# The Evolutionary Dynamics of Incubation Periods

Bertrand Ottino-Löffler
Steve Strogatz, Jacob Scott

02/22/21

# The Incubation Period

# The Incubation Period

**Definition**

The **Incubation Period** of a disease is defined to be the time between first exposure to a contagion and observation of first symptoms.

# The Incubation Period


RICHMOND TIMES-DISPATCH: SUNDAY, JULY 11, 1915.

# ed Danger to Everybody's Health–and No Remedy for It.

A 181.4

B 82.4

C 118.4

y Proof That a Dish of Baked Spaghetti
"Culture" for Typhoid Germs. The Three
and C, Indicate the Temperatures of the
n Removed from the Oven—One-Half Inch
iddle and Near the Bottom. The Typhoid
Been Placed in the Mass Before Cooking

Survived in a Few Colonies Less Than an Inch Below the Baked Surface, While in the Centre of the Dish, with Its Mild Temperature of 82.4 Degrees, the Colonies Were Abundant and Active.

## How a Dish of Baked Spaghetti Gave 93 Eaters Typhoid Fever

By Wilbur A. Sawyer, M. D.

to wash their hands
disinfectant. The family
ical directions how to
will not convey germs

authorities is to detect
h "sanitary isolation."
quarantine, as for

# The Incubation Period

NINETY-THREE PERSONS INFECTED BY A TYPHOID CARRIER AT A PUBLIC DINNER

WILBUR A. SAWYER, M.D.
Director of the Hygienic Laboratory of the California State Board of Health
BERKELEY, CAL.

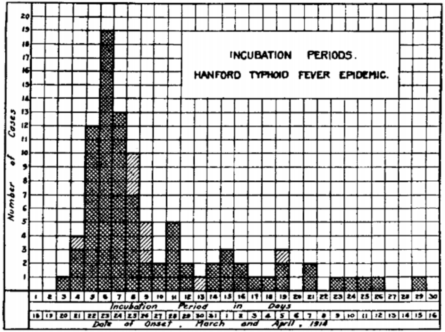



Chart of the cases in the Hanford typhoid fever epidemic, showing incubation periods and dates of onset. The heavily shaded areas represent definite cases of typhoid fever. The lightly shaded areas represent the doubtful cases.

# The Incubation Period

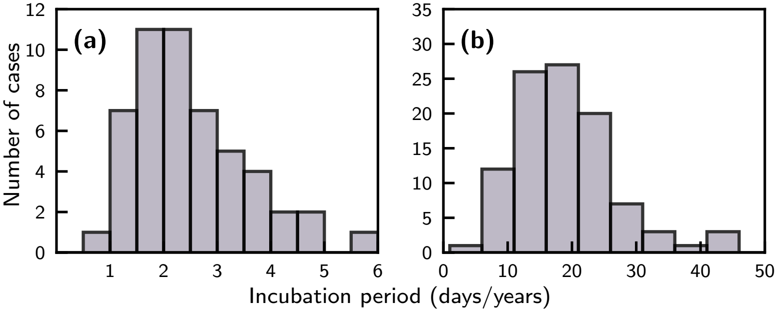
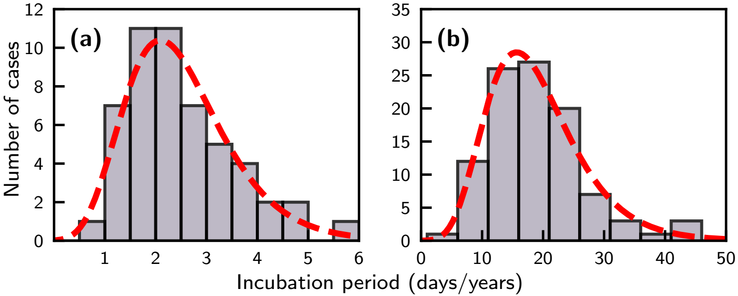



**Figure:** (a) Food-borne streptococcal sore throat (Sartwell 1950).
(b) Bladder tumors in a dye plant (Goldblatt 1949).

# Sartwell's Law (1966)

**Sartwell's Law**

*Incubation periods for diseases tend to be distributed as lognormals; more generally, they will be right-skewed.*



# Still Used, 50+ Years Later

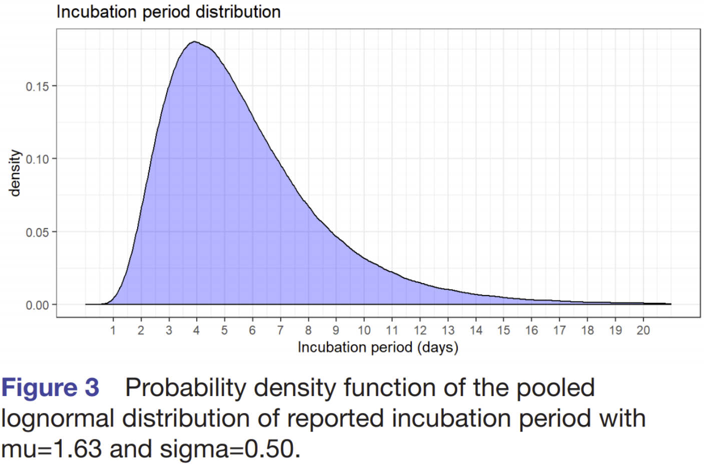



**Figure:** Lognormal fit for COVID-19 (McAloon 2020).

# What Do They Have In Common?

# Evolutionary Graph Theory Is A Common Factor

# Evolutionary Graph Theory Is A Common Factor

| **The Illness** … | … **Takes over the** … | … **Which is a** … |
|---|---|---|
| Typhoid | well-mixed gut microbiome | Complete graph |
| Leukemia | healthy bone marrow cells | 3D lattice |
| Influenza | uncompromised tracheal cells | 2D lattice |

# Viruses?

*Viruses* **2018**, *10*(11), 627; https://doi.org/10.3390/v10110627 Open Access

*Review*

## Causes and Consequences of Spatial Within-Host Viral Spread

by Molly E. Gallagher [1], Christopher B. Brooke [2,3], Ruian Ke [4] and Katia Koelle [1,*]

1 Department of Biology, Emory University, Atlanta, GA 30322, USA

Virus-Cell Interactions

## Influenza A Virus Uses Intercellular Connections To Spread to Neighboring Cells

Kari L. Roberts, Balaji Manicassamy, Robert A. Lamb

D. S. Lyles, Editor

DOI

## Influenza virus exploits tunneling nanotubes for cell-to-cell spread

Amrita Kumar, Jin Hyang Kim, Priya Ranjan, Maureen G. Metcalfe, Weiping Cao, Margarita Mishina, Shivaprakash Gangappa, Zhu Guo, Edward S. Boyden, Sherif Zaki, Ian York, Adolfo García-Sastre, Michael Shaw & Suryaprakash Sambhara

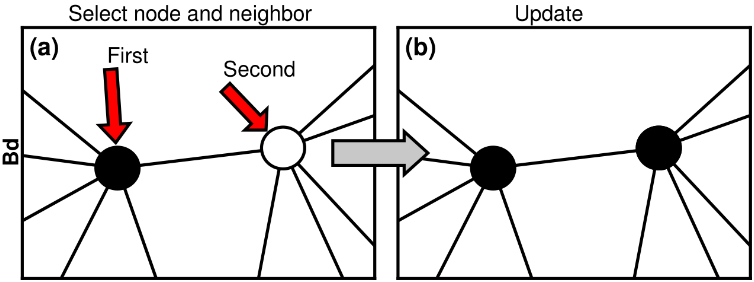
*Scientific Reports* **7**, Article number: 40360 (2017) | Download Citation

# Evolutionary Graph Theory

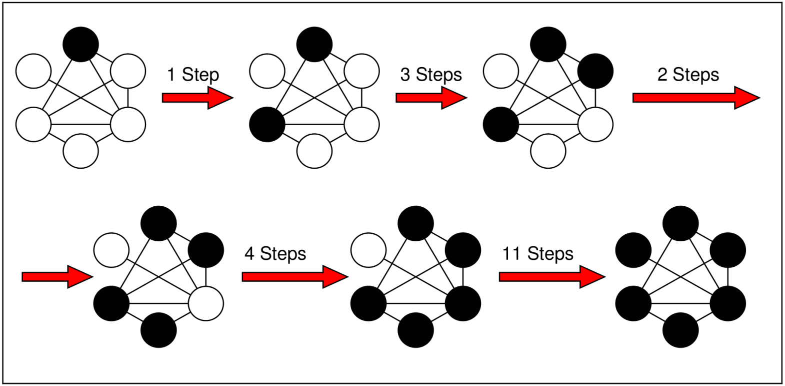
**Definition**

The **Moran Birth-death (Bd) model** consists of three steps:
1. With probability proportional to fitness ($r$), randomly select a node on the network to give birth.
2. Uniformly randomly select a neighbor of the first node to die.
3. The dying node takes on the type of the birthing node.

# The Moran Model



# The Moran Model: Takeover



# Complete Graph: $r = \infty$

# Complete Graph: $r = \infty$

At every time step:

1) Select a random node A from the available mutants.
2) Choose random node B from the $N - 1$ neighbors of the first.
3) If B is healthy, turn it into a mutant.
4) Repeat for $T$ steps until every node is a mutant.

# Complete Graph: Simplified

At every time step:

1) ~~Select a random node A from the available mutants.~~
1) Choose a random node B from a set of $N - 1$.
2) If we haven't seen B before, we label and return it.
3) Repeat for $T$ steps until every node is labeled.

# The Coupon Collector's Problem

**The Coupon Collector's Problem**

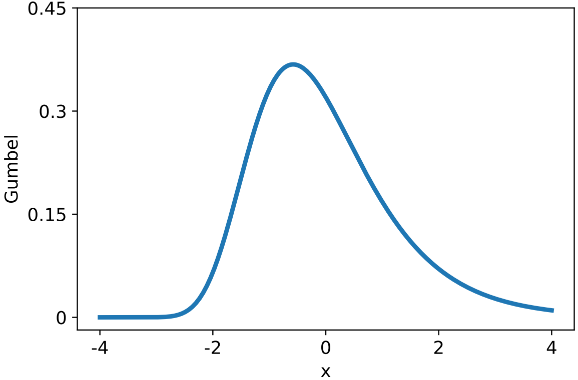
*Each day, a kid gets one trading card, uniformly at random. Given that there are $N$ distinct cards, what is the distribution of times $T$ required to form a complete set?*

# The Complete Graph

**Theorem**

$$\frac{T - E[T]}{N} \xrightarrow{d} Gumbel(-\gamma, 1),$$

*(Where* $\gamma =$ *the Euler-Mascheroni constant* $\approx 0.5772$*.)*



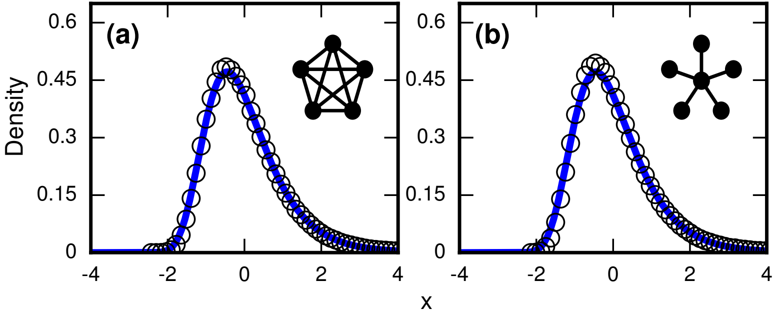
# Complete Graph and Star Graph

**Complete Graph:**

$$\frac{T - N(\log(N) + \gamma)}{N} \xrightarrow{d} \text{Gumbel}(-\gamma, 1). \tag{1}$$

**Star Graph:**

$$\frac{T - N^2(\log(N) + \gamma - 1)}{N^2} \xrightarrow{d} \text{Gumbel}(-\gamma, 1). \tag{2}$$



# Lattices

# Lattices: A Problem

- **Configuration is important!**
- It is hard to predict the exact rate of new mutants appearing.

# Lattices and Moran

# Lattices: Surface Area to Volume

To understand lattices, do the following:

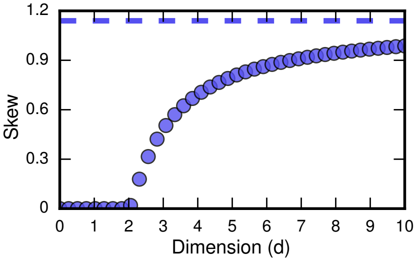
1) Make an analogy to first-passage percolation.
2) Use surface area to volume scaling.
3) Pray.

# Lattice: skew

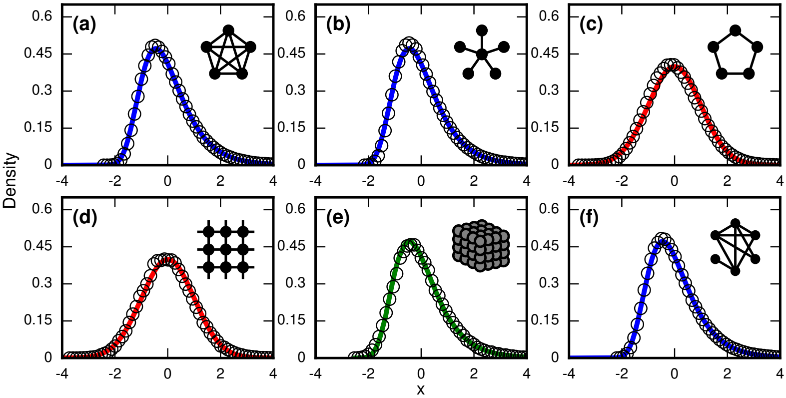
**Theorem**

*Letting $\eta = 1 - 1/d$, the asymptotic skew of the takeover times for a $d > 2$ dimensional lattice is given by*

$$Skew(d) = \frac{2\zeta(3\eta)}{\zeta(2\eta)^{3/2}}, \text{ where } \zeta(x) = \sum_{n=1}^{\infty} \frac{1}{n^x}.$$



# Results for Infinite $r$



# Non-infinite fitness?

# Fitness and Skew for Complete Graph

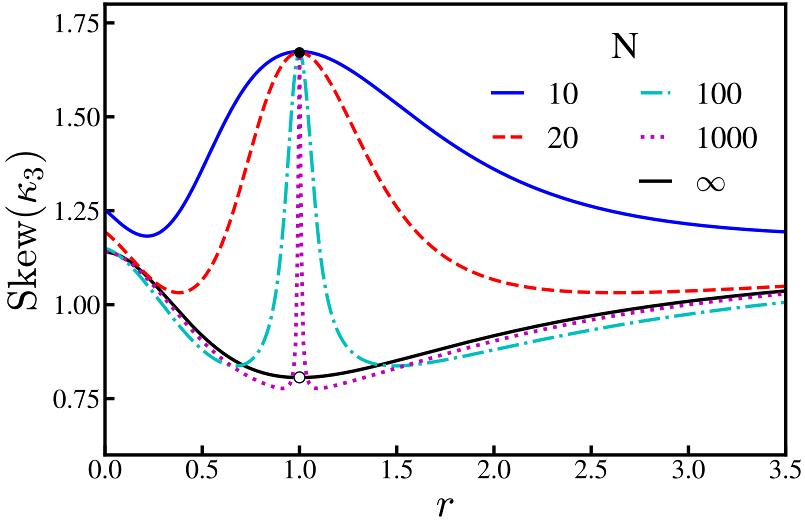



**Figure:** Hathcock 2019

# Realism?

# Red = Lognormal, Blue = Gumbel

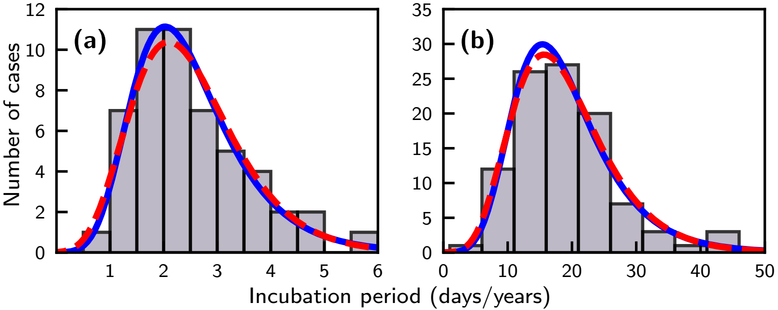



**Figure:** (a) Food-borne streptococcal sore throat (Sartwell 1950).
(b) Bladder tumors in a dye plant (Goldblatt 1949).

# Main Point

Common aspects of disease growth:

- **Evolutionary Network Dynamics**
- **The Coupon Collector's Problem**

Together, they help justify Sartwell's Law.

# Questions?

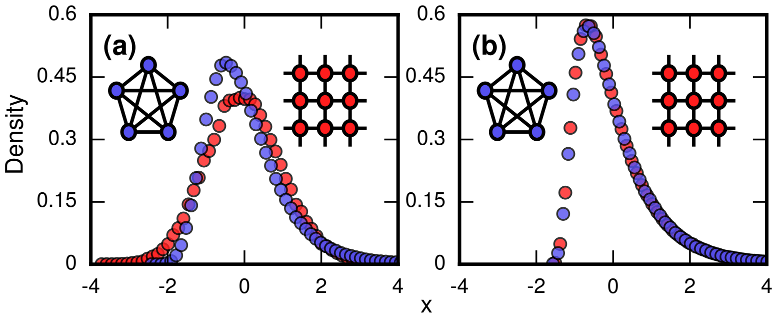



**Figure:** (a) $r = \infty$. (b) $r = 1$.

All slides available at: ottinoloffler.com

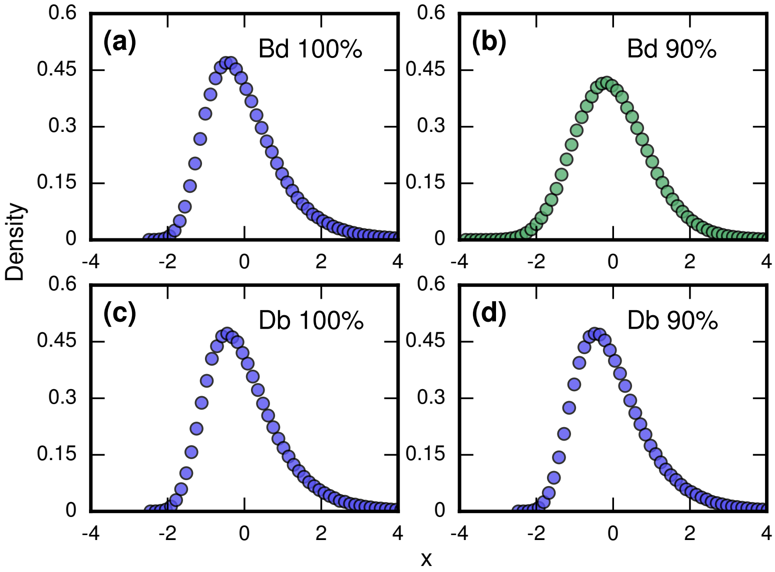
# Selected References (I)


- B Ottino-Löffler, J G Scott, & SH Strogatz, Evolutionary Dynamics of Incubation Periods, eLife 6:e30212 (2017).
- B Ottino-Löffler, J G Scott, & SH Strogatz, Takeover Times for a Simple Model of Network Infection, Phys Rev E 96m 012313 (2017).
- D Hathcock, & SH Strogatz, Fitness Dependence of the Fixation-Time Distribution for Evolutionary Dynamics on Graphs, Phys Rev E 100 012408 (2019).
- Y Bakhtin, Universal Statistics of Incubation Periods and Other Detection Times via Diffusion Models, Bull Math Bio 81(4) 1070 (2018).
- WA Sawyer, Ninety-Three Persons Infected by a Typhoid Carrier at a Public Dinner, Journal of the American Medical Association 63(18) (1914).
- PE Sartwell, The Distribution of Incubation Periods of Infectious Disease, Am J Hyg 51 310 (1950).
- MW Goldblatt, Vesical tumours induced by chemical compounds, Occupational and Environmental Medicine 6:65–81 (1949).
- PAP Moran, The Effect of Selection in a Haploid Genetic Population, Proc Camb Phil Soc 54(8) (1958).
- E Lieverman, C Hauert, & M A Nowak, Evolutionary Dynamics on Graphs, Nature 433(7023) (2005).

# Selected References (II)


- P Erdős & A Rényi, On a Classical Problem of Probability Theory, Publ Math Inst Hung Acad Sci 6 (1961).
- LE Baum & P Billingsley, Asymptotic Distributions for the Coupon Collector's Problem, The Annals of Mathematical Statistics 36(6) (1965).
- A Auffinger, M Damron, & J Hanson, 50 years of First Passage Percolation, `arxiv.org/abs/1511.03262` (2016).
- ME Gallagher, CB Brooke, R Ke, & K Koelle, Causes and Consequences of Spatial Within-Host Viral Spread, Viruses 10(11) 627 (2018).
- S Wieland, Z Makowska, B Campana, D Calabrese, MT Dill, J Chung, FV Chisari, MH Heim, Simultaneous Detection of Hepatitis C Virus and Interferon Stimulated Gene Expression in Infected Human Liver, Hepatology 59(6) (2013).
- F Graw, A Balagopal, AJ Kandthil, SC Ray, DL Thomas, & RM Ribeiro, Inferring Viral Dynamics in Chronically HCV Infected Patients from the Spatial Distribution of Infected Hepatocytes, PLOS Comp Bio 10(11) e1003934 (2014).
- KL Roberts, B Manicassamy, & RA Lamb, Influenza A Virus Uses Intercellular Connections to Spread to Neighboring Cells, Journal of Virology 89(3) 1537 (2015).
- A Kumar, JH Kim, P Ranjan, MG Metcalfe, W Cao, M Mishina, S Gangappa, Z Guo, ES Boyden, S Zaki, & et al., Influenza Virus Exploits Tunneling Nanotubes for Cell-To-Cell Spread. Sci. Rep. 7 40360 (2017).

# Summary: Truncation



# Summary: Complex Networks

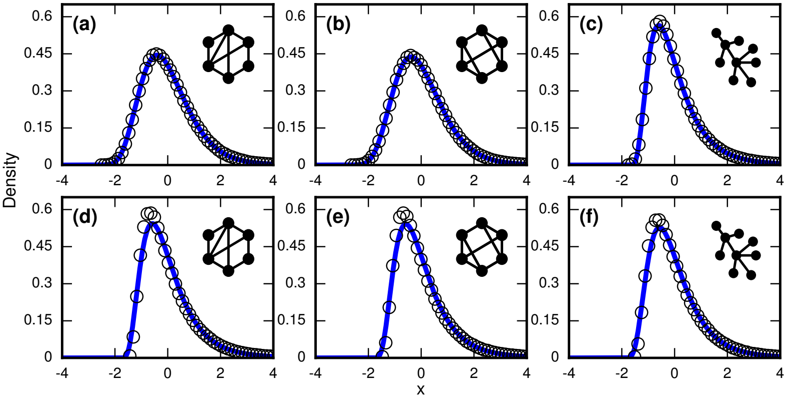



**Figure:** Top row: $r = \infty$. Bottom row: $r = 1$.