

La visión de un bioquímico: Dinámica de los virus, desde el individuo infectado a la epidemia

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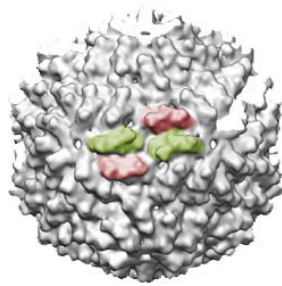


*Centro de Investigación Biomédica
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y Digestivas (CIBERehd), Barcelona*

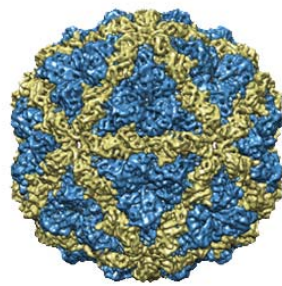


¿Qué son los virus?

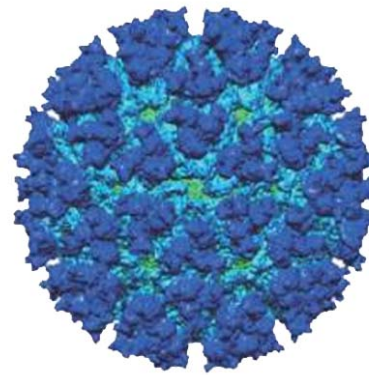
- *Partículas infecciosas transmisibles compuestas por una o más moléculas de ácido nucleico (el material genético), rodeadas de proteína y a veces, además, de lípidos y azúcares*
- *Solamente se multiplican dentro de una célula*
- *Tienen dos de las propiedades características de la vida: replicación y capacidad de evolución. Las otras son metabolismo y compartimentación*



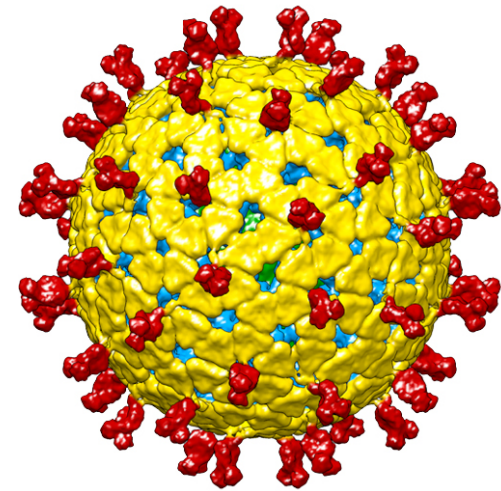
L-Av



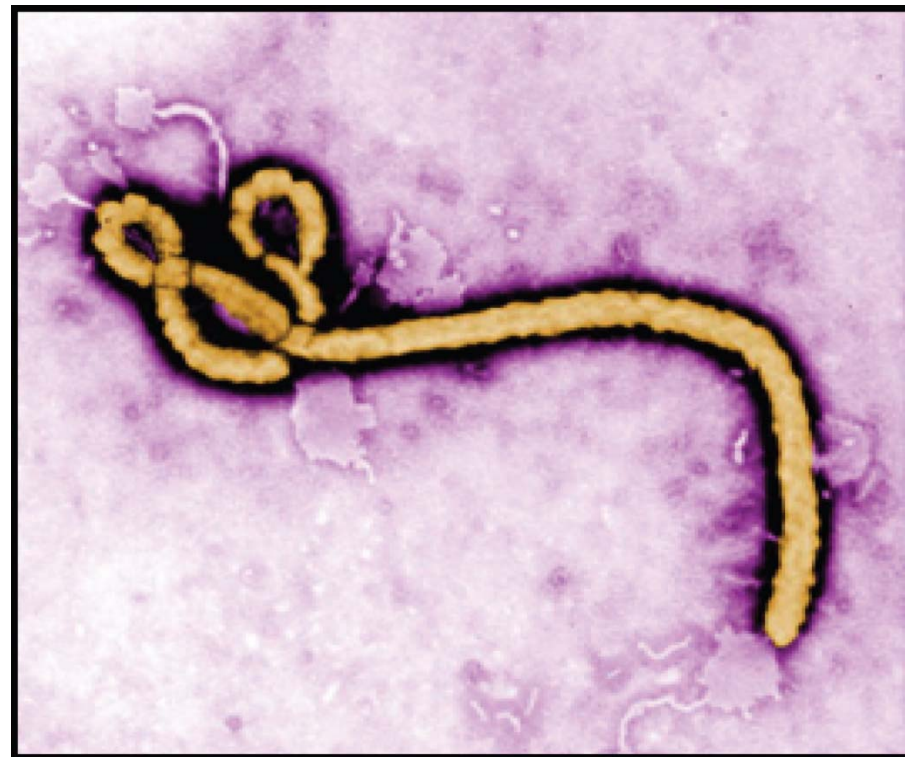
PcV



SINV



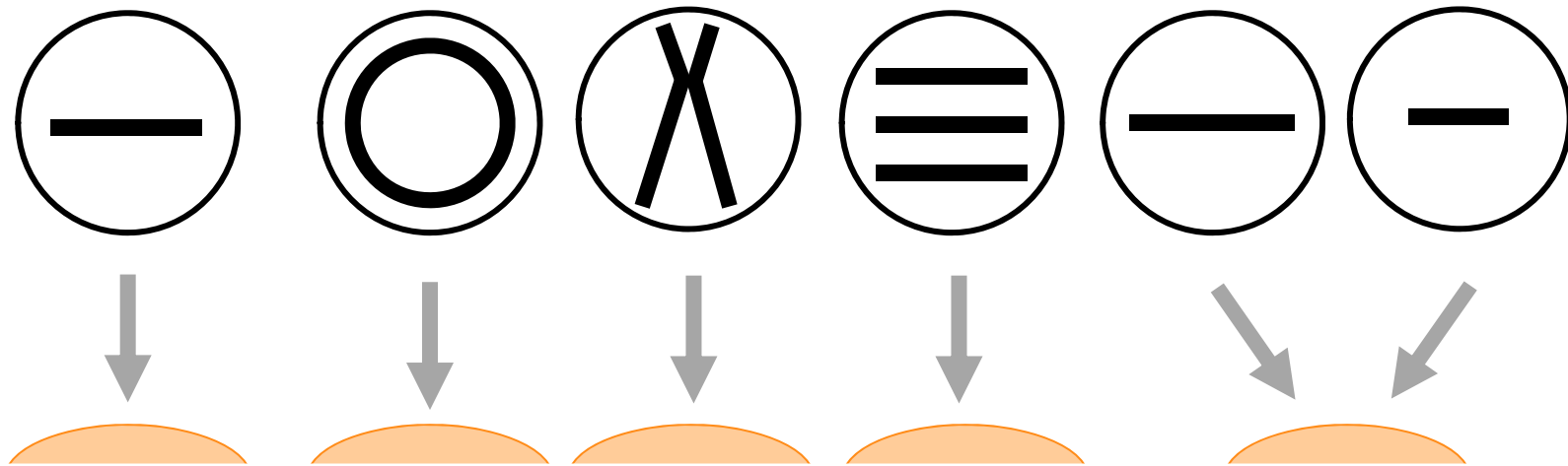
RV



Ebola

20 nm

Virus diversity and abundance



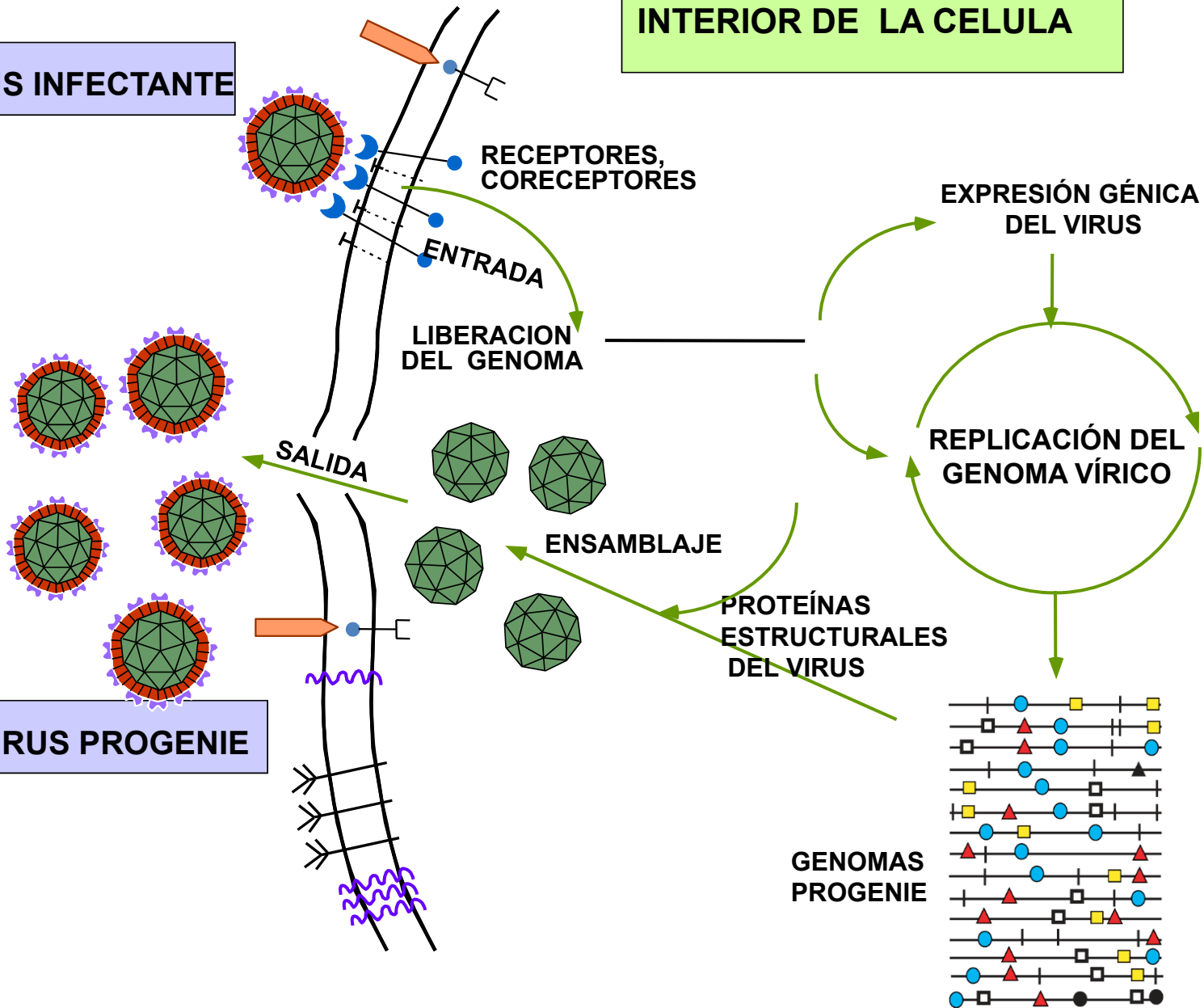
- *10^8 virus particles in 1 ml sea water*
- *$10^{31} - 10^{32}$ virus particles in the biosphere (200 million tons of C)*
- *10 times more virus particles than cells*
- *10^{23} infections per second; 1-10 min to copy a viral genome*
- *An infected organism may contain 10^{10} to 10^{12} infectious particles at any given time*

Domingo, E. Virus as Populations, 2nd ed. Elsevier, 2020

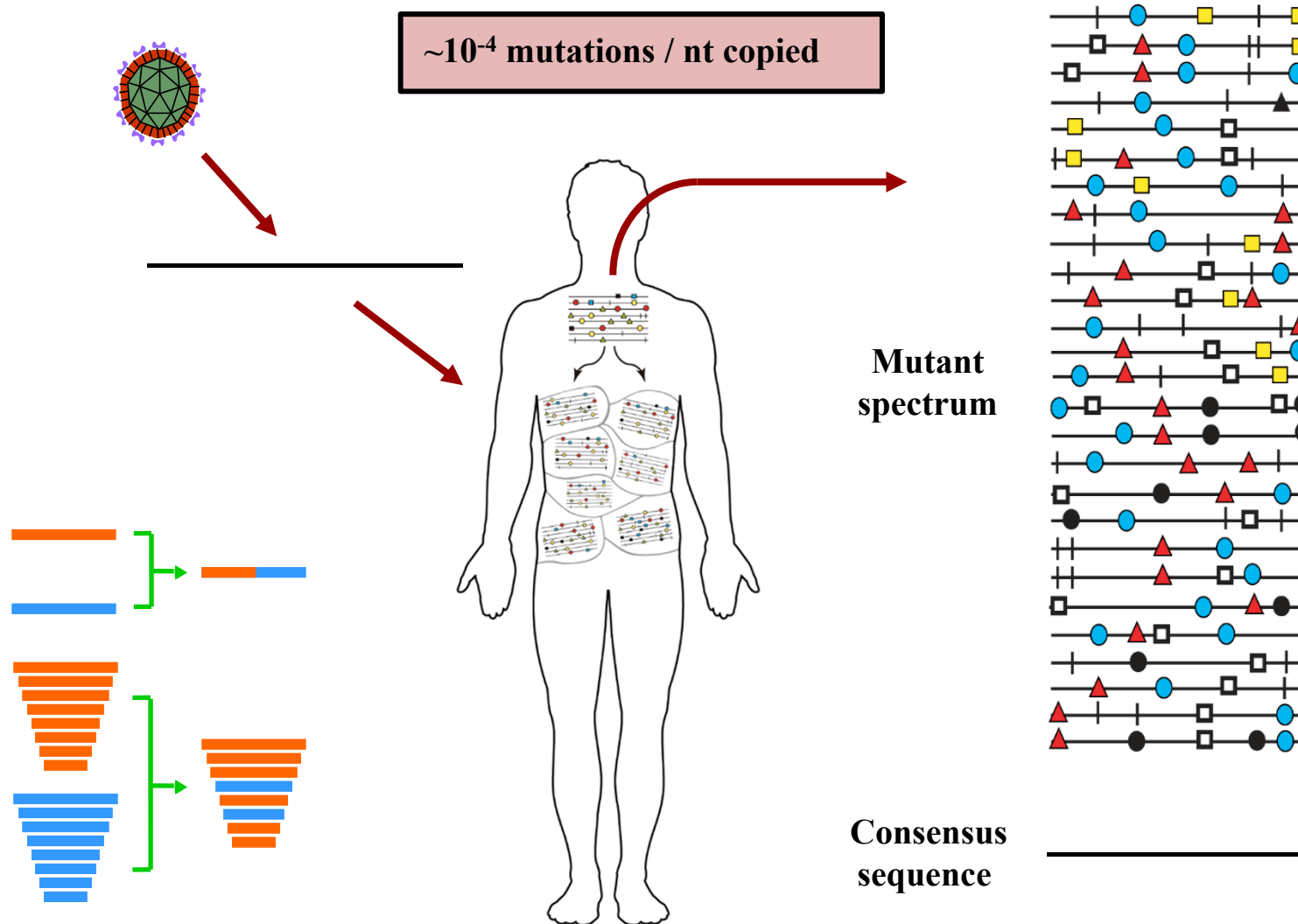
VIRUS INFECTANTE

INTERIOR DE LA CELULA

VIRUS PROGENIE



Viral quasispecies



Domingo et al. Cell 13:735-44, 1978

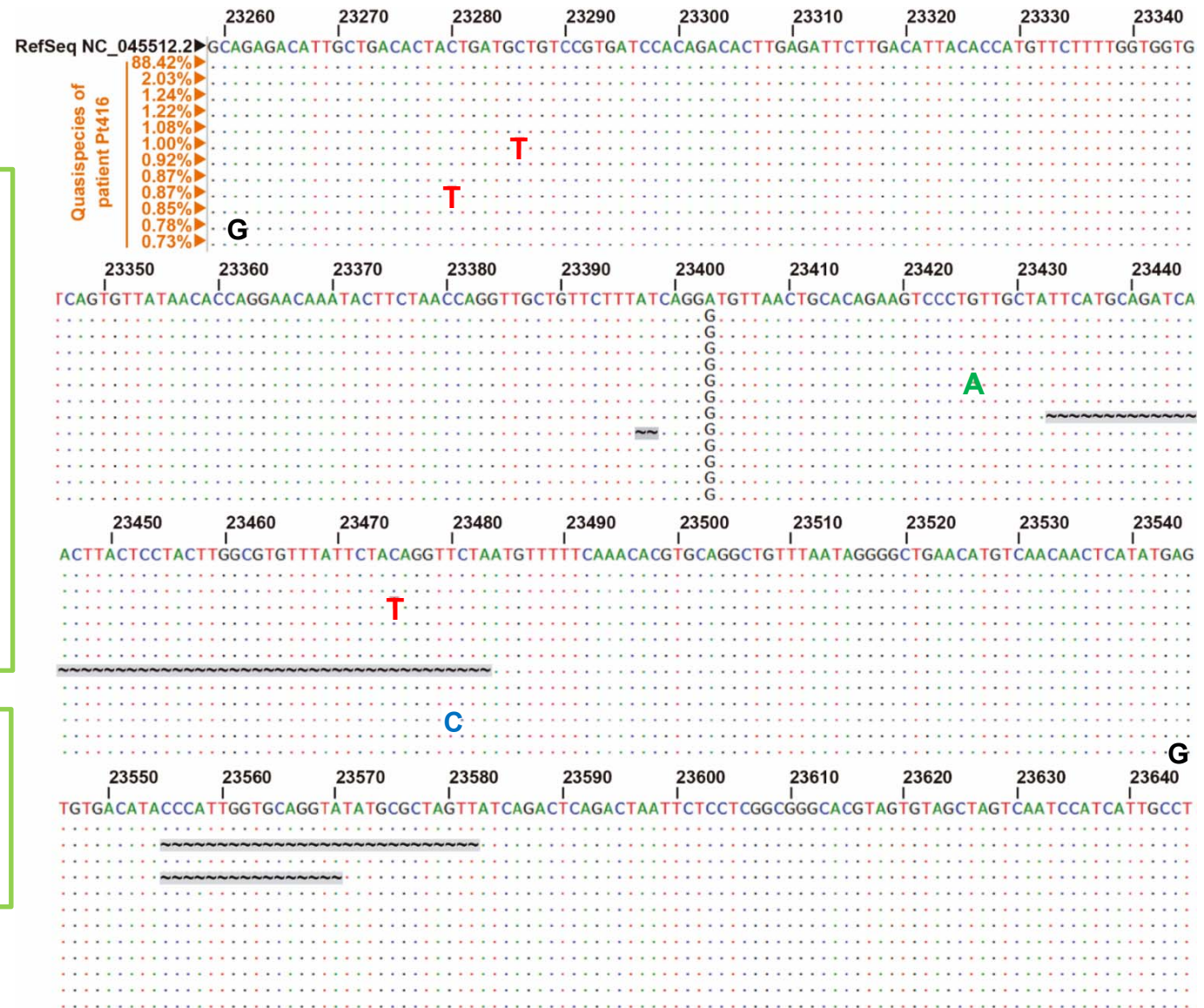
Domingo and Perales PloS Genetics 15:e1008271, 2019

Domingo, García-Crespo and Perales Annu. Rev. Virol., 8: 51-72, 2021

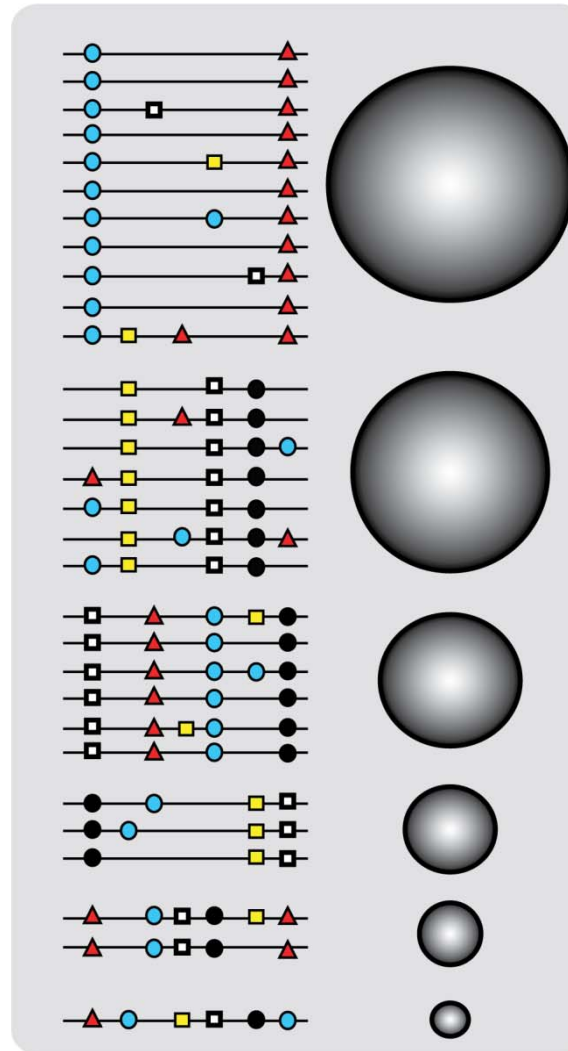
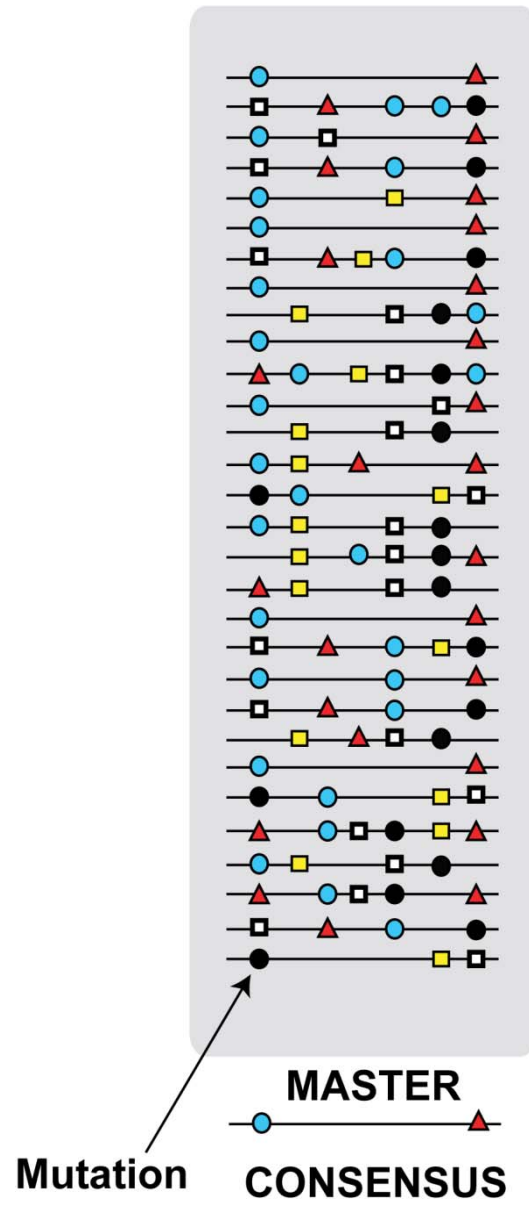
Mutant spectrum in a SARS-CoV-2-infected patient

Comparative analysis
of SARS-CoV-2
isolates from 30
infected patients who
developed mild
(n=10), moderate
(n=10) and severe
(exitus) (n=10)
COVID-19

Around 50 isolates
(nsp12 and S)
analyzed to date

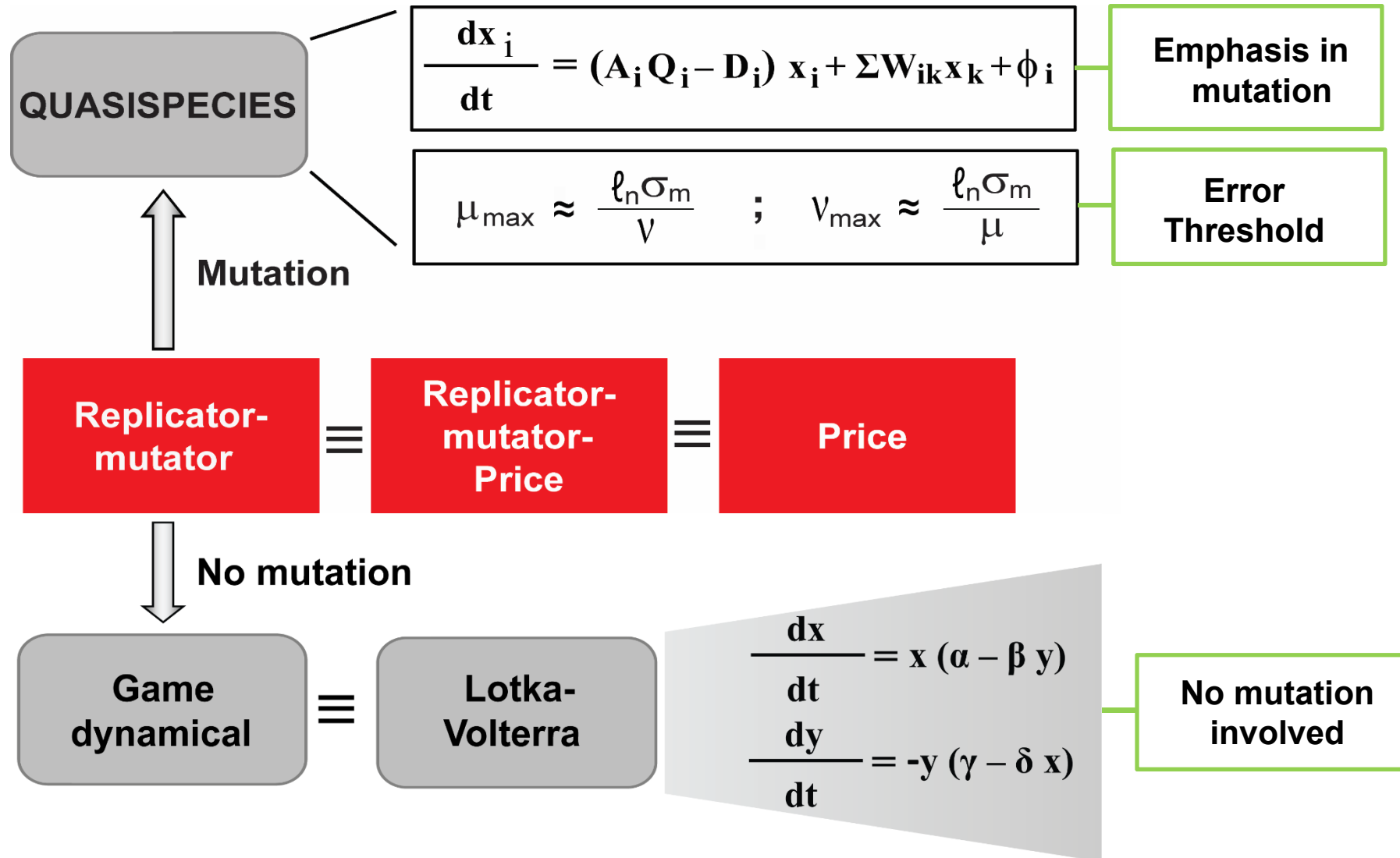


VIRAL QUASISPECIES



A seemingly random distribution of genomes may hide subpopulations discernible by bioinformatic procedures [partition analysis of quasispecies (PAQ); quasispecies evolution, network-based transmission infERENCE (QUENTIN); DISSEQT]

*Baccam et al. Bioinformatics 17: 16-22, 2001
Skums et al. Bioinformatics 34:163-170, 2018
Hennigsson et al. Virus Evol. 5 (2): vez028, 2019*



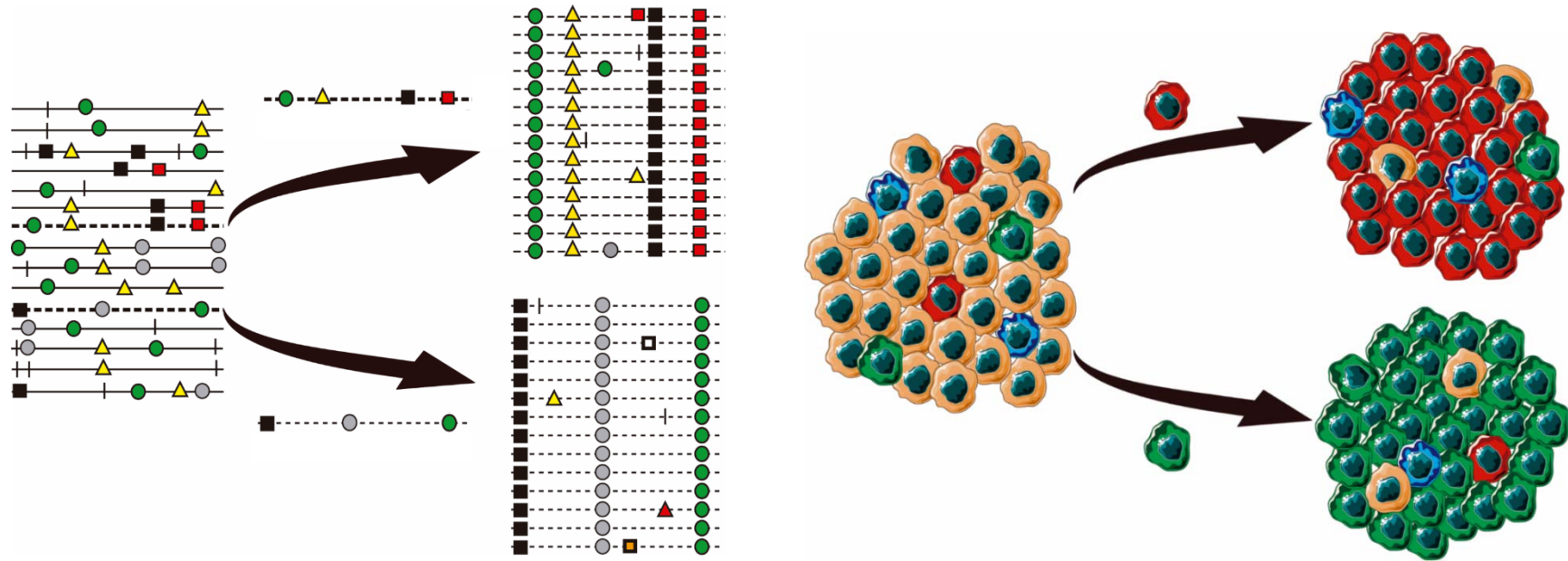
Page and Nowak, J.Theor. Biol. 219:93-98,2002

Domingo and Schuster, Curr. Top. Microbiol. Immunol. Vol. 392, 2016

Basis of quasispecies dynamics of RNA viruses

- *High mutation rates*
 10^{-3} to 10^{-5} subst./nt, due to absence of error correction
 $\sim 10^6$ -fold higher than for cellular DNA
 - *Rapid genome replication and high virus turnover in infected hosts*
 - *Principles of Darwinian evolution*
Genetic variation (mutation, recombination, reassortment)
Competition
Selection
 - *Intra-population interactions: complementation, cooperation, and interference*
 - *Bottleneck events*
- Extensions:*
Cellular communities (tumor cells, eukaryotic parasites, bacteria) and prions

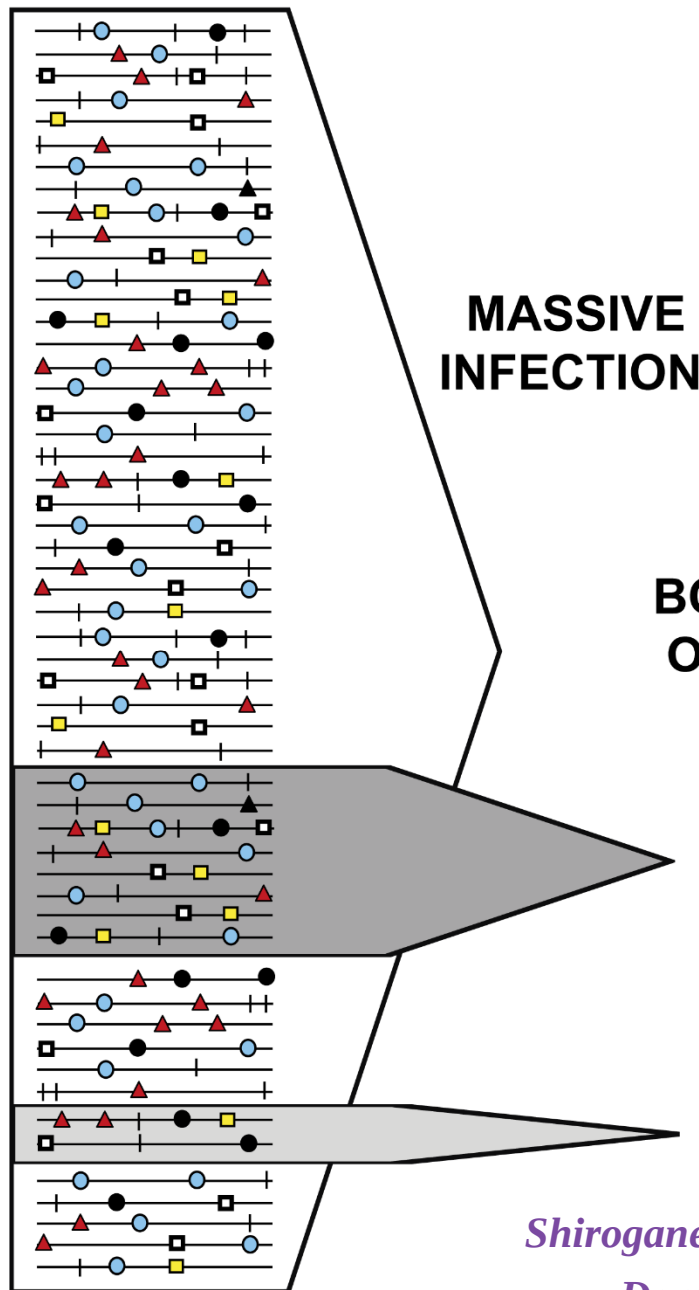
Parallel between tumor cell and viral quasispecies dynamics



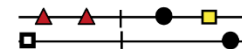
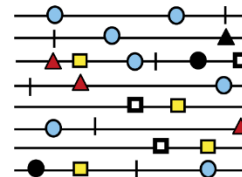
There are genetic, epigenetic, and stochastic factors that influence tumor heterogeneity, with consequences for cancer treatment failure

Domingo, E. Virus as Populations, 2nd ed. Elsevier, 2020

Hayford, C.E. et al. PLoS Biol. 19(6): e3000797, 2021



**BOTTLENECKS
OF DIFFERENT
INTENSITY**



*Individual genomes
from the same mutant
swarm may interact
(often through their
expression products)
and give rise to positive
interactions
(complementation) or
negative interactions
(interference)*

*Bottlenecks may relieve
interactions and
promote genetic drift*

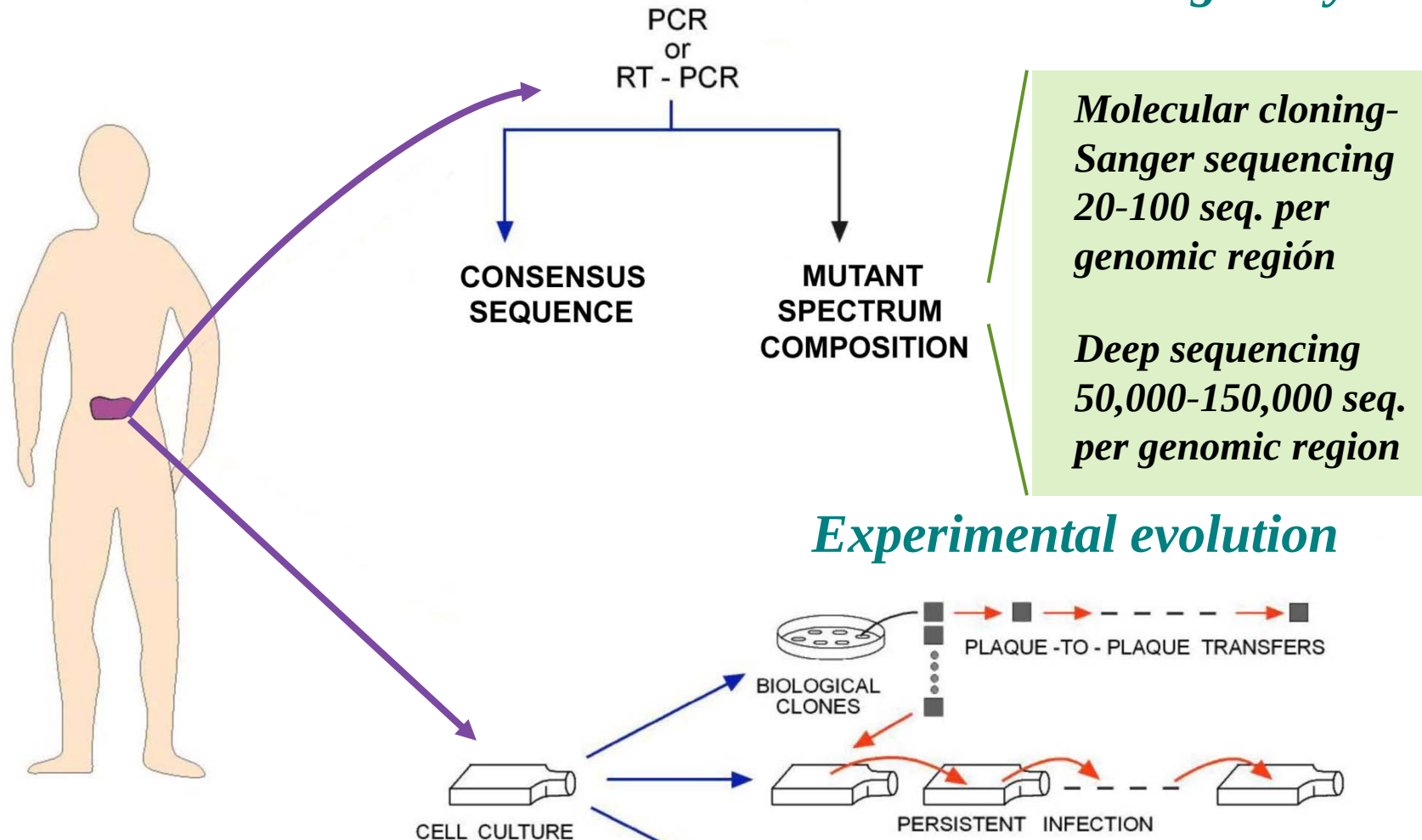
Shirogane Y et al. Curr Top Microbiol Immunol 392: 219-229, 2016

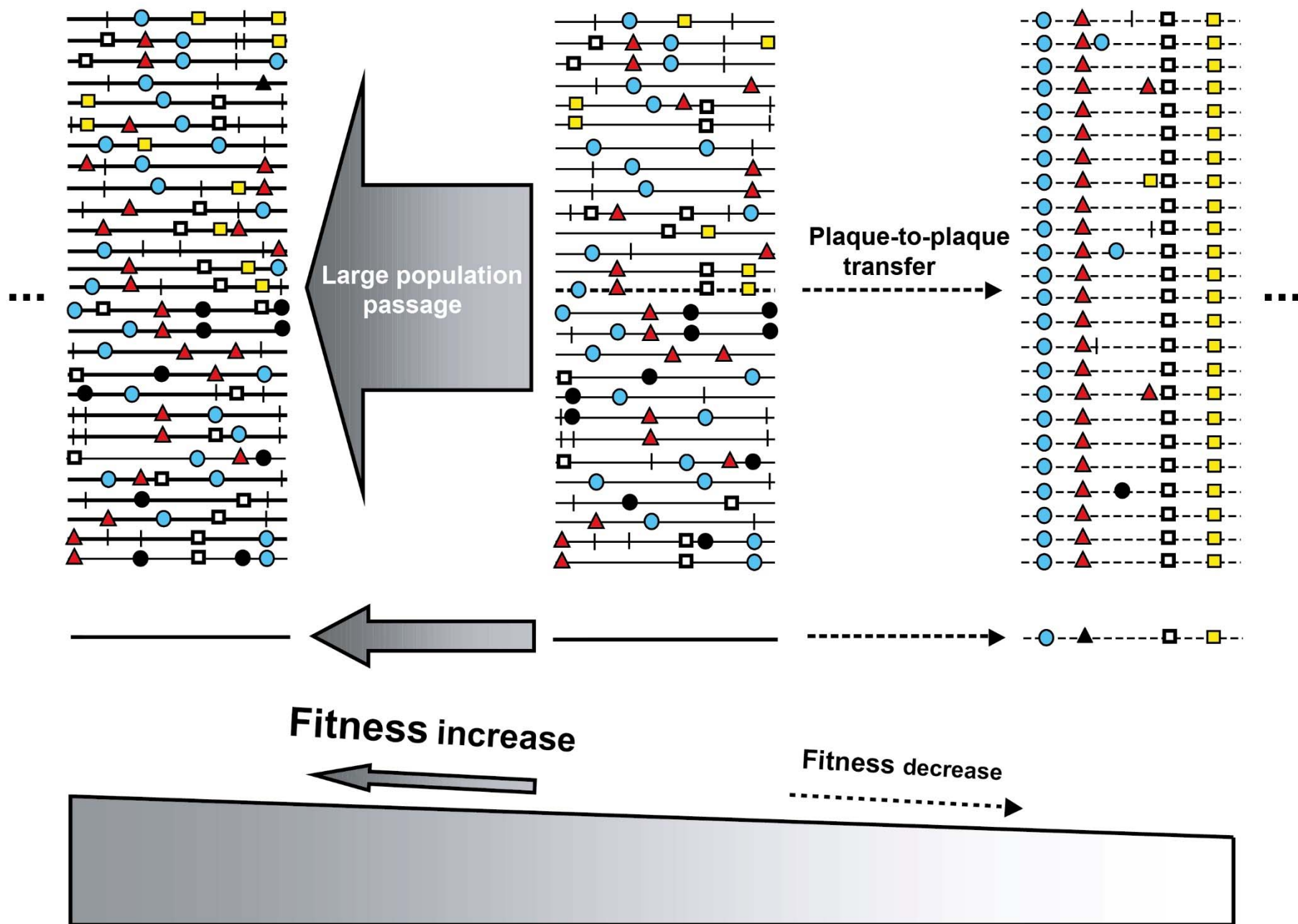
Domingo, E., Perales, C., PLoS Genet. 15(10):e1008271, 2019

El tratamiento matemático de las infecciones víricas tiene dos niveles principales:

- ***Infección individual con énfasis en mutación***
- ***Transmisión y expansión epidémica, con participación de parámetros poblacionales***

Intra-host heterogeneity





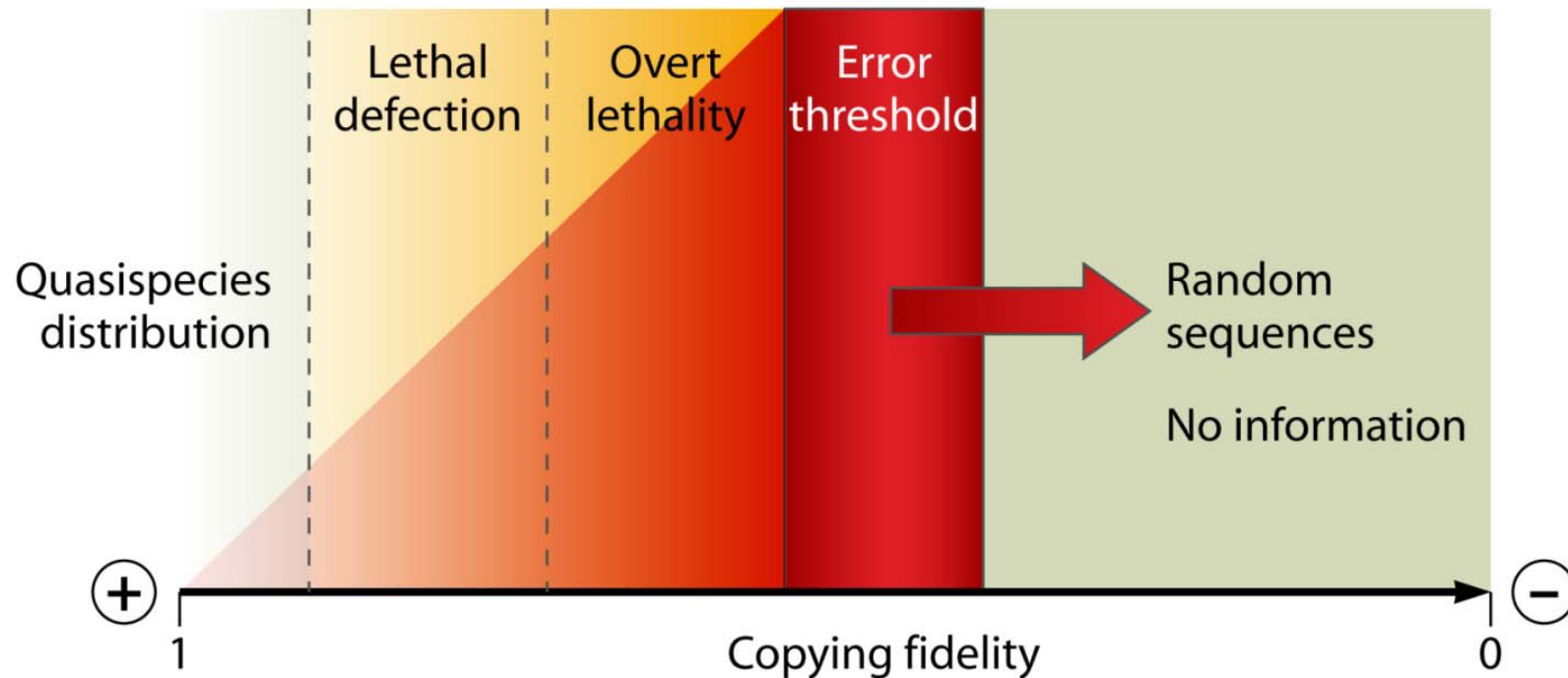
La teoría de cuasiespecies aplicada a virus tiene como característica principal que la mutación (el cambio genético en general) es inherente al propio proceso de replicación

$$\frac{dx_i}{dt} = (A_i Q_i - D_i) x_i + \sum W_{ik} x_k + \phi_i$$

Una de las implicaciones de la dinámica de cuasiespecies es la vulnerabilidad frente a aumentos de la tasa de error: la transición hacia la “catástrofe de error” o violación del “umbral de error”

$$\mu_{\max} \approx \frac{\ell_n \sigma_m}{V} \quad ; \quad V_{\max} \approx \frac{\ell_n \sigma_m}{\mu}$$

Lethal mutagenesis of viruses produced by nucleotide analogues

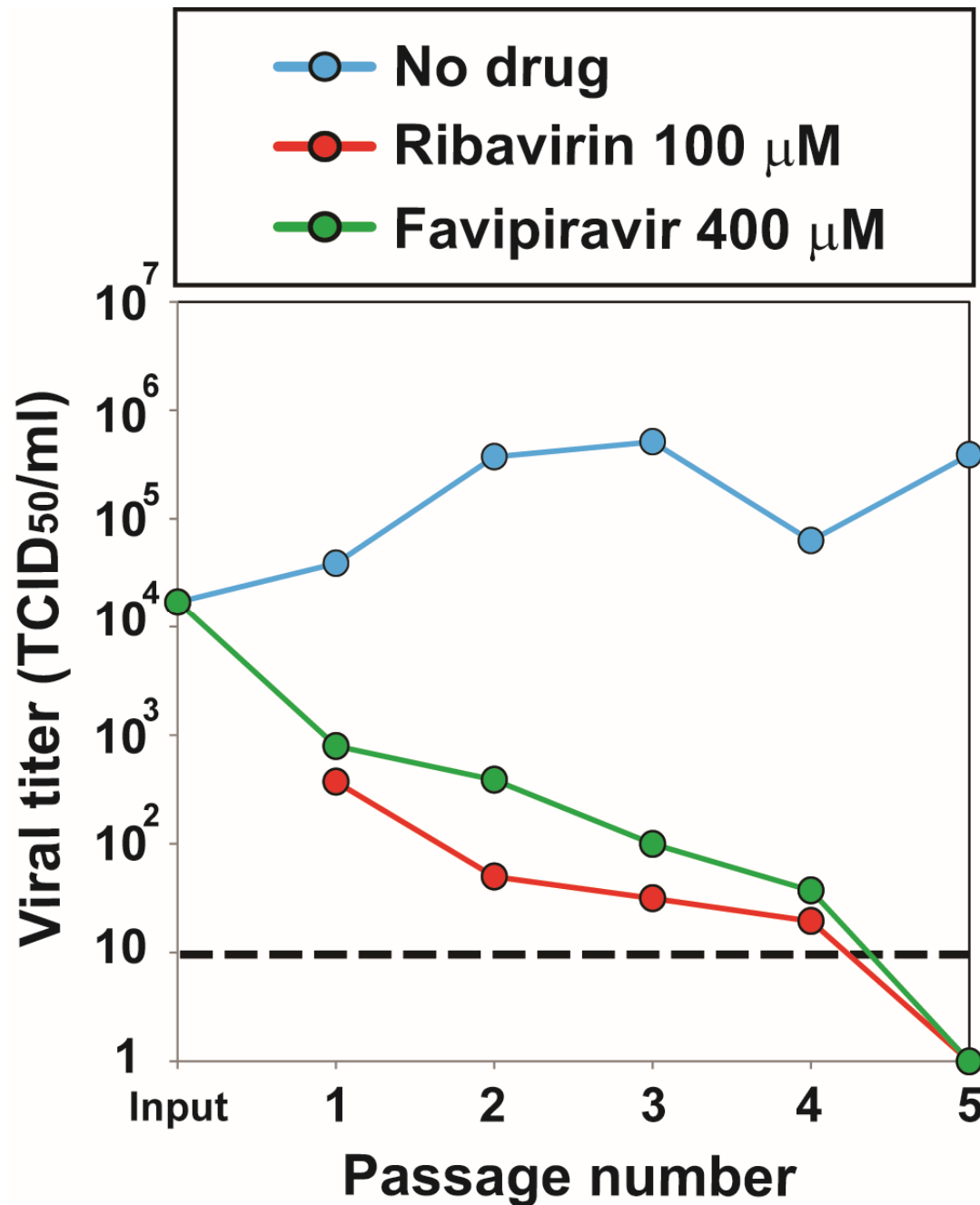


Error threshold: maximum mutation rate at which the dominant (master) sequence can stabilize the mutant ensemble

Lethal mutagenesis: loss of infectivity due to an excess of mutations

Loeb, L.A., Nat. Rev. Cancer 11: 450-457, 2011

Perales et al Future Medicinal Chemistry 11(13): 1645-1657, 2019

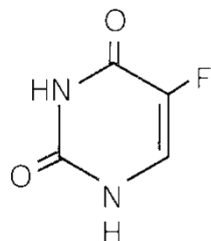


Extinction of HCV

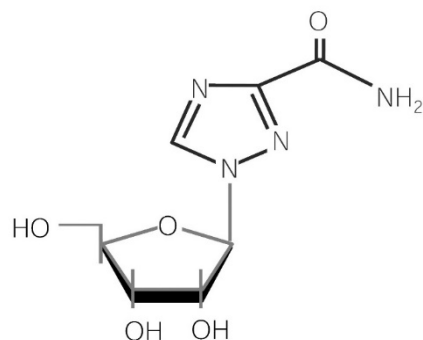
Decrease of specific infectivity precedes extinction. A virus is considered extinct when no intracellular and extracellular infectivity and viral RNA are detected, including after blind passages in absence of drug

Base pairing behavior of nucleotide analogues

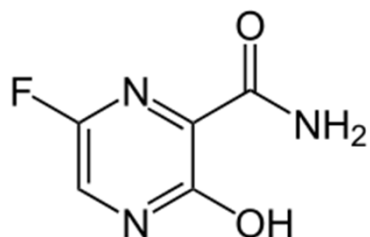
5-Fluorouracil



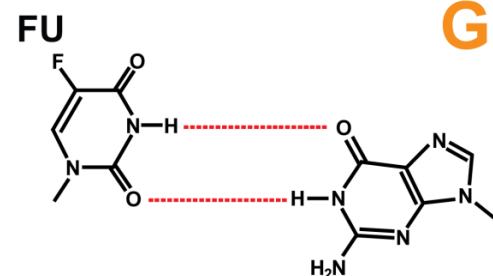
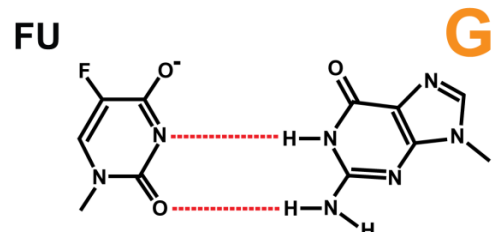
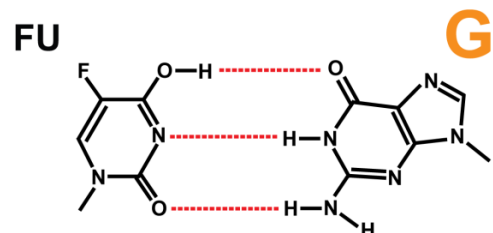
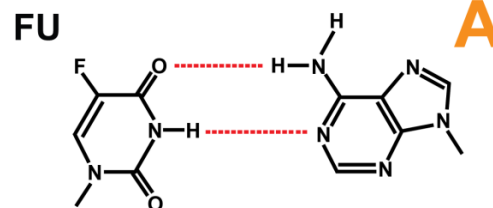
Ribavirin



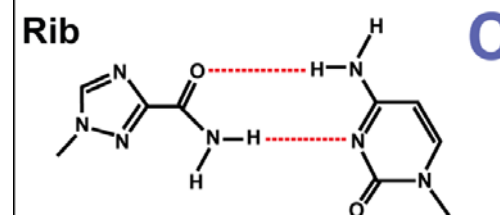
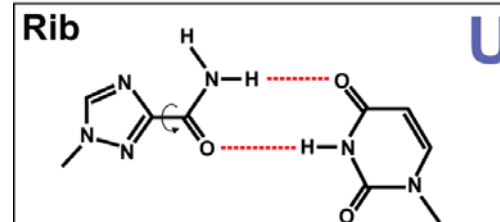
Favipiravir



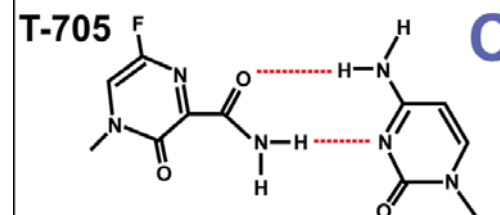
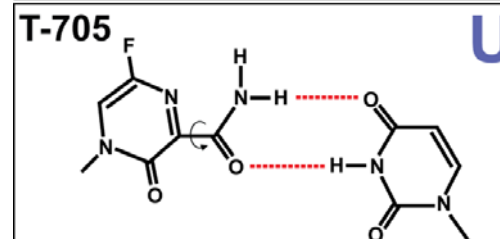
5-FLUOROURACIL



RIBAVIRIN



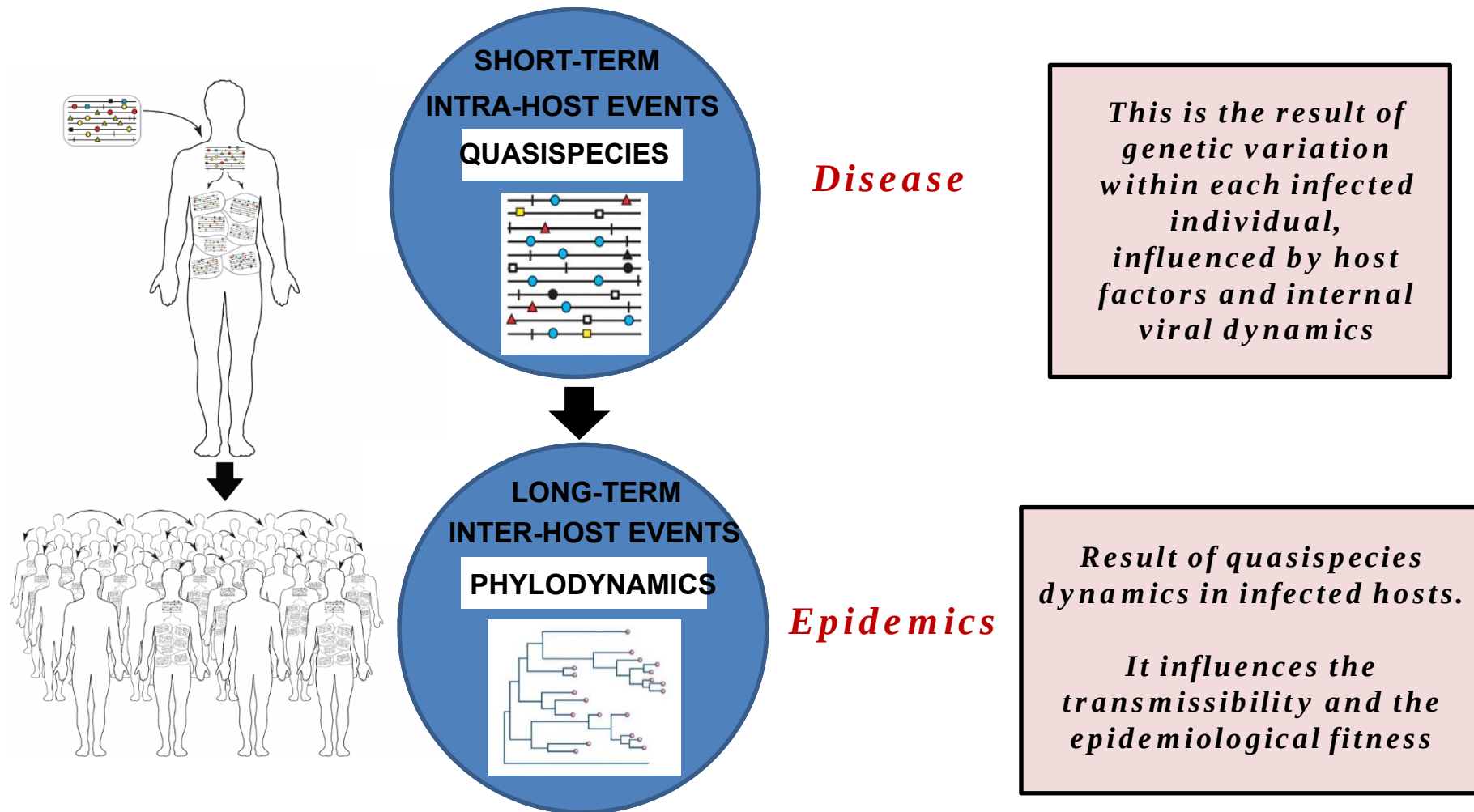
T-705, FAVIPRAVIR



Domingo, E. *Virus as Populations*, 2nd ed. Academic Press, Elsevier, 2020

- *Los espectros de mutantes que conforman las cuasiespecies víricas representan la primera fase en el proceso de diversificación de virus en la naturaleza*
- *La multiplicación de los virus en varios hospedadores susceptibles (originando brotes de enfermedad, epidemias y pandemias) se trata en un segundo grupo de ecuaciones que describen la dinámica de transmisión y expansión, con puntos de solape con otros agentes patógenos*
- *Hay conexiones entre cuasiespecies y dinámica de propagación de los virus*

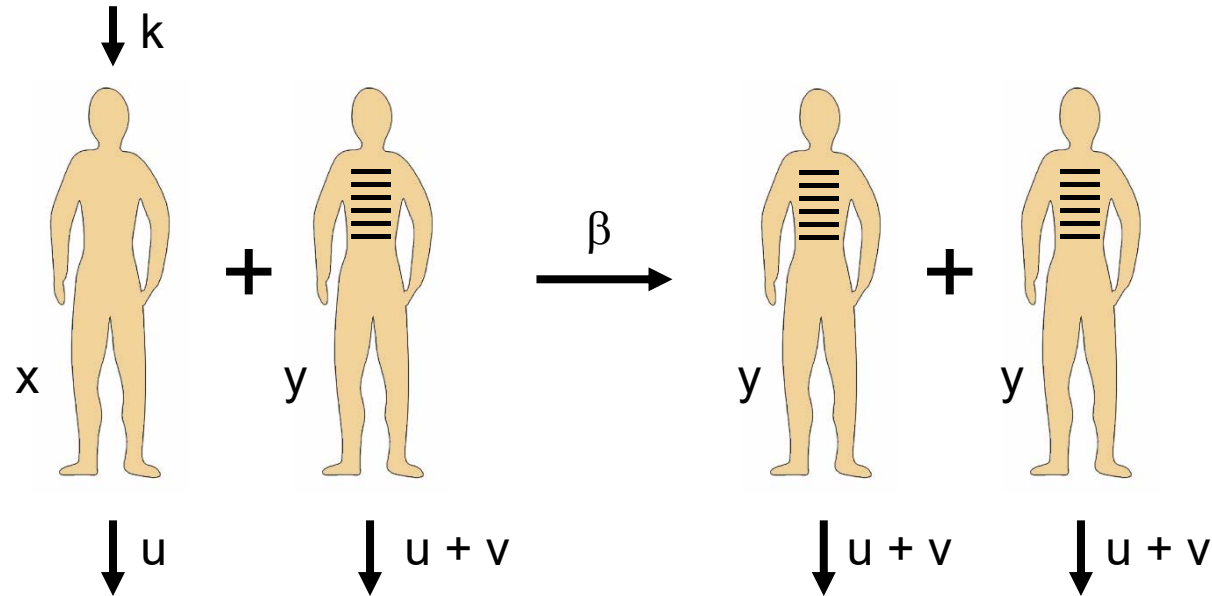
Two phases in viral evolution



Geoghegan J.L. and Holmes E.C. Genetics 210: 1151–1162, 2018
Domingo, E. et al. Infection Genetics and Evolution, 82:104278, 2020

Basic model of infection dynamics

(Anderson, R.M., May, R.M., and Nowak, M.A.)

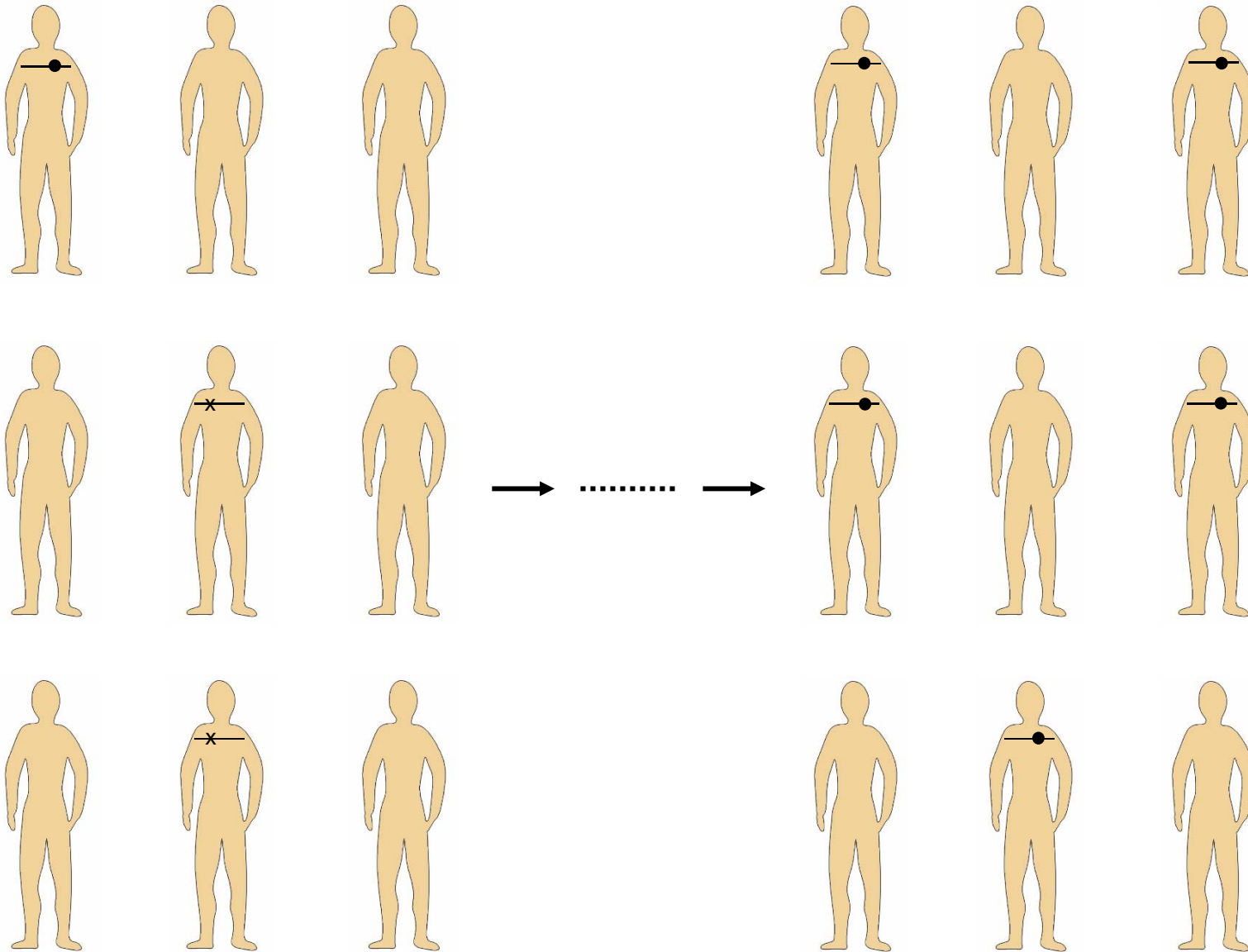


$$\frac{dx}{dt} = k - ux - \beta xy$$

$$\frac{dy}{dt} = y (\beta x - u - v)$$

$$R_0 = \frac{\beta}{u + v} \cdot \frac{k}{u}$$

R_0 = Basic reproductive ratio



$$R_0 (-\bullet-) > R_0 (*-)$$

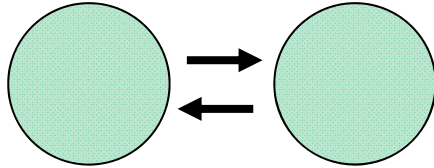
Conditions for a Second Wave of COVID-19 Due to Interactions Between Disease Dynamics and Social Processes

Sansao A. Pedro¹, Frank T. Ndjomatchoua², Peter Jentsch^{3,4}, Jean M. Tchuenche⁵, Madhur Anand³ and Chris T. Bauch^{4}*

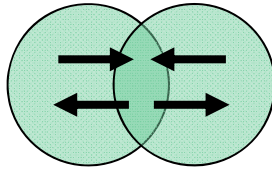
¹ Departamento de Matemática e Informática, Universidade Eduardo Mondlane, Maputo, Mozambique, ² Sustainable Impact Platform, Geospatial Science and Modelling Cluster, International Rice Research Institute, Metro Manila, Philippines, ³ School of Environmental Sciences, University of Guelph, Guelph, ON, Canada, ⁴ Department of Applied Mathematics, University of Waterloo, Waterloo, ON, Canada, ⁵ Avenir Health, Glastonbury, CT, United States

*Pedro, S. A. et al. Front Phys. 10.3389, 2020
Polo, D. et al. Water Res. 186: 116404, 2020*

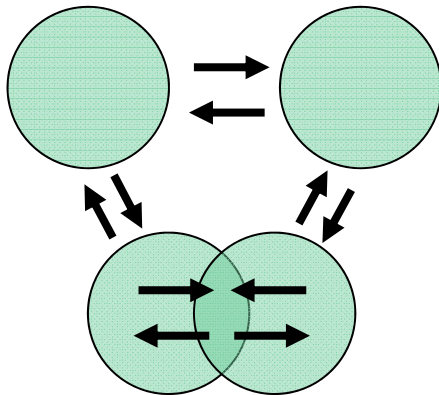
*Separate habitats,
spatial heterogeneity*



Overlapping habitats



Multi-component habitats



Vector-mediated virus traffic

Host movements

- ***Low probability of epidemiological isolation***
- ***Isolation should be almost absolute to be effective***

Permanent (sympatric species) or transient overlaps

Reservoir, potentially susceptible, and known spillover populations

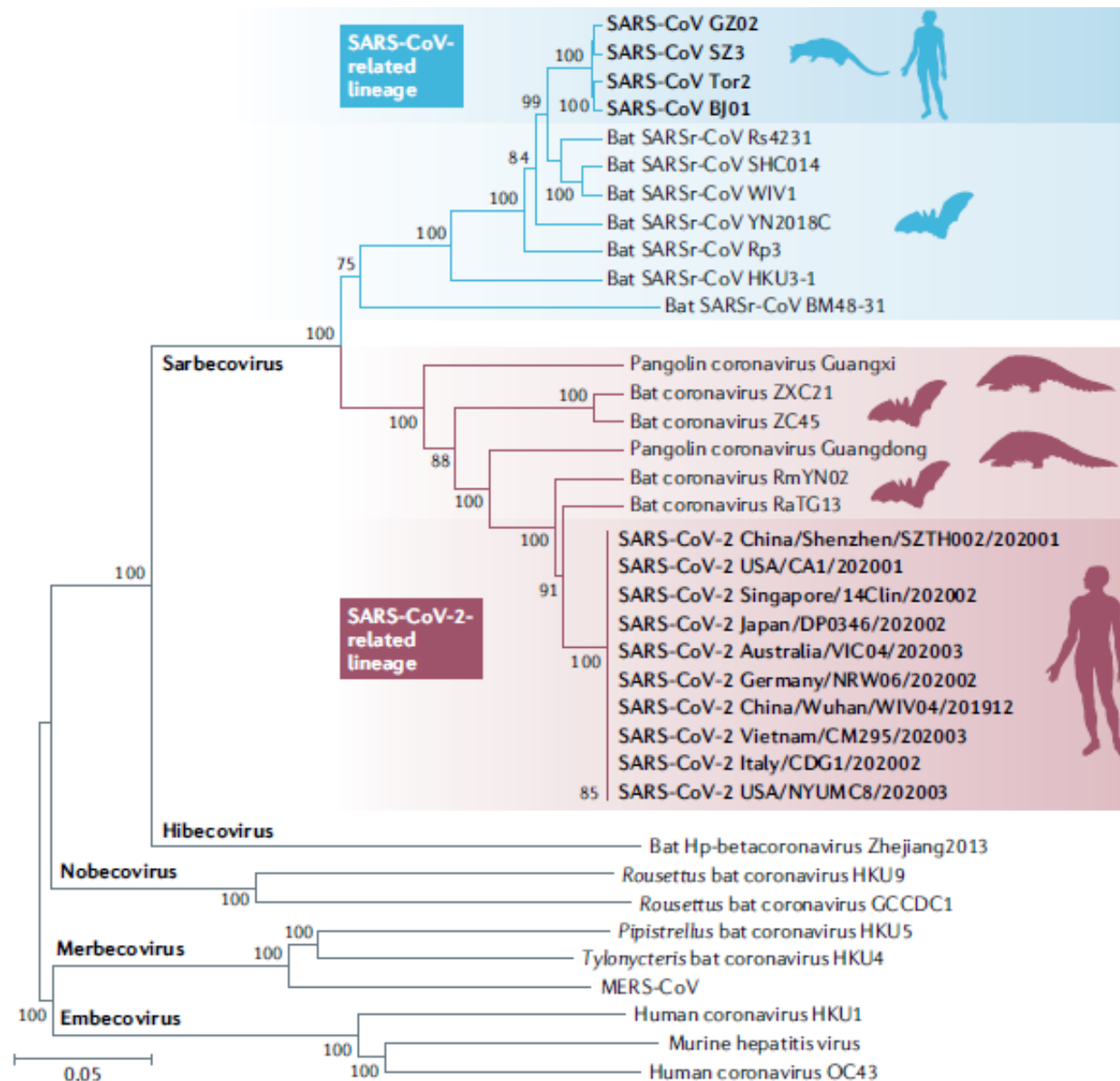
Preferred habitats can feed the boundary and overlapping habitats

Number and duration of encounters affect R_0

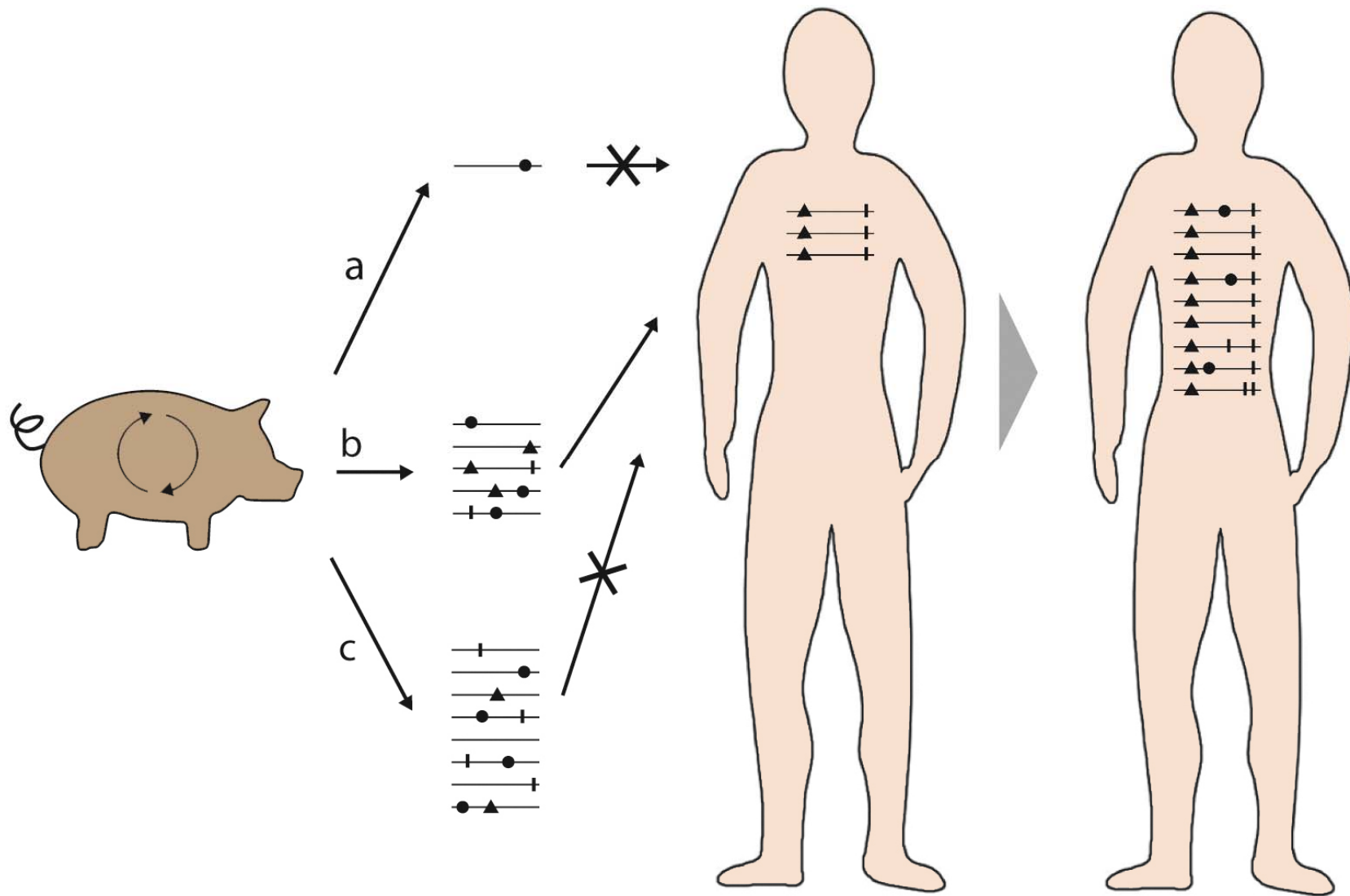
- ***General models can be applied to specific viruses by including experimental parameter values***
- ***Models calculate probabilities of emergence but emergences are unpredictable***

- *La dinámica de virus y sus vectores (animales, insectos), conjuntamente con factores sociológicos, ecológicos y ambientales, determinan la periódica emergencia y reemergencia de virus en la naturaleza. Durante las últimas décadas ha emergido en promedio un nuevo virus humano por año*
- *Se considera que la gran mayoría de nuevos virus humanos tienen un origen zoonótico (notablemente primates, murciélagos, roedores, aves e insectos)*
- *La emergencia de nuevos virus tiene aspectos de complejidad biológica, en el sentido de que es resultado de varios factores pero que no puede explicarse meramente por la “suma” de los factores*

Evolution of SARS-CoV



Hu, B. et al Nature Reviews Microbiology 19(3):141-154, 2021



Domingo, E. Virus as Populations, 2nd. ed. Academic Press, Elsevier, 2020

*SOCIOLOGIC, ECOLOGIC,
ENVIRONMENTAL FACTORS*

A Venn diagram consisting of two overlapping ovals. The top oval is light purple and contains the text 'SOCIOLOGIC, ECOLOGIC, ENVIRONMENTAL FACTORS' and 'DEMOGRAPHIC CHANGES OF VIRAL HOSTS AND VECTORS'. The bottom oval is teal and contains the text 'VIRUS ADAPTABILITY'. The intersection of the two ovals is a bright blue shape containing the word 'EMERGENCE'.

*DEMOGRAPHIC CHANGES
OF VIRAL HOSTS AND VECTORS*

EMERGENCE

*VIRUS
ADAPTABILITY*

*ADEQUATE USE OF ANTIBIOTICS
AND ANTIVIRAL AGENTS, MULTIVALENT VACCINES
NEW ANTIVIRAL STRATEGIES*

INFECTIOUS DISEASE CONTROL

*GLOBAL SURVEILLANCE AND INFORMATION.
APPLICATION OF NEW SEQUENCING TECHNIQUES,
BIOINFORMATICS TOOLS , AND THEORETICAL MODELS.
STRONG POLITICAL ACTION TO SOLVE THE ORIGINS OF
POVERTY, SOCIAL UNREST AND ENVIRONMENTAL
DETERIORATION*

RESUMEN (I)

- *La persistencia de los virus en la biosfera se debe en buena parte a su poder de adaptación a ambientes cambiantes (a distintos hospedadores, a distintos tejidos y órganos dentro del mismo organismo, etc.). La adaptación se asocia a cambios genéticos continuos que son inherentes a su maquinaria de replicación*
- *La teoría de cuasiespecies consideró por vez primera el error de copia como parte de la replicación, ha ayudado al entendimiento de los mecanismos de adaptación de los virus y ha inspirado nuevos abordajes para combatirlos, como es la mutagénesis letal*

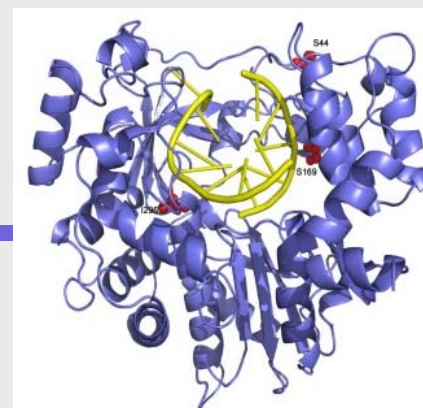
RESUMEN (II)

- *La generación de diversidad genética en una población de virus durante su replicación se describe mediante la ecuación de producción de copias erróneas (cuasiespecies)*
- *La existencia de un umbral de error es la base de la mutagénesis letal como estrategia antiviral*
- *La expansión de virus a nivel epidemiológico tiene un tratamiento matemático en el que intervienen parámetros poblacionales y factores de transmisión*
- *Queda mucho por investigar a nivel teórico y experimental en la conexión entre cuasiespecies y epidemiología de virus*



***Carlos Briones
Jordi Gómez***

***Nuria Verdaguer
Cristina Ferrer-Orta***



Celia Perales, Ana Isabel de Ávila, Isabel Gallego

***Carlos García-Crespo
María Eugenia Soria
Brenda Martínez-González
Lucia Vázquez-Sirvent
Pilar Somovilla
Antoni Durán-Pastor***

***Carmen Ayuso
Ignacio Gadea

Soledad Delgado
Federico Morán
Cecilio López-Galíndez***

***Pablo Mínguez
Carlos Llorens
Beatriz Soriano
Ricardo Ramos***