The Evolutionary Dynamics of Incubation Periods

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01/12/21

Outline

1. Personal background
2. What are incubation periods? Sartwell's law?
3. Introducing the Moran model(s)
4. Infinite r, complete graph and star graph
5. Lattices, critical dimensions
6. Future directions

I Am An Applied Mathematician

Previously:

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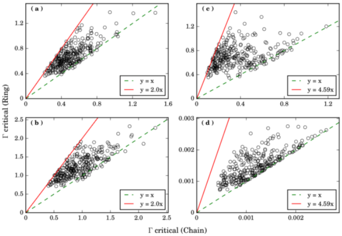
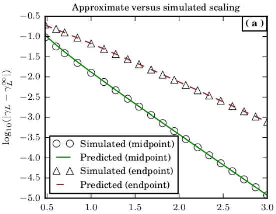
Previously:
Asymptotic Analysis!





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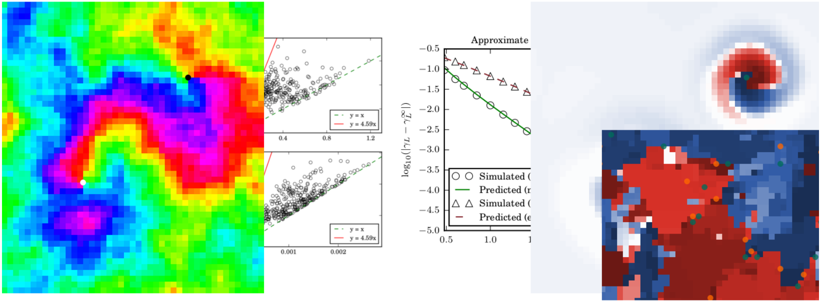

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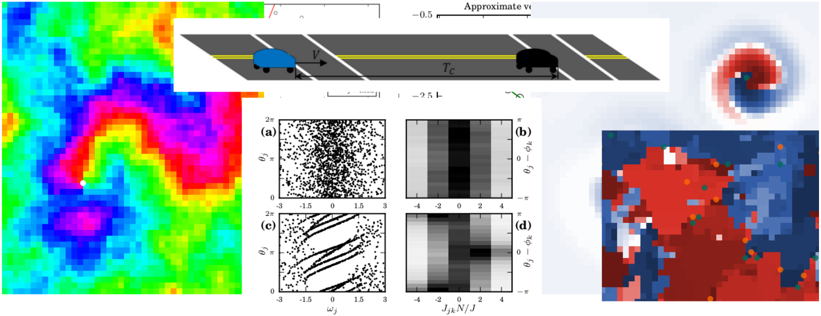

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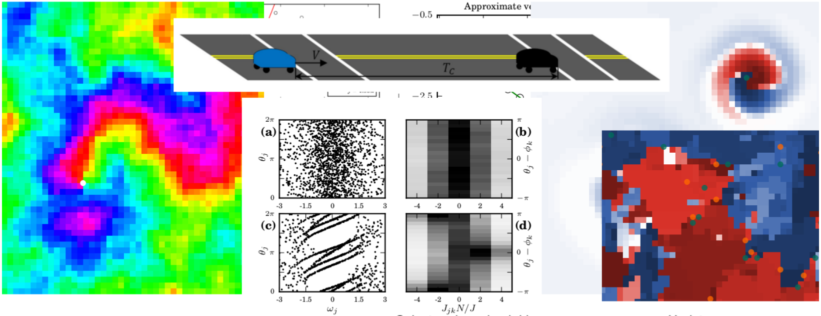
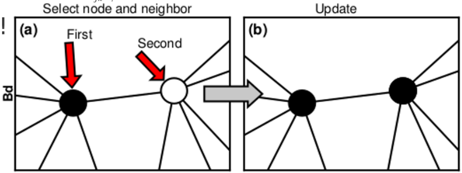


Today: Evolutionary dynamics!
Probability!
Stochastic Processes!
Typhoid!



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

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.

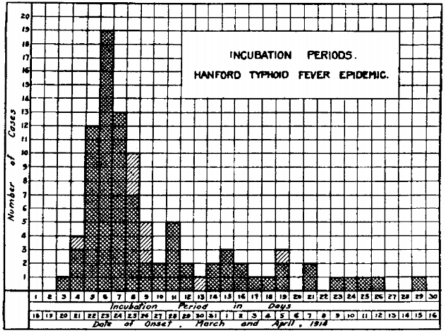


Chart of the cases in the Hanford typhoid fever epidemic, showing incubation periods and dates of onset. The heavily shaded areas represent definite cases of typhoid fever. The lightly shaded areas represent the doubtful cases.

The Incubation Period

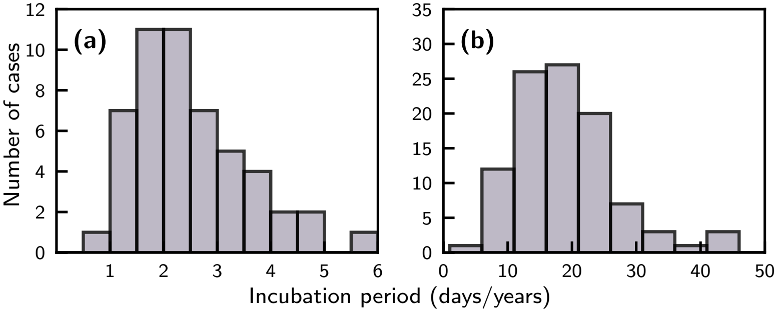
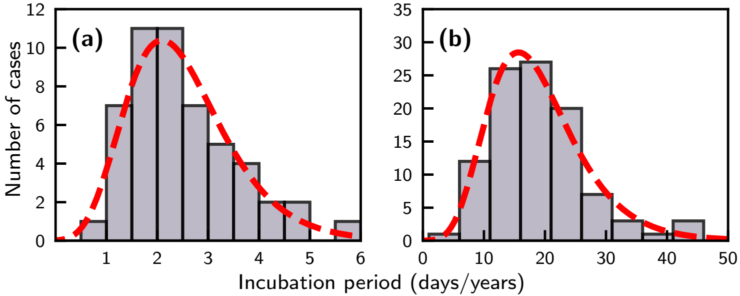


Figure: (a) Food-borne streptococcal sore throat (Sartwell 1950).
(b) Bladder tumors in a dye plant (Goldblatt 1949).

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

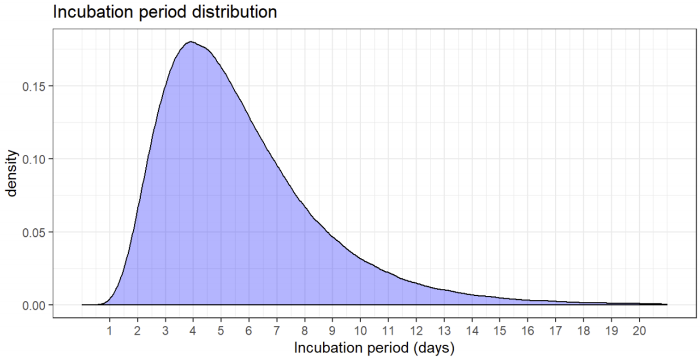


Figure 3 Probability density function of the pooled lognormal distribution of reported incubation period with mu=1.63 and sigma=0.50.

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

- We emulate the **Incubation Period** of a disease via the **The Takeover/Fixation Time** of an evolutionary takeover process on a network.

Evolutionary Graph Theory

Definition

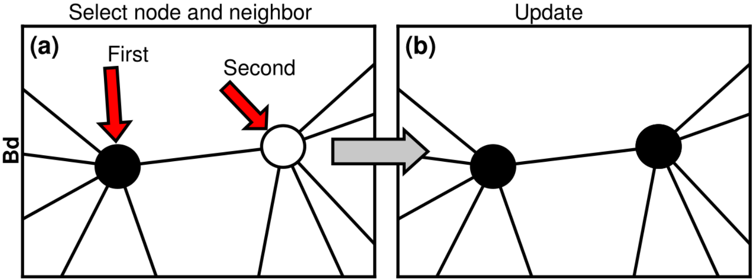
The **Fixation (or Takeover) Time** of a network evolutionary process is the time between the appearance of a single invader and 100% of the resident nodes being replaced by invaders.

Evolutionary Graph Theory

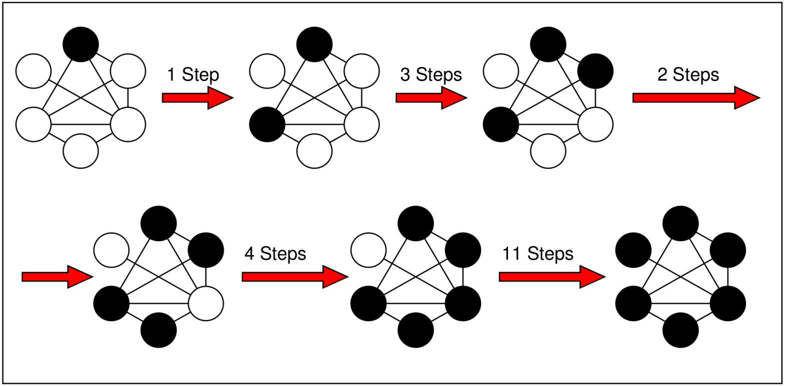
Definition

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

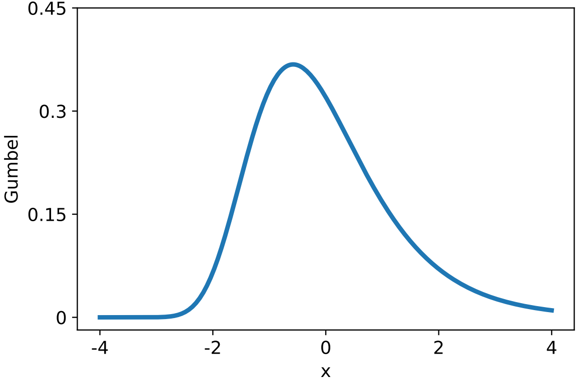
Each day, a kid gets one trading card, uniformly at random. Given that there are N distinct cards, what is the distribution of times T required to form a complete set?

The Complete Graph

Theorem

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

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



Proof Method

1) Find the probability p_m of a new invader appearing in the next step.
2) Notice the takeover time is a sum of geometric variables, $T_N = \sum_{m=1}^{N-1} \text{Geo}\left(p_m\right).$

Proof Method

Find the characteristic function of the normalized takeover time

$$\Phi(s) := E\left[\exp\left(is\frac{T_N - \mu}{\sigma}\right)\right],$$

and use approximation methods to show that Φ converges to a second characteristic function of known distribution.

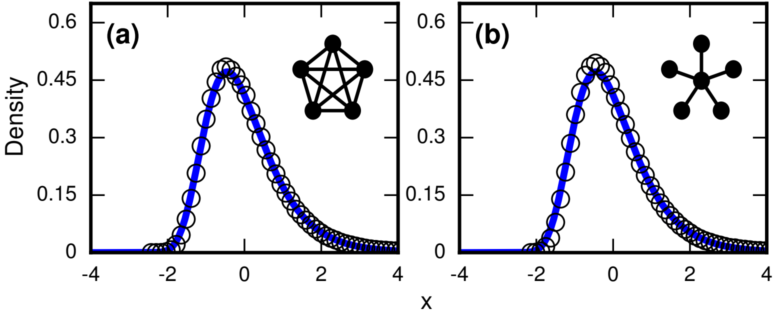
Complete Graph and Star Graph

Complete Graph:

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

Star Graph:

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



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.

Lattices: Surface Area to Volume

In general, predict

$$p_m \propto \frac{1}{m} \cdot \text{Surface area of of the invader cluster}$$
$$\propto \frac{\min(m, N-m)^{1-1/d}}{m}.$$

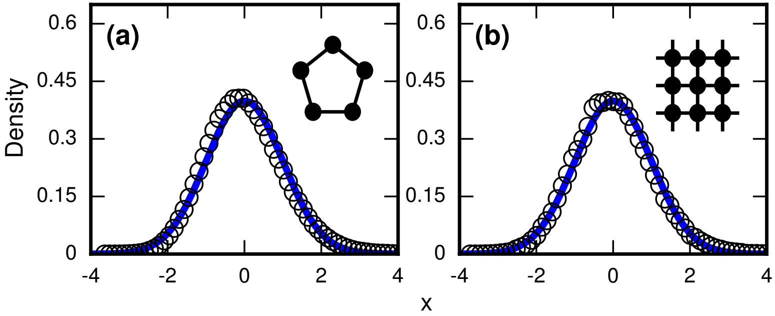
Therefore, the takeover time looks like

$$T \approx \sum_{m=1}^{N-1} \text{Geo}\left(\frac{\min(m, N-m)^{1-1/d}}{m}\right).$$

Lattices: Low Dimensions First

- Low dimensional surface area to volume ratios are “flat” in an objective way.
- Therefore, the Lindeberg-Feller central limit theorem applies.

Lattices: $d = 1$ and $d = 2$



Lattices: No Closed-Form for High Dimensions

Lattices: Skew Results

Lemma

If the independent random variables X_i have variances σ_i^2 and skews κ_i, then their sum has a skew of

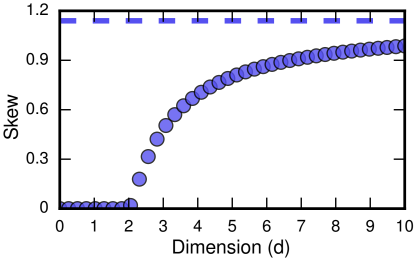
$$Skew\left(\sum_i X_i\right) = \frac{\sum_i \kappa_i \sigma_i^3}{\left(\sum_i \sigma_i^2\right)^{3/2}}$$

Lattice: $d \geq 3$.

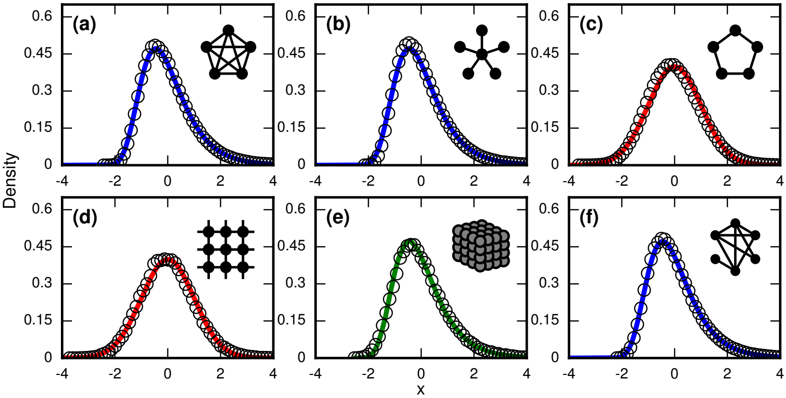
Theorem

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

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



Results for Infinite r



Non-infinite fitness?

Non-infinite fitness?

- Fact: We can only record an incubation period if someone *actually* gets sick.
- Therefore, we need to condition on the population X_n hitting N before ever hitting 0.

Fitness and Skew for Complete Graph

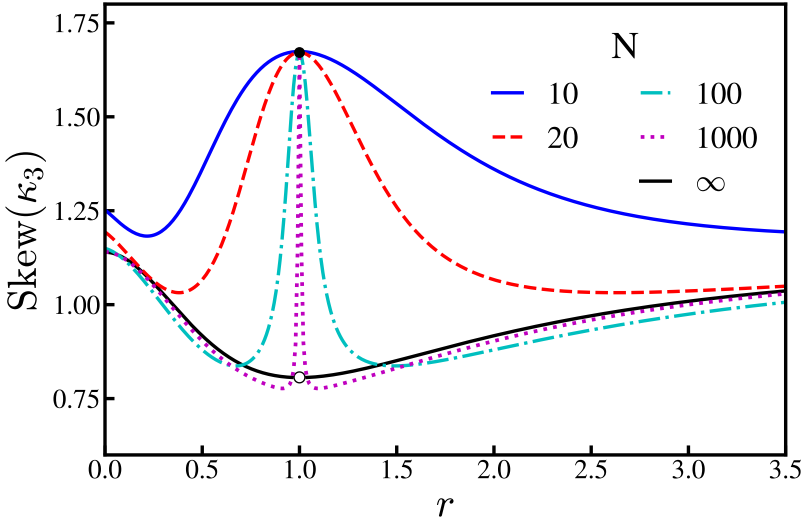


Figure: Hathcock 2019

Realism?

Red = Lognormal, Blue = Gumbel

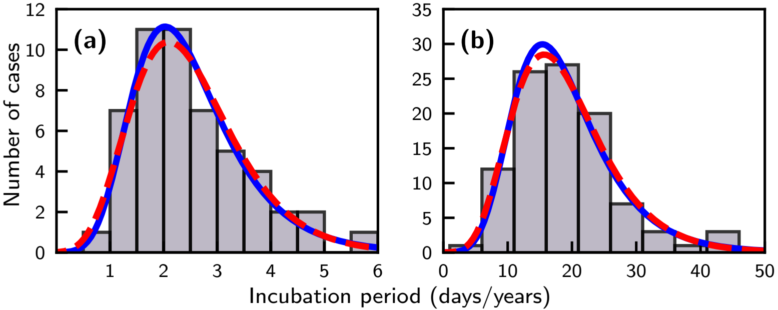


Figure: (a) Food-borne streptococcal sore throat (Sartwell 1950).
(b) Bladder tumors in a dye plant (Goldblatt 1949).

Main Point

Common aspects of disease growth:

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

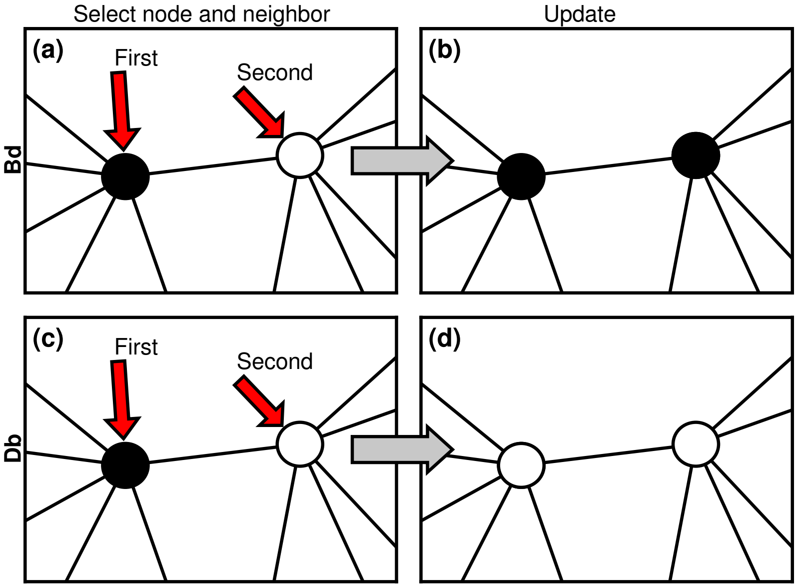
Together, they help justify Sartwell's Law.

Future Directions: Incubation Periods

Step order	Fitness-step first	Fitness-step second	Both fitness-steps
Birth first	Bd	bD	BD
Death first	Db	dB	DB

DOI: https://doi.org/10.7554/eLife.30212.006

The Moran Model



Future Directions: Incubation Periods

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- Diagnose universality within variants of Moran model.
- Connect to surface growth problems (e.g., KPZ).
- Is it possible back-derive disease properties from incubation times?

Future Directions: Growth Models

- Inconsistent growth rates lead to distribution shapes.
- What other consequences do randomized growth rates induce?

Future Directions: Seascape Fisher Equation

$$dy = \left(\mu y - ay^2 + D\nabla^2 y\right) dt + \sigma y dW,$$

Where y is a population, and dW is a Wiener process.

Future Directions: Growth Models

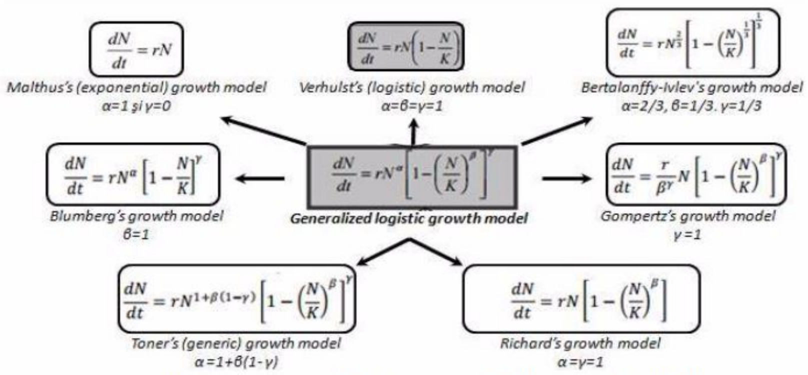
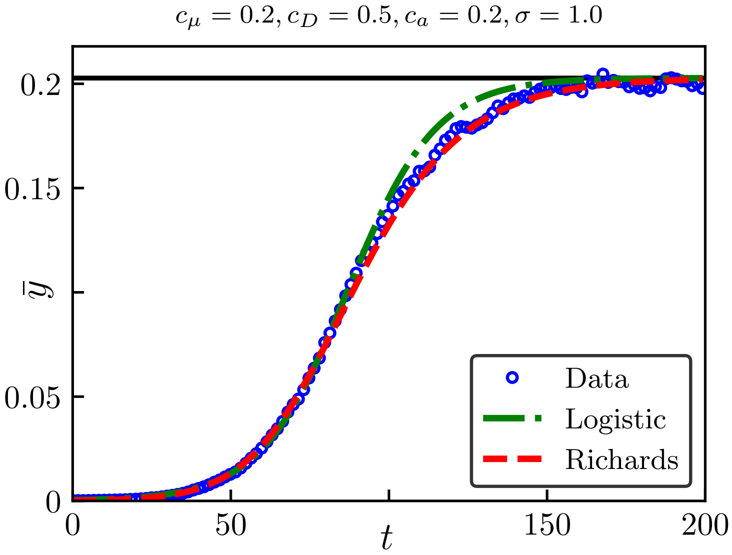


FIG. 3. The generalized logistic curve and its derivative models [11]

Figure: Cioruta (2016)

Future Directions: Growth Models with Diffusion



Future Directions: Gene Oscillators

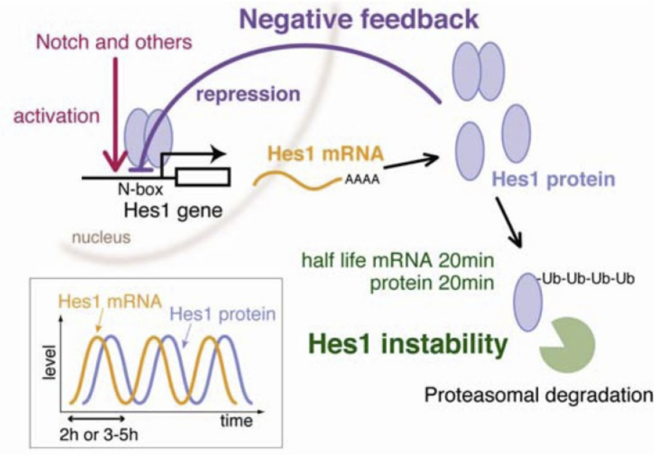
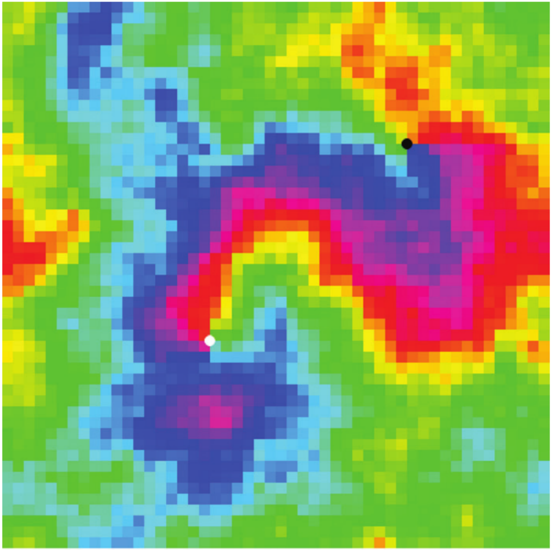


Figure: Takahashi (2011)

Can Delayed Oscillators Produce Patterns? Glasses?



Questions?

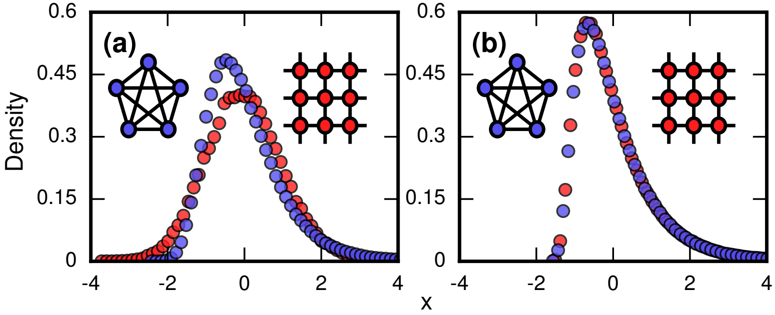


Figure: (a) $r = \infty$. (b) $r = 1$.

All slides available at: ottinoloffler.com

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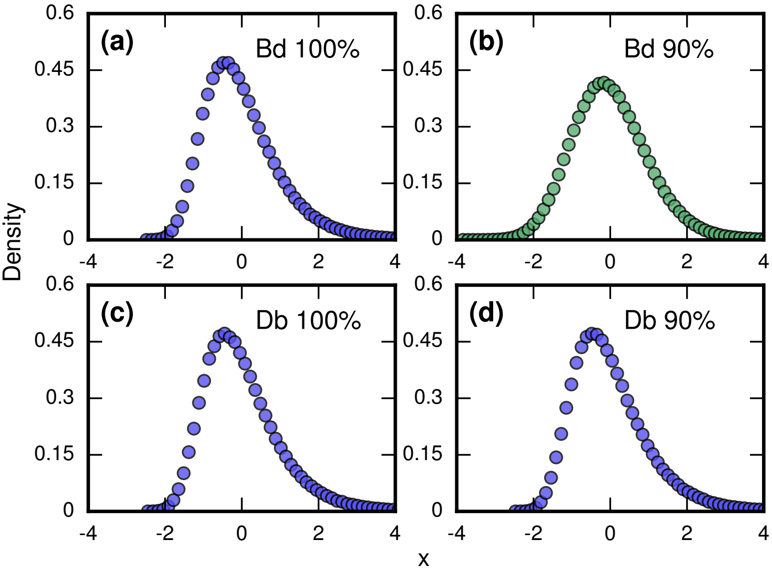
Summary: Truncation



Summary: Complex Networks

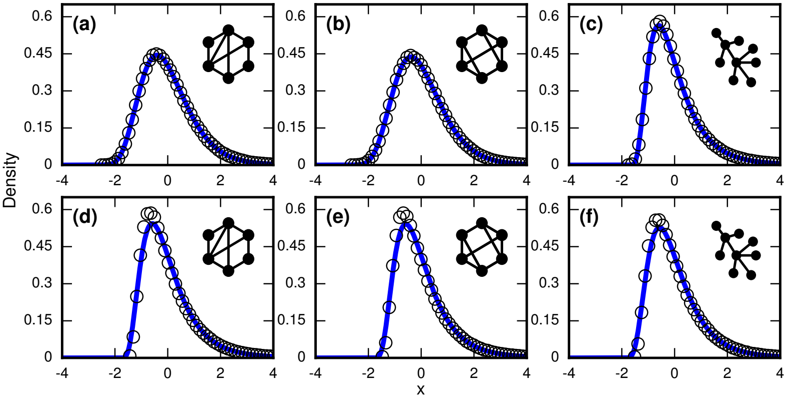


Figure: Top row: $r = \infty$. Bottom row: $r = 1$.