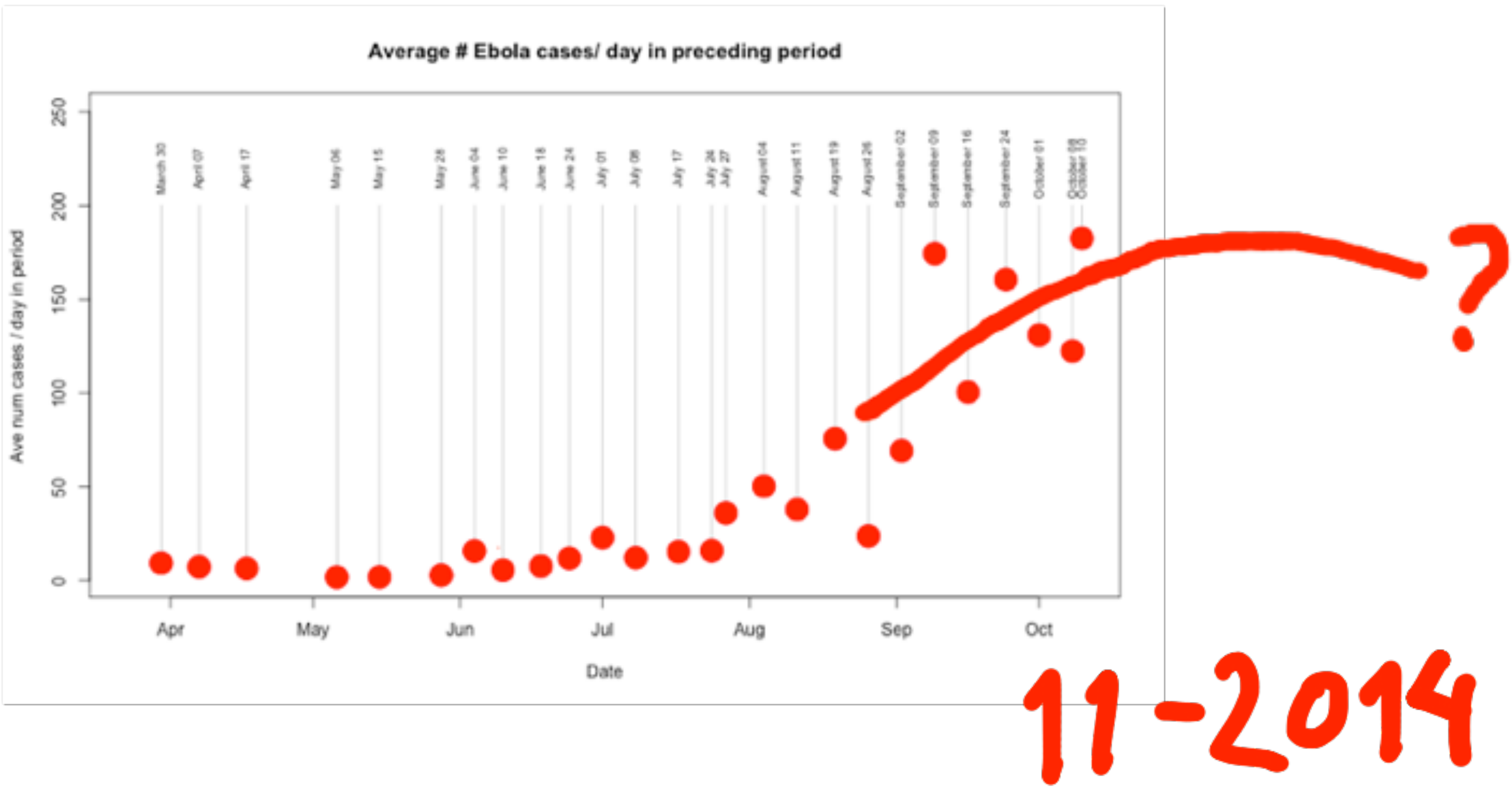
Ebola: reported cases



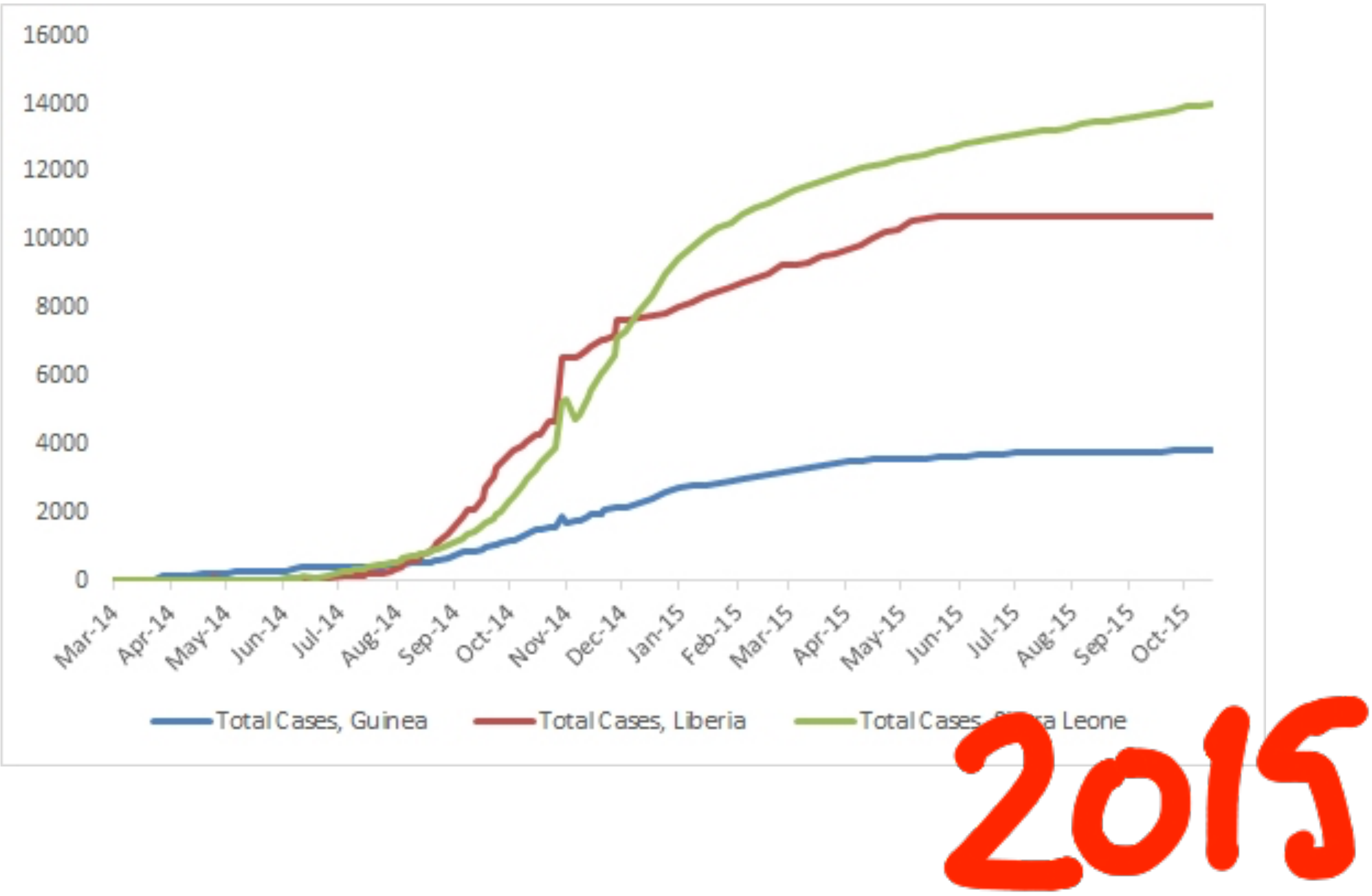
Ebola: cases *per time unit*



Ebola: cases *per time unit*

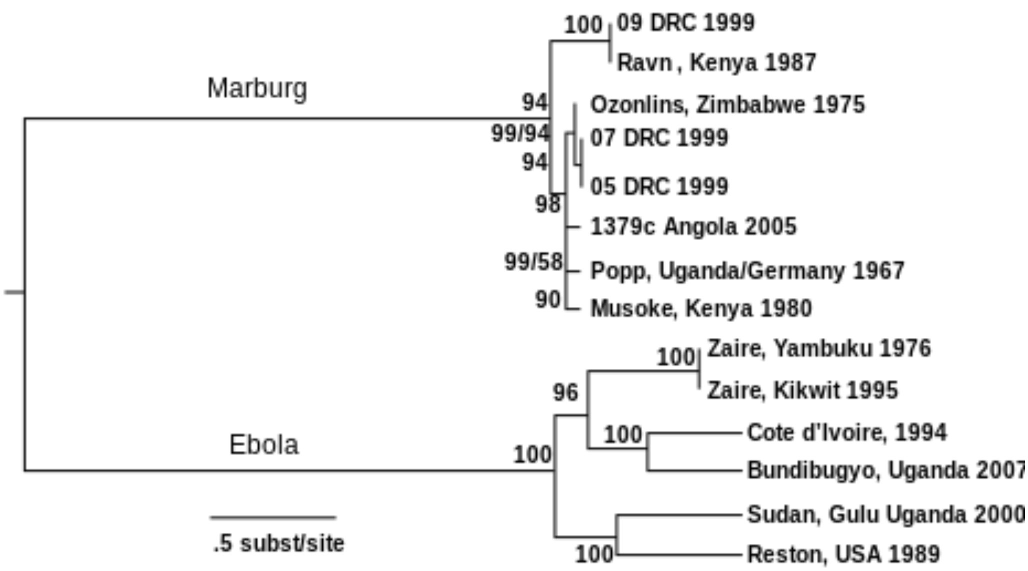


Ebola: cumulative cases



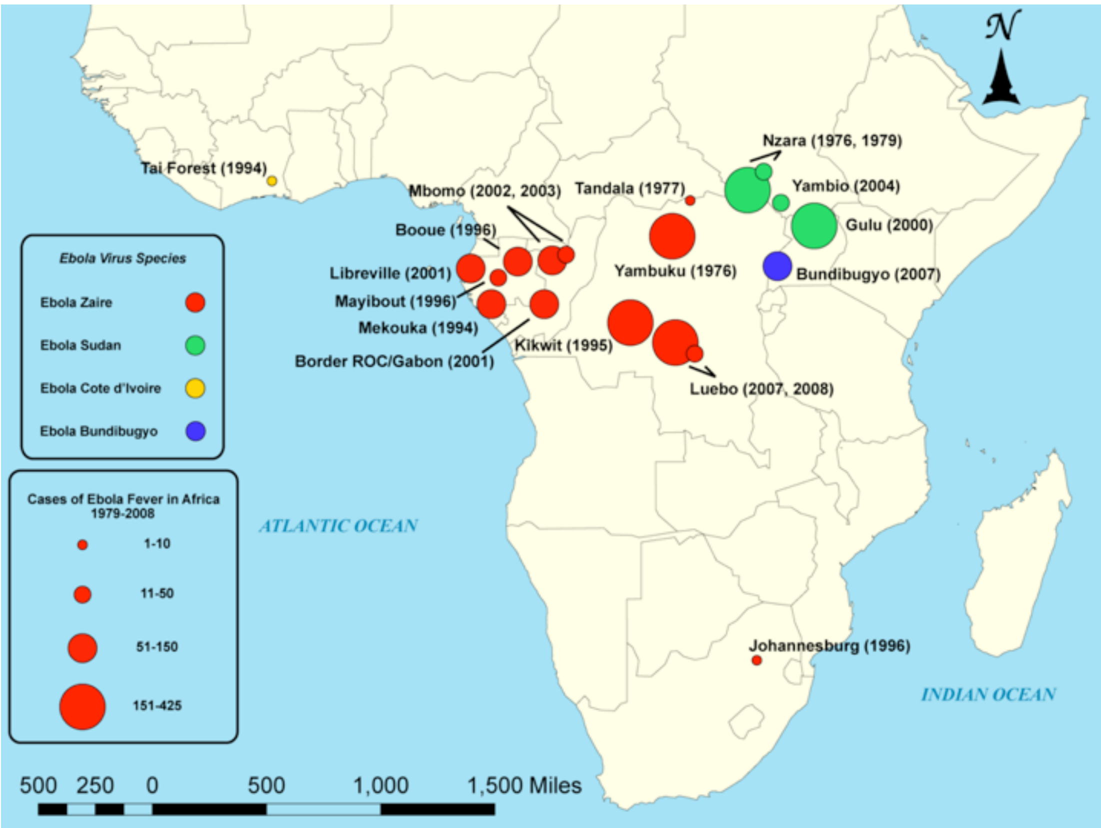

AP Photo/Jerome Delay

Ebola is evolving



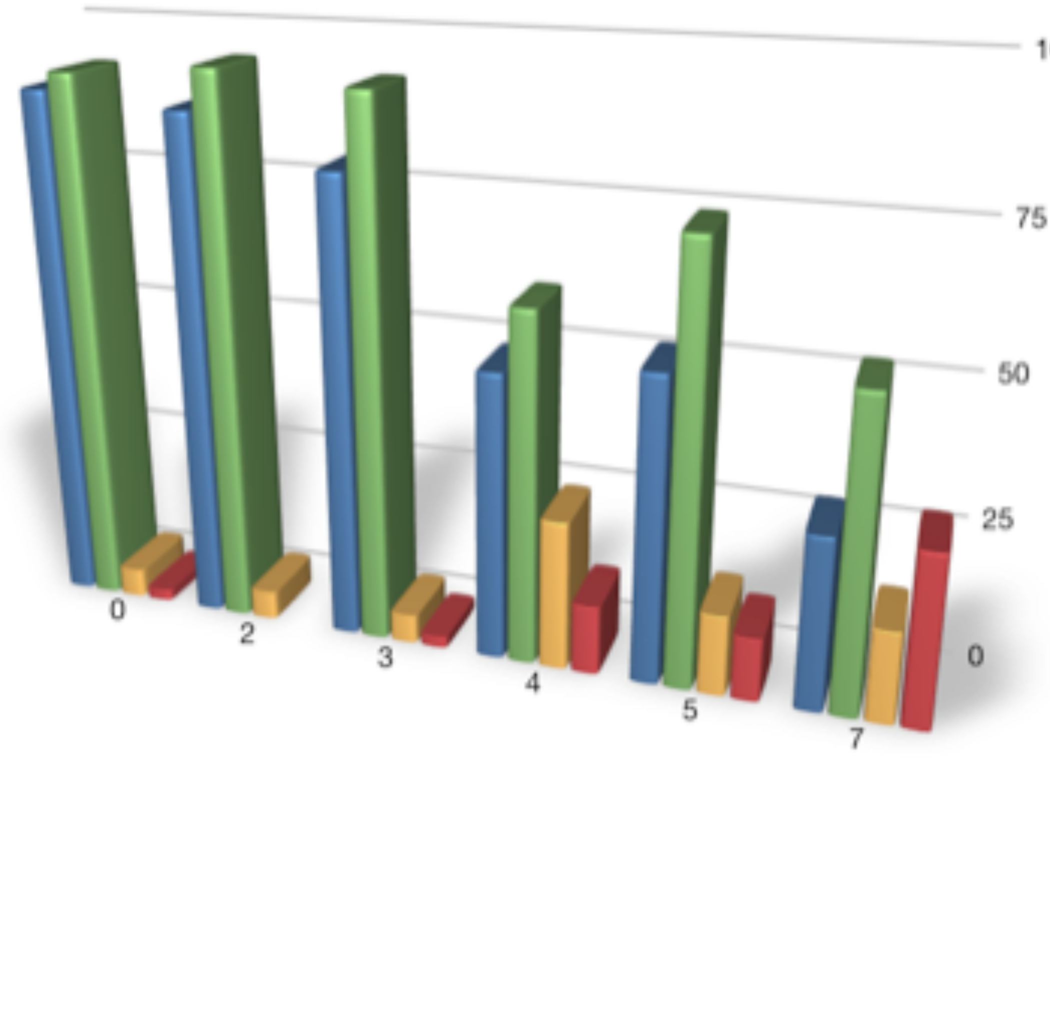
Wikipedia

Ebola evolution: consequences?

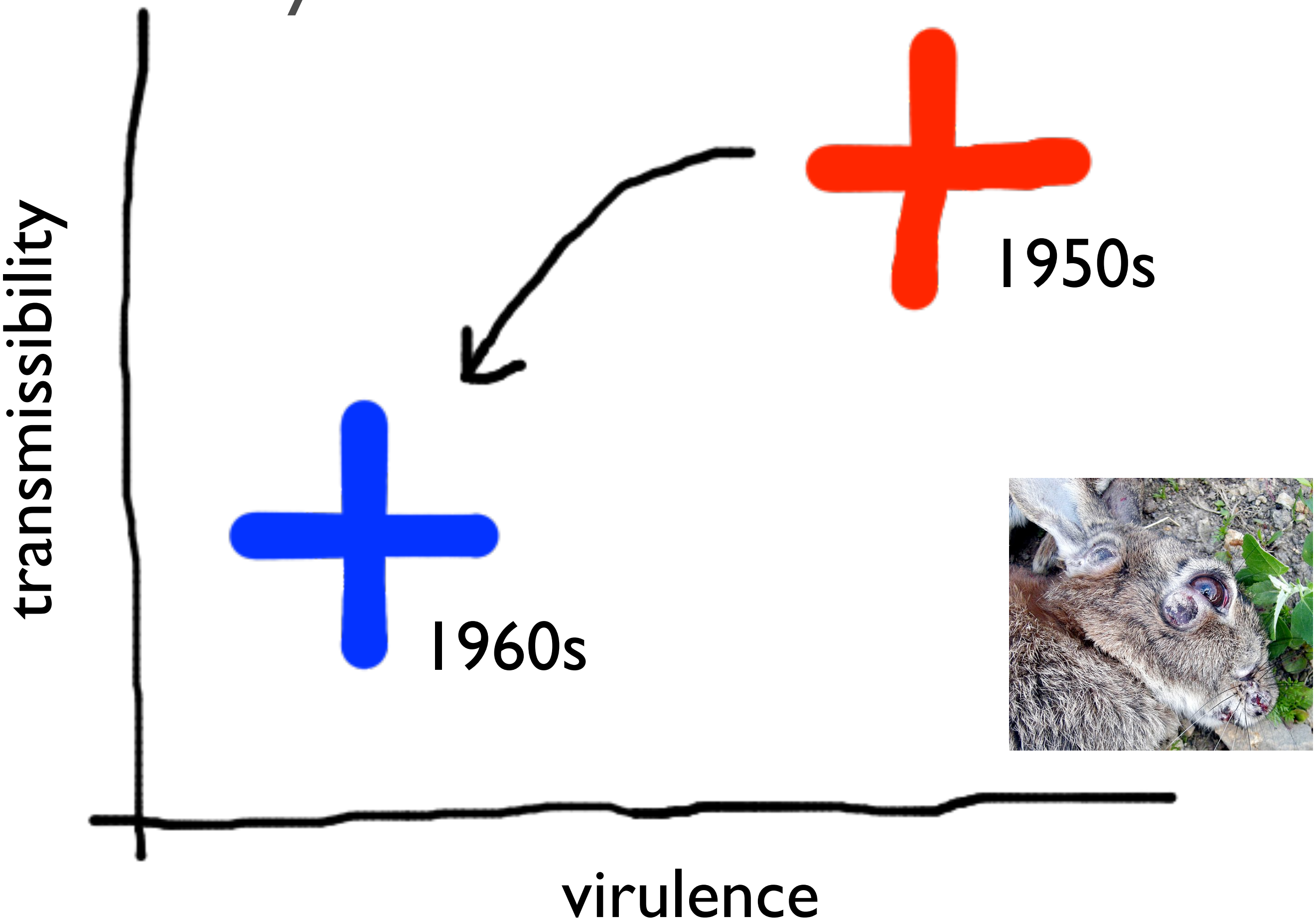


Wikipedia

Myxomatosis in rabbits



Myxomatosis in Australia



Evolutionary Theory in a Nutshell

‘Fitness is maximised’

OK. But by whom or what ?

Levels of organisation

ecosystem

biodiversity, nutrient cycles

population

competition, predation, epidemiology, social interactions

individual

birth, death, development, behaviour

within-individual

physiology, learning, infection, immune response

Host-Virus Interactions

Epidémiologie

$$\frac{dS}{dt} = [\text{host reproduction}] - \mu S - \beta SI$$

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

Individu
↓
Population

β paramètre de transmission
μ mortalité de base
α mortalité induite, virulence

Virulence

- augmentation mortalité par le parasite
  - variation considérable
    - + Ebola virus : 0.5 day^{-1}
    - + Influenza : 0.05 – 0.005 day^{-1}
    - + *Campilobacter* (estomac) : 0.00005 day^{-1}
    - + *Escherichia coli* : 0 – 0.05 day^{-1}

- « morbidité, » stérilisation
  - pas considérés ici

Taux de reproduction de base

Population sans parasites en équilibre

$$[\text{host reproduction}] = \mu \bar{S}$$

Parasite envahit si

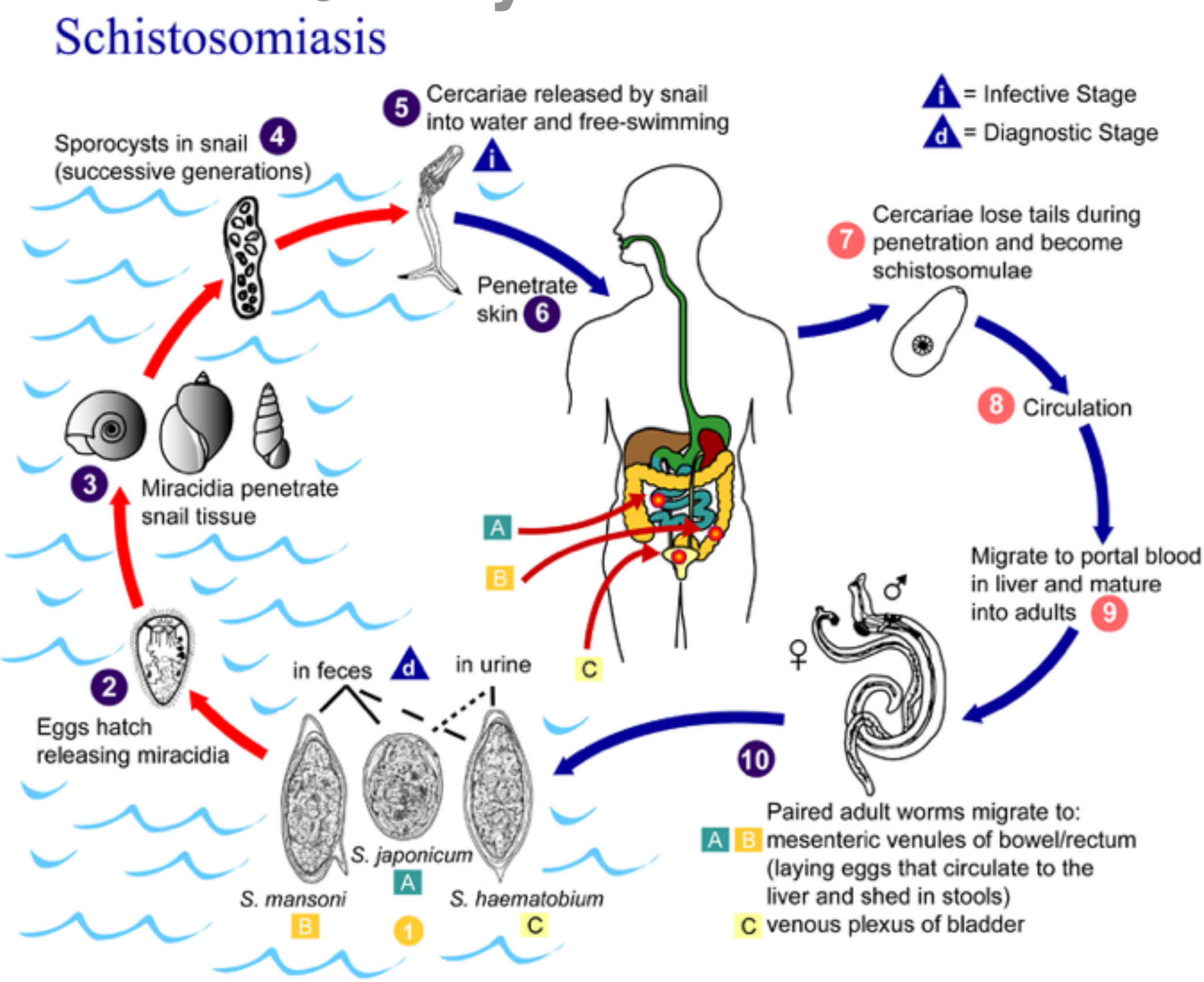
$$\beta \bar{S} > \mu + \alpha$$

$$\frac{\beta \bar{S}}{\mu + \alpha} > 1$$

$$R_0 > 1$$

Taux de reproduction de base

R_0 easy to calculate?



« Dynamique adaptative »

- théorie des jeux dans un cadre écologique
- pour deriver la valeur sélective (fitness)
  - + en lieu de simplement *supposer* l'expression
- pour predire la réponse evolutive
  - + stratégies evolutivement stable
  - + branchement évolutif

Articles par Metz, Kisdi, Geritz, Law, Rand, Dieckmann…

Epidémiologie + Evolution

$$\frac{dS}{dt} = [\text{host reproduction}] - \mu S - \beta SI - \beta^* SJ$$

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

$$\frac{dJ}{dt} = \beta^* SJ - (\mu + \alpha^*)J$$

I souche residente, J souche mutante

L'invasion des mutants

- Resident *I* en équilibre endemique

  $$dI/dt = 0$$

- Le mutant *J* envahit si

  $$dJ/dt > 0$$

  (quand il est rare, *J* << *I*)

- Invasion si

  $$\frac{\beta^* \bar{S}}{\mu + \alpha^*} > 1$$

R_0

Epidémiologie + Evolution

$$\frac{dS}{dt} = [\text{host reproduction}] - \mu S - \beta SI - \beta^* SJ$$
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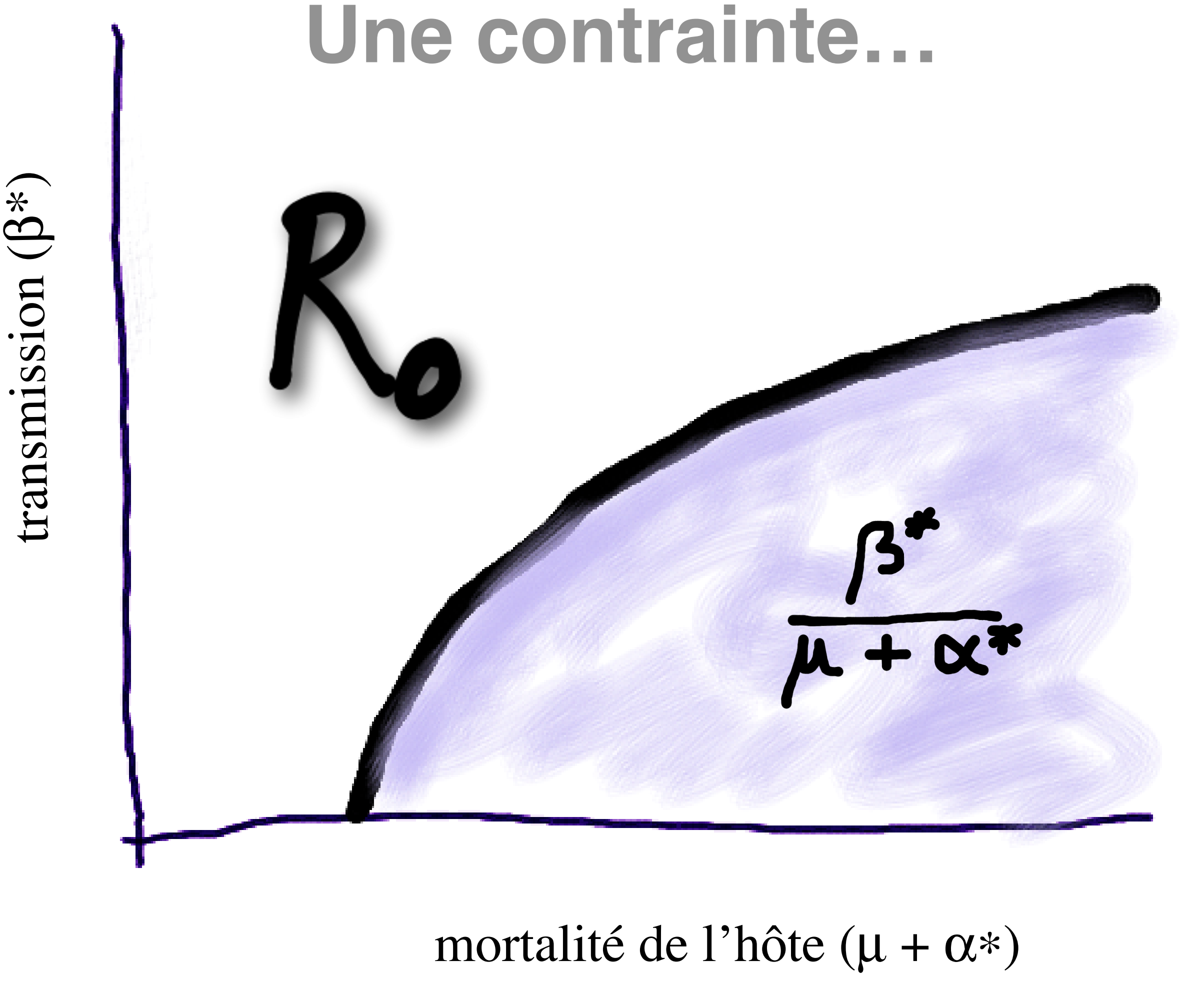
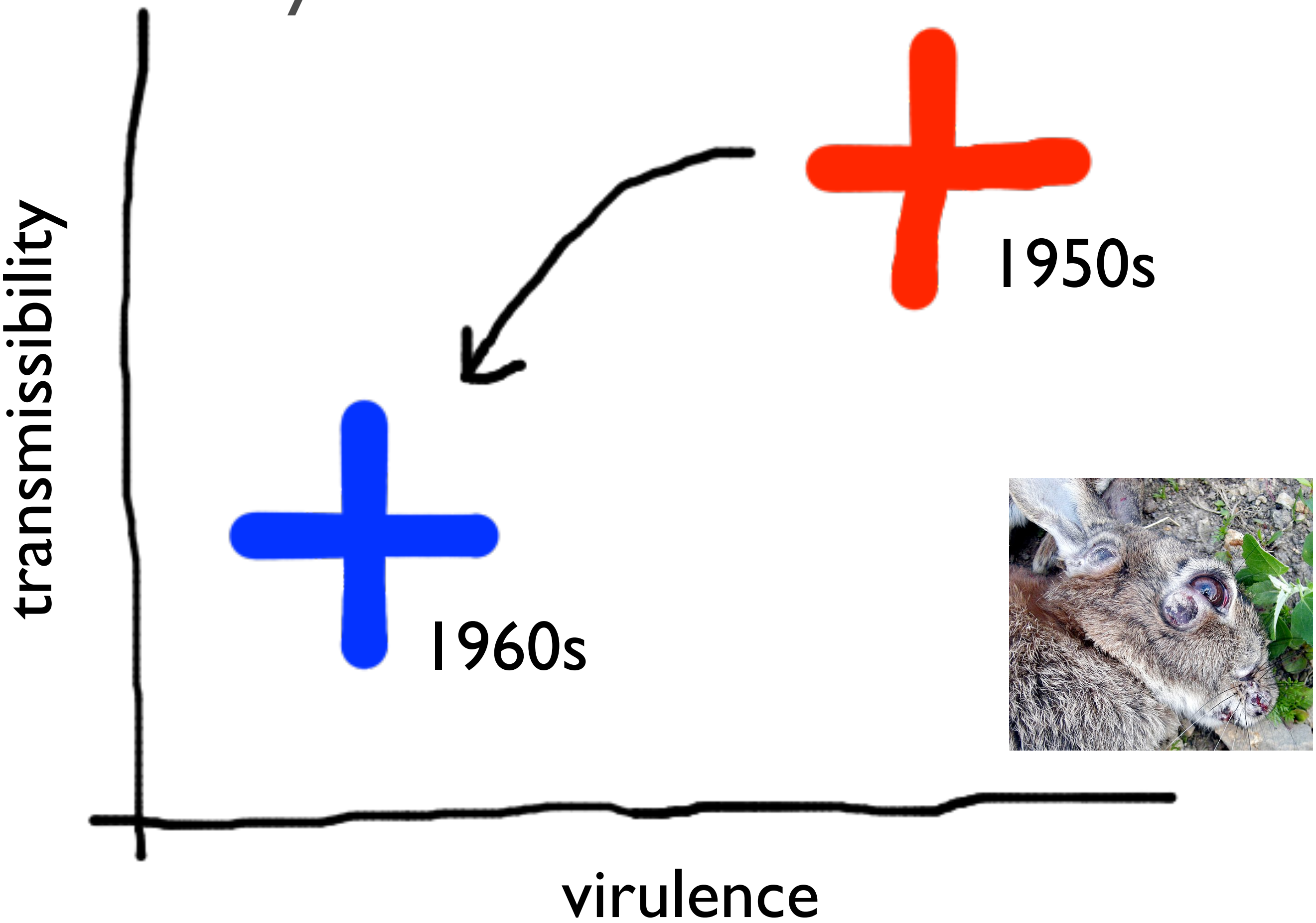
R_0

Une contrainte…



Myxomatosis in Australia



Levels of organisation

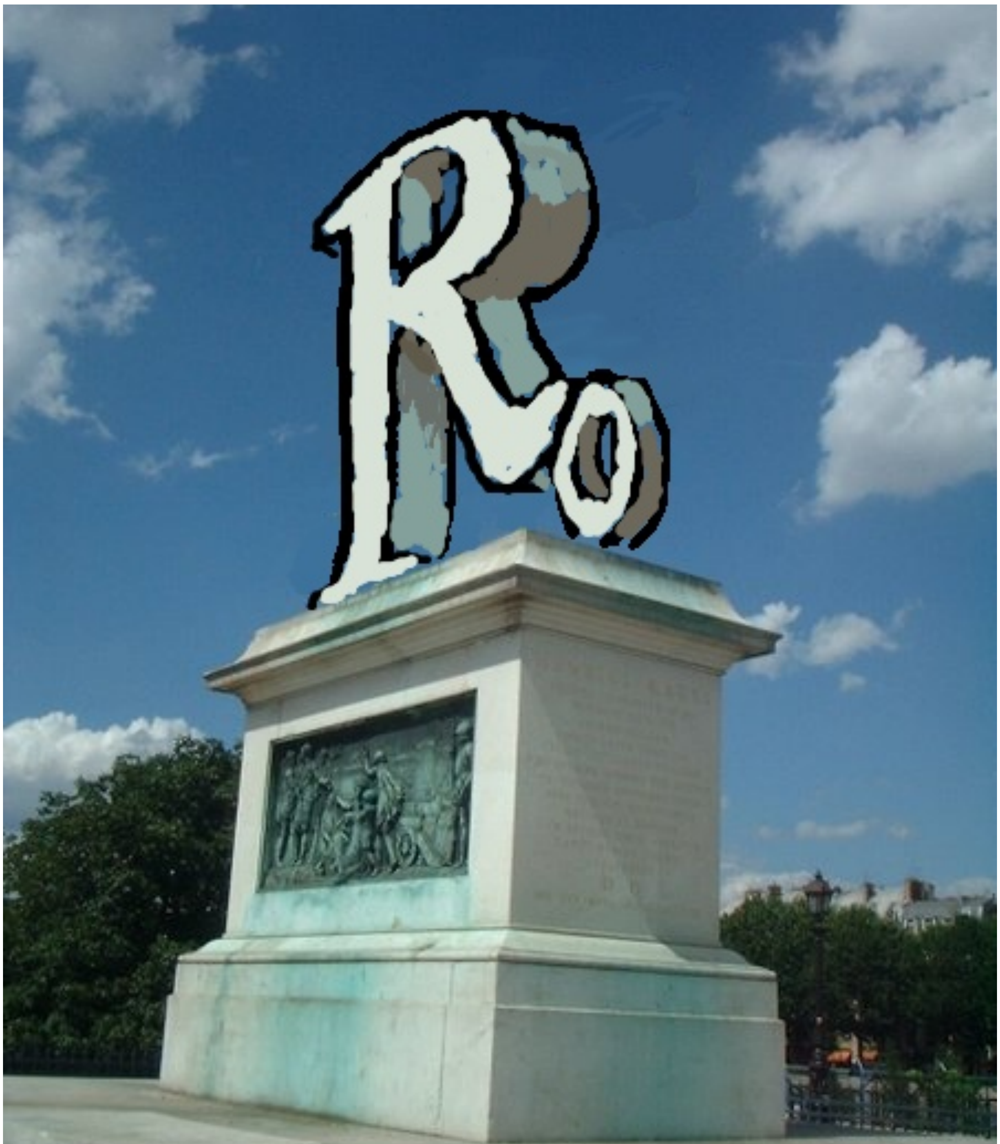
ecosystem
biodiversity, nutrient cycles

population
competition, predation, epidemiology, social interaction

R_0

individual
birth, death, development, behaviour

within-individual
physiology, infection, immune response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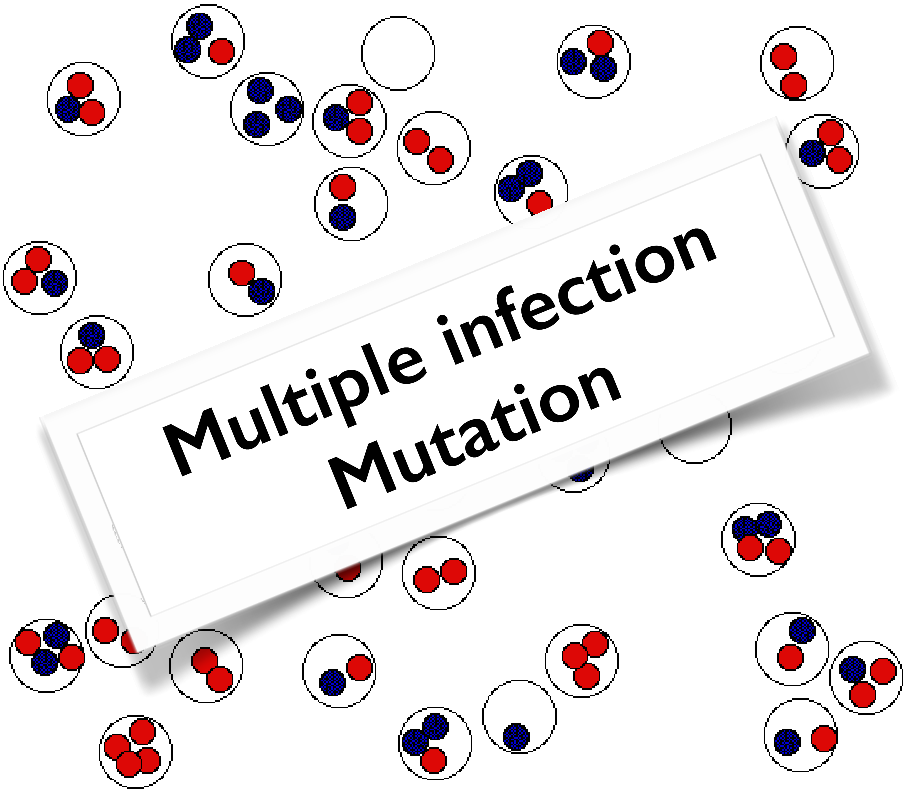
A Joyful Easter

Emergent fuzziness

Very often spatial and temporal boundaries of emerging entities are not clear-cut

Parasite heterogeneity



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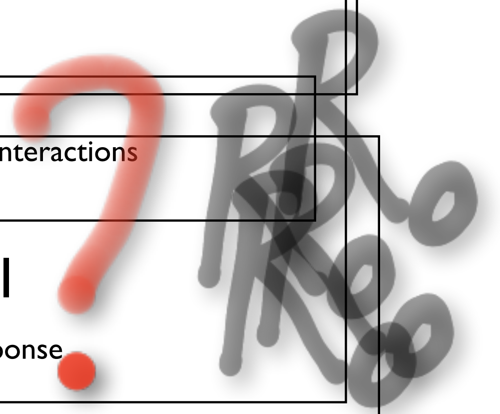


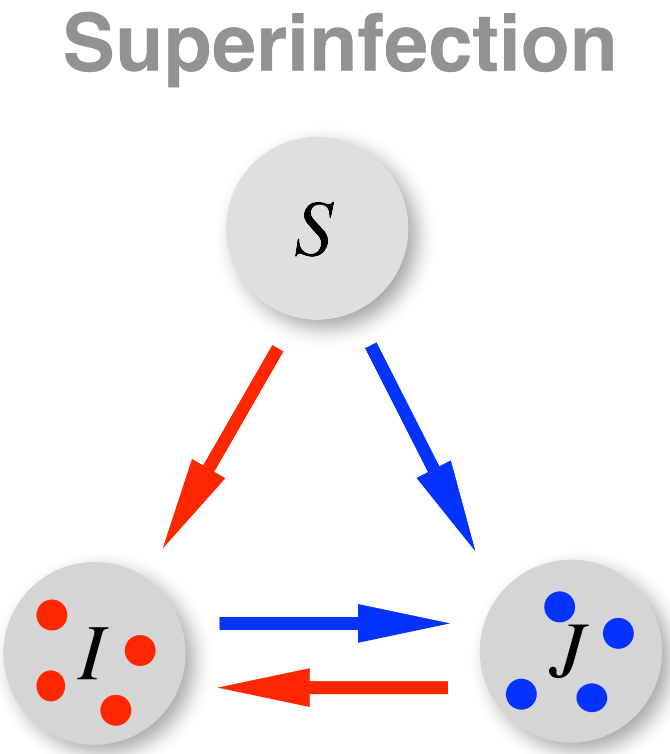

Ro
Apologies to
Daumier

Infections multiples

- parasites partagent leurs hôtes
- reduit transmission en long terme
- favorise transmission en court terme
- mène à une virulence augmentée
  - Eshel 1977
  - Levin & Pimentel 1981
  - Nowak & May 1994
  - van Baalen & Sabelis 1995

Modèles compétition intra-hôte

- Superinfection
  - la souche la plus virulente remplace les autres
    - (Levin & Pimentel 1981, Nowak & May 1994)
  - chaque souche a une chance de gagner
    - Gandon et al. 2001, 2002)
- Coinfection
  - les souches coexistent à l'intérieur de l'hôte
    - (Eshel 1977, van Baalen & Sabelis 1995)


Superinfection
S
I
J

E+E+Superinfection

$$\frac{dS}{dt} = [\text{host repr.}] - \mu S - \beta SI - \beta^* SJ$$

$$\frac{dI}{dt} = \beta SI - (\mu + \alpha)I \\ \qquad - \sigma(\alpha, \alpha^*)\beta^* JI + \sigma(\alpha^*, \alpha)\beta JI$$

$$\frac{dJ}{dt} = \beta^* SJ - (\mu + \alpha^*)J \\ \qquad + \sigma(\alpha, \alpha^*)\beta^* JI - \sigma(\alpha^*, \alpha)\beta JI$$

Superinfection

σ : Aggressivité intra-hôte

Invasion

le mutant envahit si

$$\frac{\beta^*\bar{S} + \sigma\beta^*\bar{I}}{\mu + \alpha^* + \sigma\beta\bar{I}} > 1$$

fitness ≠ taux de reproduction de base !

$$R_0 = \frac{\beta^*\bar{S}}{\mu + \alpha^*}$$

- virulence optimale maximise

$$\frac{\beta^* \bar{S} + \sigma\beta^* \bar{I}}{\mu + \alpha^* + \sigma\beta\bar{I}}$$

- en contraste avec cas simple, dépend de plein de choses
  - densité hôtes saines,
  - densité hôtes infectés (avec souche residente)
  - stratégie de la souche residente

Parasites

Typically have highly structured populations

- within-host
- among-host

in terms of

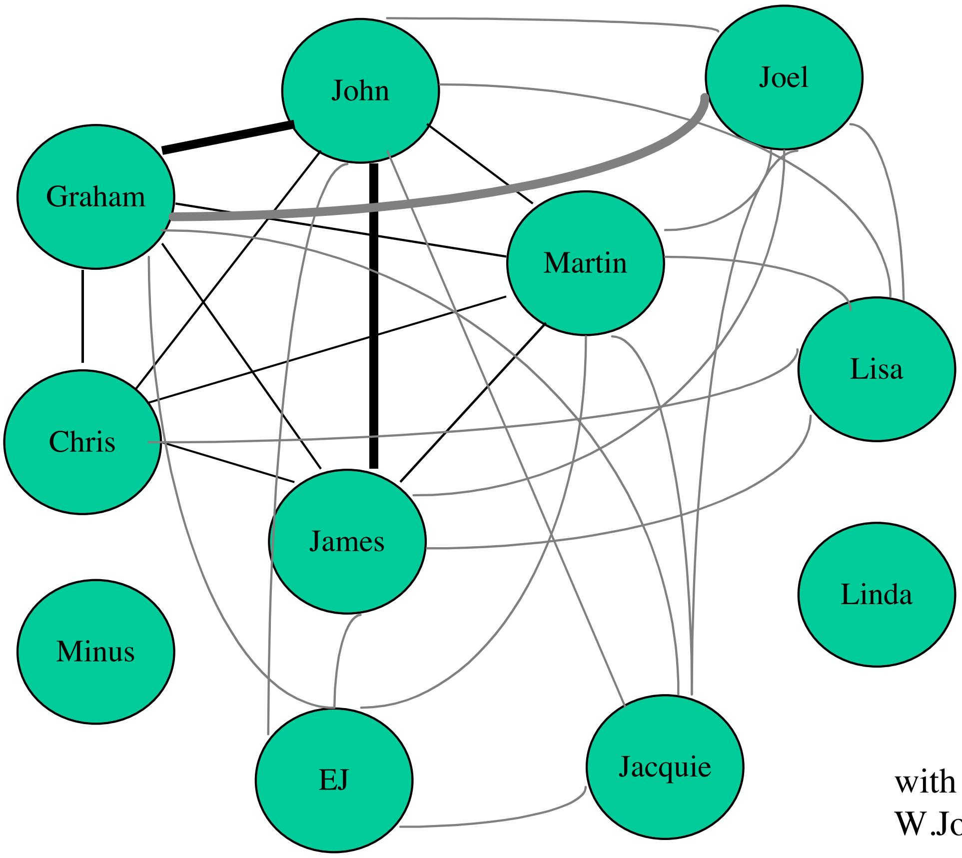
- dynamics
- genetics

Transmission

- βxy infections par unité de temps
- Proportionnel rencontres individus sains et infectés
- Double densité : 4 fois plus de rencontres ?!?
- Structure de contact

Network model:
are my friends' friends friends of mine?

14th October 1996,
University of Warwick



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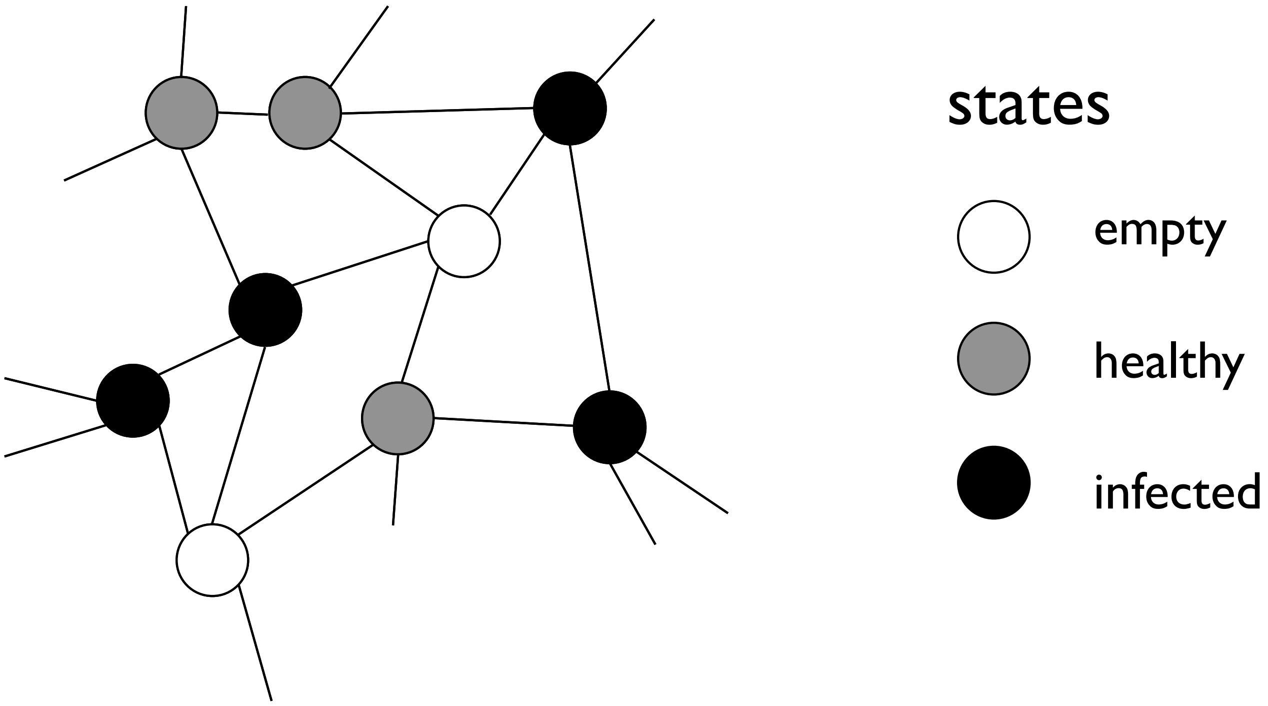
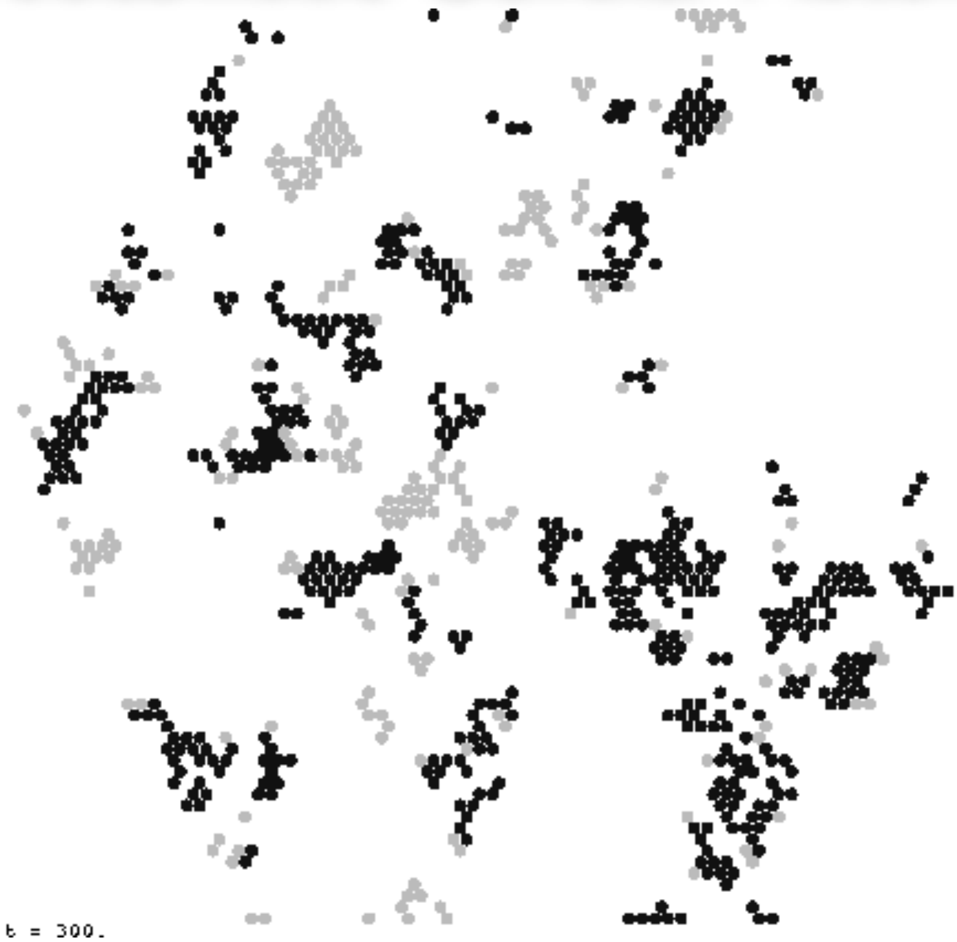
Probabilistic Cellular Automata

A lattice of sites



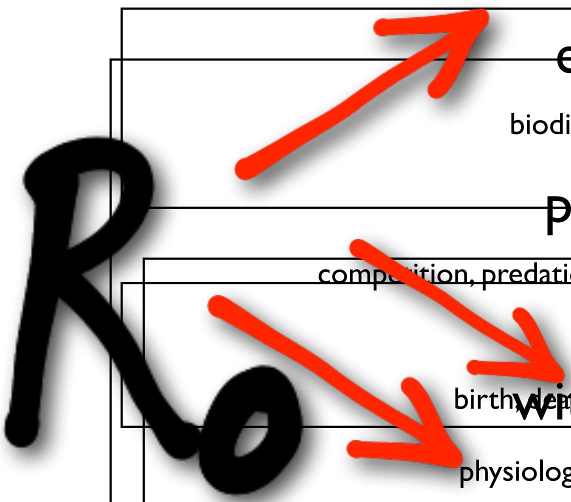
Probabilistic Cellular Automata



Probabilistic Cellular Automata

- \+ Nice toys
- \+ Colourful movies
- – Difficult to generalise
- – Difficult to test

Levels of organisation



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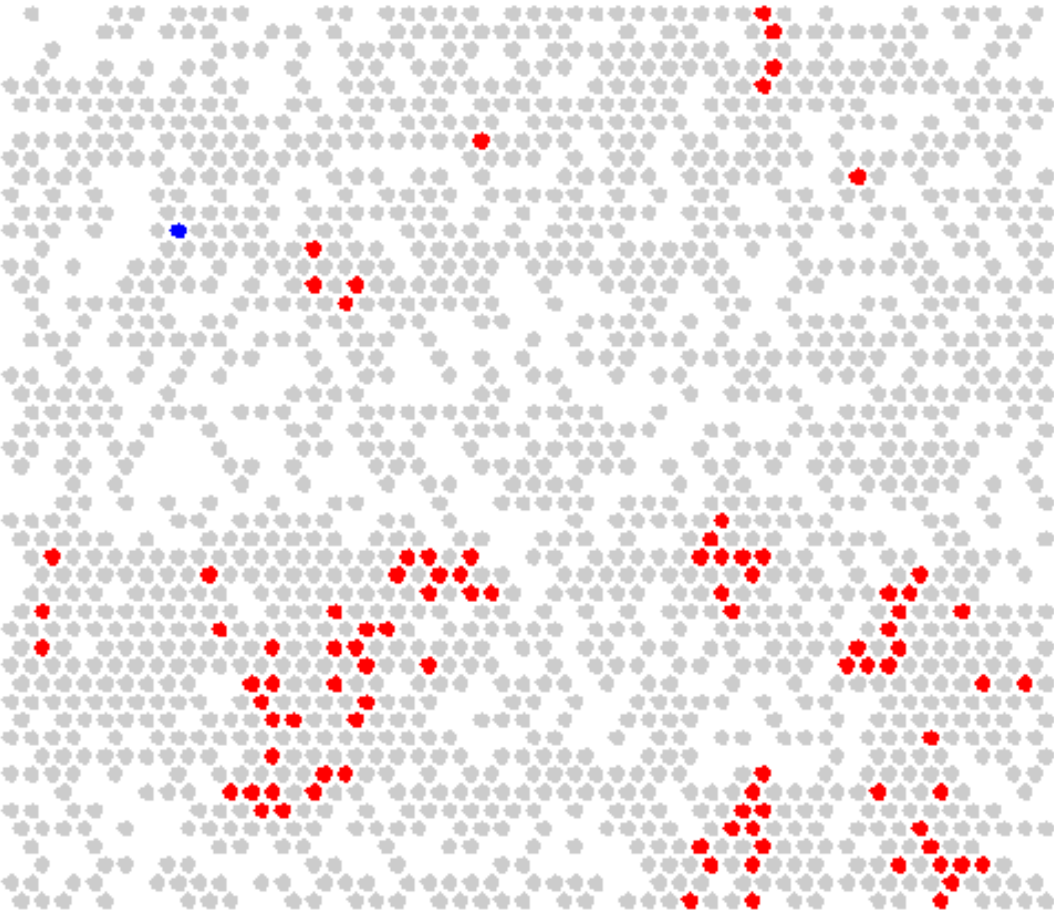
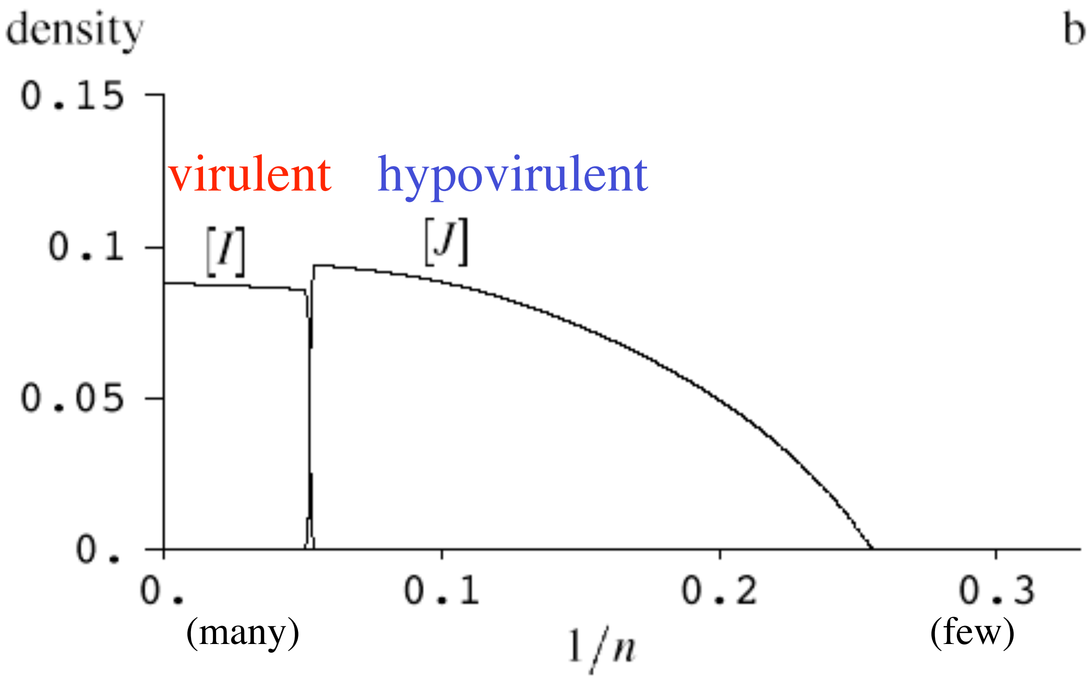


Regular lattice



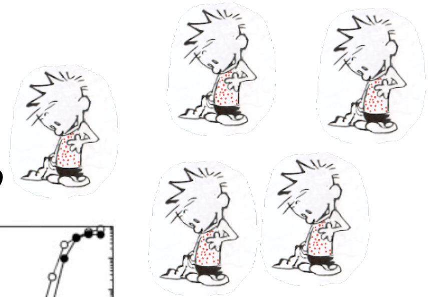
n: number of contacts

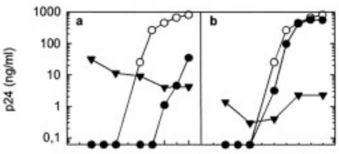
Parasites

Many candidate units of adaptation:

- A genetic strain?
- A quasispecies?
- An infection?
- A cluster of infections?
- A clone?
- An individual.

...ATTGCGAATATCCTCATAAGGCAC...
...ATTGCGAATATCCTCACAAGGCAC...
...ATTGCGAAAATCCTCATAAGGCAC...
...ATTGTGAATATCCTCATAAGGCAC...





Take-home messages

Whenever we talk of ‘the’ parasite or ‘the’ host, we should stop and reflect a minute about what we mean by it.

Units of adaptation exist but may be spread over different levels of organisation and difficult to characterise.

Apologies to Gustave Doré

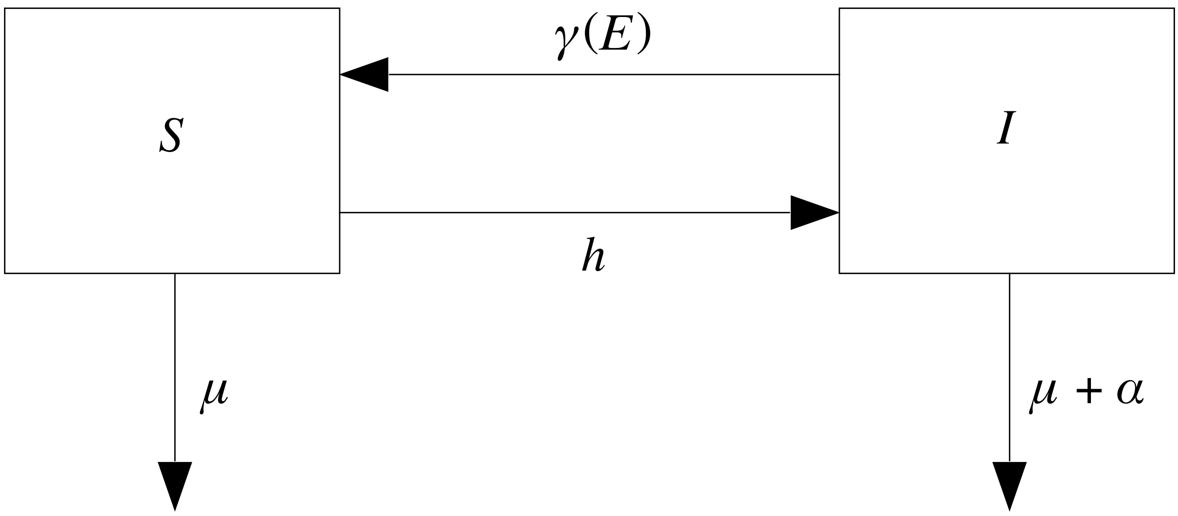


Figure 1. A simple *SIS* model for infection, in which a host can either be healthy and susceptible, or infected. The force of infection is h, recovery rate is $\gamma(E)$, background mortality rare is μ, disease-induced mortality rate is α.

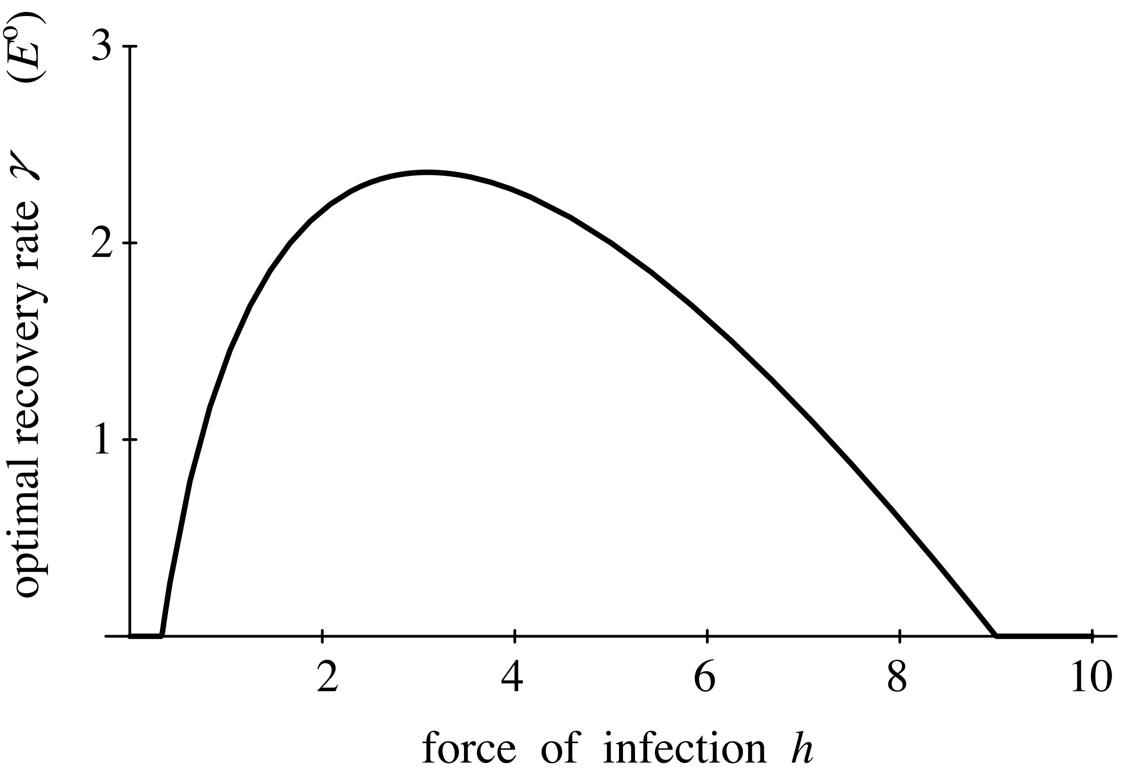
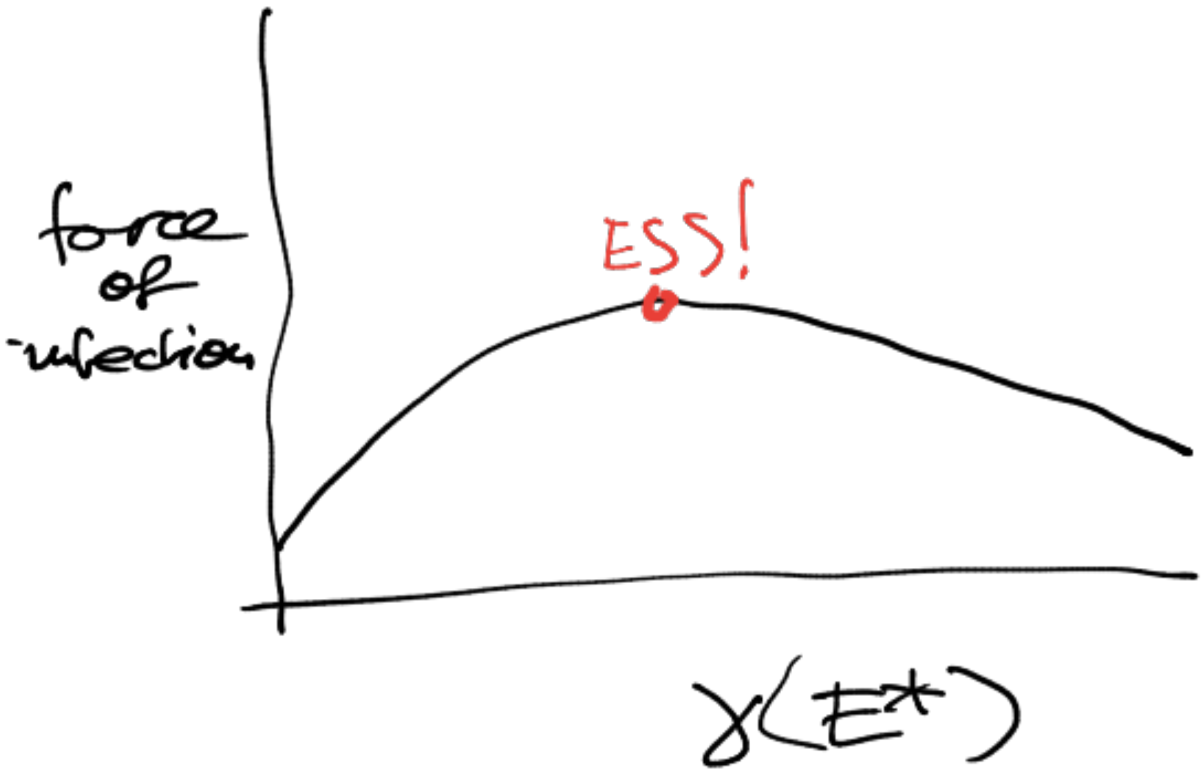


Figure 2. Optimal investment in recovery ability $\gamma(E)$, as a function of the force of infection h. (Parameter values: $\mu=1$, $\alpha=2$, $c=0.05$.)



E* : investissement moyen


AP Photo/Jerome Delay