Lessons from Phage biology

-- from the dominant life on earth

*Escherichia coli*  
*Lambda bacteriophage*
Lessons:

• Networks: they do something!

• Phage games: Play random if many...

• Immunity, a game of new versus old
  ...................for all diseases at all times
  ...................red-queen for idea spreading
Two ways to be a phage

Virulent phages:
Infect $\rightarrow$ 1 hour $\rightarrow$ kill + 100 new phages

Temperate phages:

+immunity
Temperate phages have "brains":

Network of proteins that regulate each other,
Cyan: regulators, form the "brain",
Blue + brown: structure and work
About:

\( \textbf{Lysogeny:} \rightarrow \textbf{Lytic} \)

+ setting the switch....

\[
\frac{dLyt}{dt} = N \frac{K_2^{h2}}{K_2^{h2} + Lys^{h2}} - \frac{Lyt}{\tau_{Lyt}}
\]
Lambda phage count:

Only goes lytic if two phage infect simultaneously (Kourilsky, 1983)

Slope=2
What is needed?
Philosophy:

**Fitness of motif** = Robustness

= chance that random parameters make motif function

Functions: a) differentiate 1 from 2 phage infections, b) store this information
Examples of counting motifs:

Different colours $\rightarrow$ increased phage copy number in a cell

\[
\frac{dLyt}{dt} = N A_{Lyt}(Lyt, Lys) - \frac{Lyt}{\tau_{Lyt}}
\]

\[
A_{Lyt} = r \times \frac{Lyt^{h_1} + e \frac{K_{1}^{h_1}}{r}}{K_{1}^{h_1} + Lyt^{h_1}} \times \frac{K_{2}^{h_2}}{K_{2}^{h_2} + Lys^{h_2}}
\]
Everything can work, but not equally:
Everything goes,

But not equally

And at a cost

2-protein -> CI short lived

Details:
CI self repression bad.
Cro self repression not helpful
What about noise (#proteins small):
CII help against noise (and against short lived CI),
help more when syncrony with Cro (polycistronic operon),
help even more when stopped fast (N decay fast)
(Cro self repression not hepfull, CI self activation helps a factor 2)
Network Summary:
how to deal with missing parameters

• Robust function select for:
  mutual repression
  CI self activation
  CI short lived(!)

• Noise robustness select for:
  CII presense
  CII short lived
  CII production stopped
  CII after Cro on same mRNA
  .....As indeed seen in both lambda and p22 and 186

  ..... Our understanding of function and network design+logic fairly complete..... + variant solutions
#phages > 1
Why phage play dice
Choose $q$ that minimize $P=\text{death}$
Why play stochastically

Phages fate is together (now, $p_1$), bacteria separate fates in separate random futures ($p_2*p_2..$):

$$q? = q_{\text{min}}$$

$$P = q p_1 + (1 - q) p_2$$

$$P = q^n p_1 + n q^{n-1} (1 - q) p_1 p_2 + n(n - 1) q^{n-2} (1 - q)^2 p_1 p_2^2/2 +$$

$$+ n q (1 - q)^{n-1} p_1 p_2^{n-1} + (1 - q)^n p_2^n$$
Lesson:
if ``one for all'' → play dice.
as a way to nearly secure
a play on ``both horses''

Possible implication: Collective games,
versus
Cooperative games

------ industry age, cooperative games (by collaborating, overall gain, prisoners dilemma)

------ information age, collective games, search games where max randomness is
good search strategy.
(everybody gain from information
found by somebody)
This was all Together with:

M. Avlund (PhD thesis)
I. Dodd,
S. Krishna,
S. Semsey
#phages types>1
**Immunity: a game of new and old**

*Multiple phage-bacteria model:*

- Imagine a lattice with a bacterial colony on each site

- Phages spread from colony to colony, killing everybody except a few mutants (also true for virulent phages, *Luria-Delbruck, 1941*)

- Surviving colonies grows from nearly killed one, with immunity against previous attacks
A number game
where new replace old
(innovation and immunization)

With
Stefan Bornholdt
Mogens Jensen
Ala Trusina

CMOL/NBI
Minimal Model for: Innovation and immunization:

Old can never return, only one active number per site
1 parameter: Innovation rate \( \leq \) mutation rate
All sites is immune to all pathogens it ever had.

Select a site and attempt to spread its patogen to a neighbour. If neighbour immune then nothing happens. Else neighbour gets infected.

With small probability (a parameter), select a site and infect it with a new mutant pathogen.
Disase waves:
Varying alpha:

→ both activity & diversity goes up

$\alpha N > 1 \rightarrow$ many diseases eliminated by competition, i.e. Immunity spreading ($I$) decreases
Phage Ecology:

• Bacteria phage works at high alpha → huge diversity.

• Human society works at low alpha, but maybe not very low (e.g. in Africa)

• Ignored a few effects... death, limited immunity, some diseases help each other,
One more parameter: (→2)

![Graph showing the relationship between immunity half-life (τ) and the number of diseases (# Diseases). The graph displays a peak at an immunity half-life of around 50, with a decreasing trend as τ increases. The diagram includes color-coded patterns indicating the distribution of diseases at different immunity half-lives.]
Africa ---- Europe,
Both loose
Summary:

Introduced a ``red-queen game” where ``old” must move just to stay ahead of extinction by ``new’’.

A game where host immune memory and pathogen-pathogen exclusion are included

....but where death (of host) as an organizing principle have been ignored.
Thanks to:

- Phage games: M. Avlund, I. Dodd, S. Krishna and S. Semsey
- Phage networks: I. Dodd, K. Shearwin, B. Egan and A. Trusina
- Phage function and robustness: M. Avlund, I. Dodd, S. Krishna
- Multi-epidemics: S. Bornholdt, M.H.Jensen and A. Trusina
Welcome to the Center for Models of Life

In the Center for Models of Life, C-MOL, we use methods from physics to develop models dealing with computation and communication processes in biological systems.

We primarily model regulation of living systems with the aim to understand the strategies of gene regulation and dynamics of information transfer along signalling pathways, as well as to unravel the interplay between function and evolution.

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News

> Job openings
Two positions available: Assistant Professor and Post doc... [more]

> Workshop on Phages
Experiments and Modelling in may 2006 ... [more]

> Publication
Book on physics in molecular biology ... [more]

Research Areas

> Physics of Gene Regulation
Protein concentrations in a living cell are regulated through production and degradation. Production, in turn, can be regulated at either the transcriptional... [more]

> Models of Biological Circuits
Feedback and decision taking are both elements of biological systems. In some cases, e.g. in development and in lysis-lysogeny decisions of temperate phages...

> Networks and Communication
Communication is vital at any level of life - from a cell to human society. The network structure constrains communication in a complex system and we will ... [more]

> Evolution and Dynamical