

A population dynamics model of *Streptococcus pneumoniae* using genomics & Implementing a model translation and visualisation tool

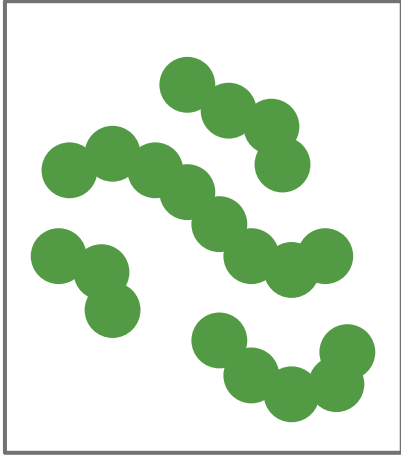
Leonie Lorenz

PhD Student | Lees group | EMBL-EBI

24.03.2025

**A population dynamics model
of *Streptococcus pneumoniae* using genomics**

Streptococcus pneumoniae

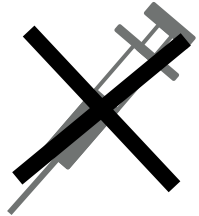
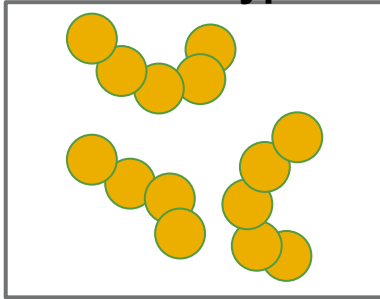


- Serotypically diverse bacteria with more than 100 serotypes
- Genetically diverse with hundreds of lineages/strains
- Major cause of diseases, including pneumonia and meningitis, especially in young children under 2 years of age and adults over 65 years of age
- Treatment: antibiotics
- Prevention: pneumococcal vaccines

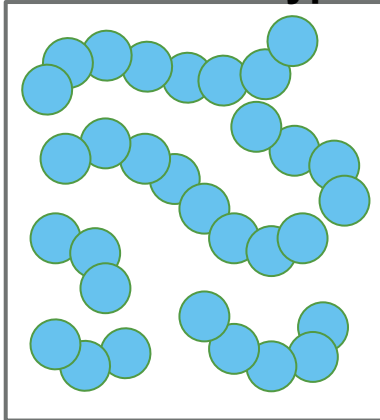
Pneumococcal vaccines



Vaccine types



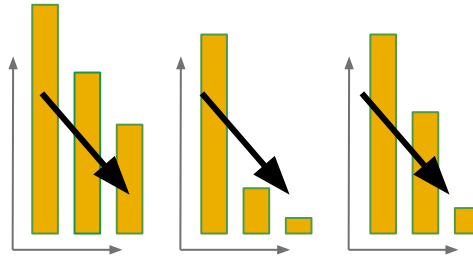
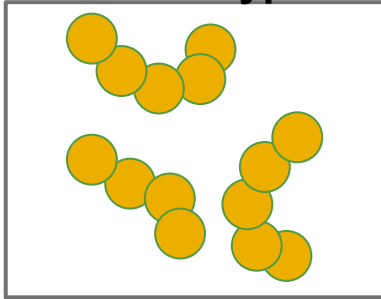
Non-vaccine types



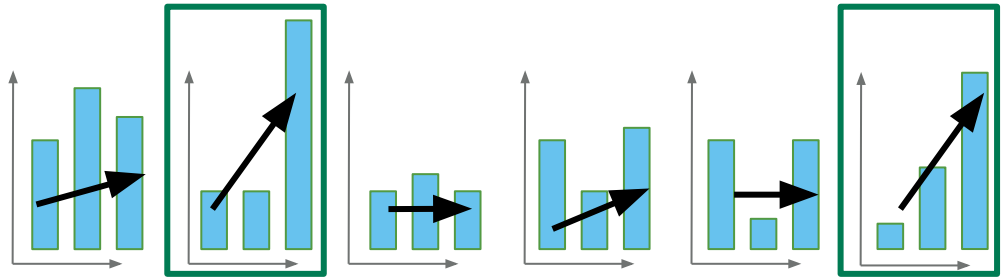
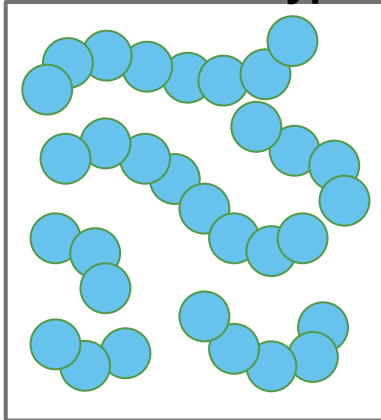
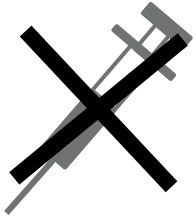
Pneumococcal vaccines



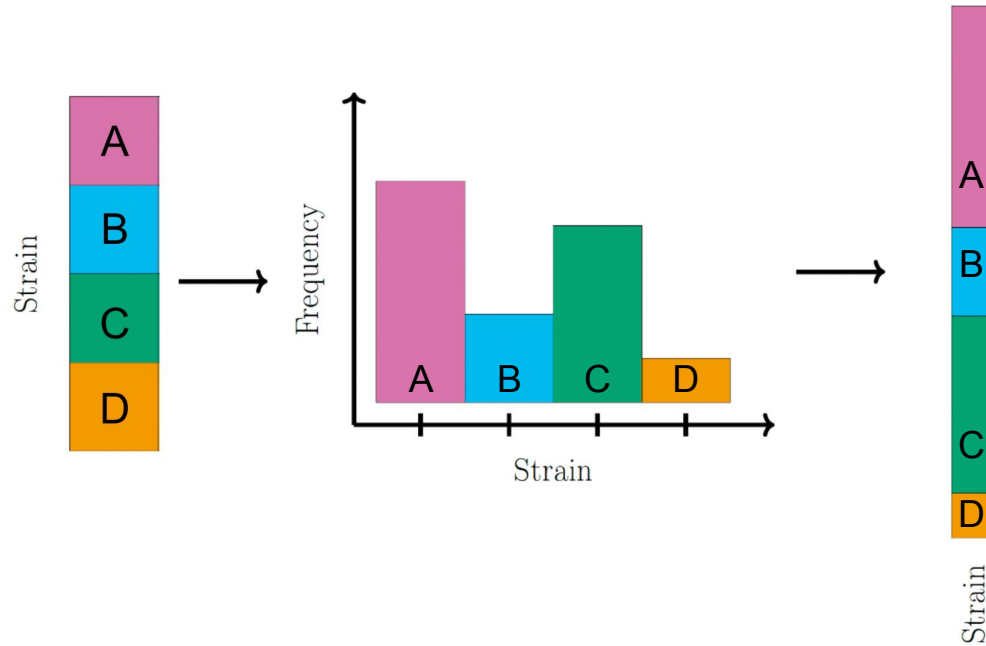
Vaccine types



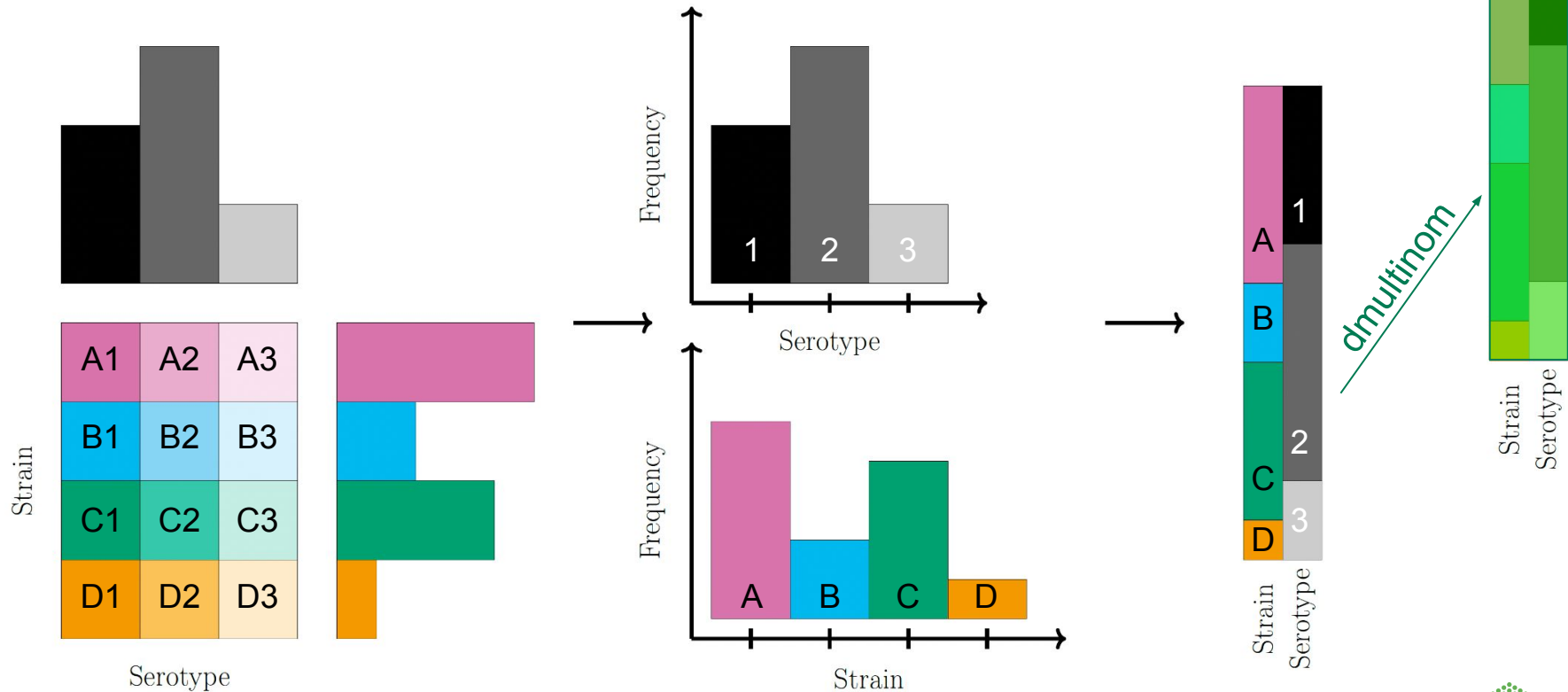
Non-vaccine types



Simple compartmental Model



Compartmental Model with Sub-compartments



Compartmental Model with Sub-compartments

Parameters:

- **NFDS** σ_f
- **prop** f
- **vaccination** v
- **migration** m

$$P_{i,j}^{t+1} = B_{i,j}^t + M_{i,j}^t$$

Population Births Migration

$$B_{i,j}^t \sim \text{Poisson}\left(K \cdot \left(\frac{p_{i,j}^t}{\sum_{i=1}^n \sum_{j=1}^l p_{i,j}^t}\right) * (1 - \mathbf{m})\right)$$

$$p_{i,j}^t = (1 + \sigma_f)^{\pi_{i,t}} * P_{i,j}^t * (1 - (v_{\text{time}}(t) * v_{\text{type}}(j) * \mathbf{v}))$$

$$\pi_{i,t} = \sum_{l \in G_i, l \in S} e_l - f_{l,t}$$

$$M_{i,j}^t \sim \text{binomial}(\hat{m}^t, m_{i,j})$$

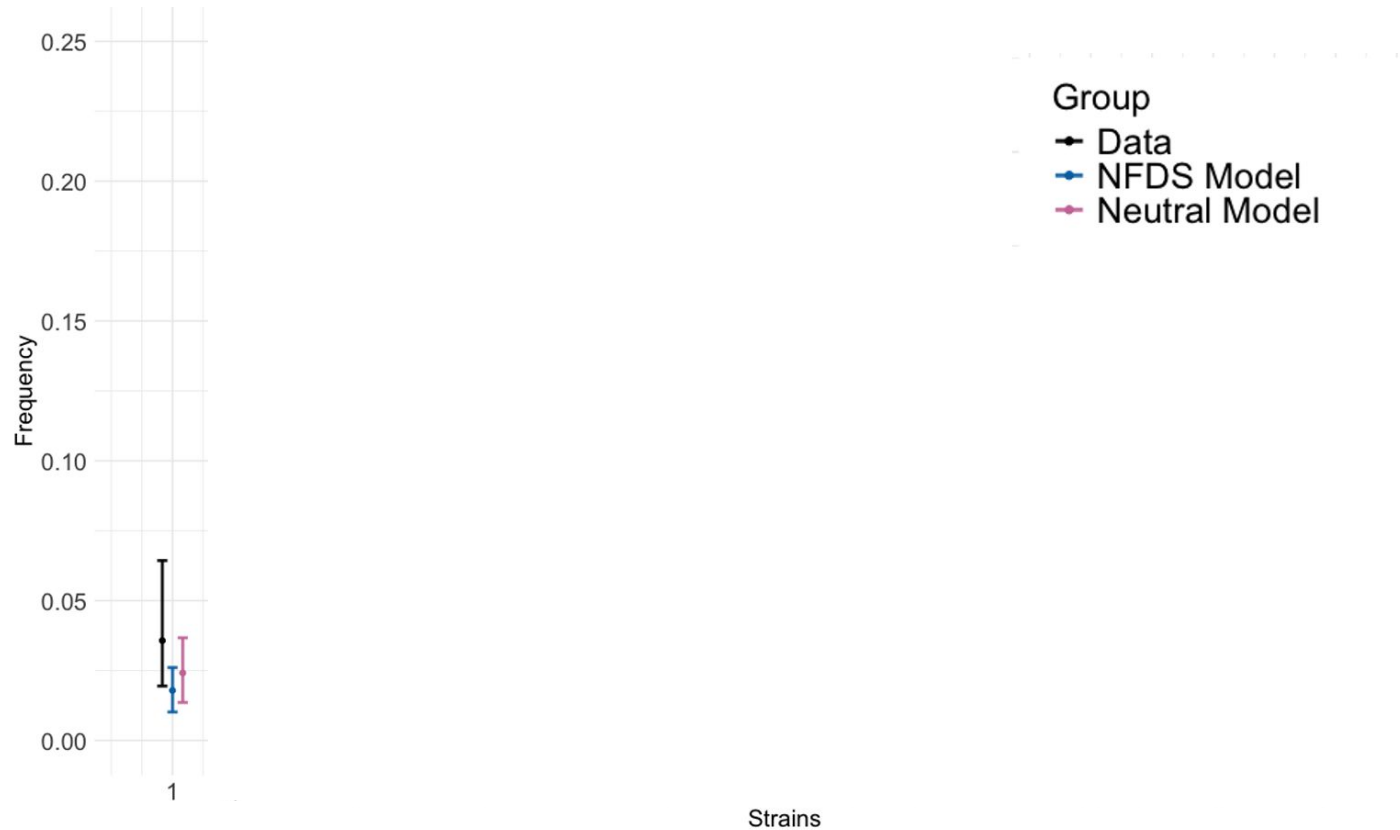
$$\hat{m}^t \sim \text{binomial}(K, \mathbf{m})$$

```

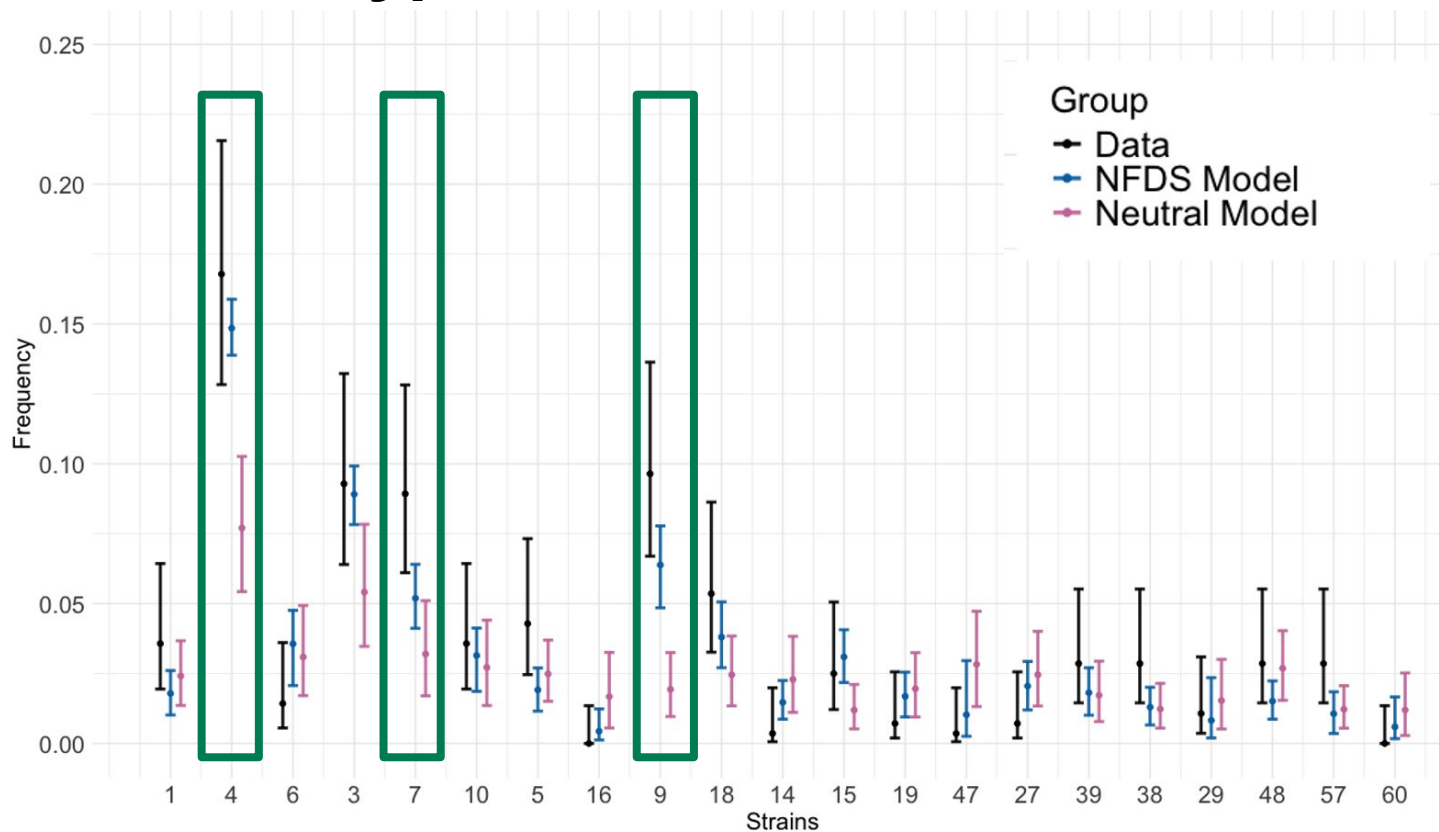
43 # identify genes that are under NFDS
44 pi_f_freq[,] <- if ((delta[i] <= prop_f * gene_no)) Genotypes[i,j] * (eq[i] - freq[i]) else 0
45 pi_f_genotypes[] <- sum(pi_f_freq[1:gene_no,i])
46
47 # Genotype specific probability to produce offspring
48 # those are the individuals' probabilities multiplied by the number of individual that have this genotype
49 probs[,] <- (1 + exp(sigma_f))^pi_f_genotypes[i] * Pop[i,j] * (1- (as.integer(time >= vacc_time) * vaccTypes[j] * v))
50
51 # generate the next generation based on the current one
52 y[,] <- if ((probs[i,j]/sum(probs[1:species_no,1:sero_no])) < 1)
53   rpois(capacity * (probs[i,j] / sum(probs[1:species_no,1:sero_no])) * (1-exp(m)) ) else rpois(capacity * 1 *(1-exp(m)) )
54
55 # m is the migration rate
56 # fitness of individuals in the community is reduced by this rate
57 # determining migration number:
58 mig_num <- rbinom(capacity, exp(m))
59 Pop_mig[,] <- rbinom(mig_num, migVec[i,j])
60
61 ## Core equation for population (assume constant size here):
62 update(Pop[,]) <- y[i,j] + Pop_mig[i,j]
63 update(Pop_tot[]) <- sum(y[i,]) + sum(Pop_mig[i,])
64
65 initial(Pop[,]) <- Pop_ini[i,j] # deterministic, user-based start value
66 initial(Pop_tot[]) <- sum(Pop_ini[i,])
67

```

Strain-serotype Model Fit to Massachusetts



Strain-serotype Model Fit to Massachusetts



Strain-serotype Model Fit - Parameter Comparison

Parameter	Massachusetts	Southampton	Nepal
neg. log likelihood	-236.12234 (-239.9329 , -233.6487)	-562.76 (-567.6667, -560.4743)	-2415.2916 (-2419.1133, -2412.7752)
Strength of NFDS σ_f	0.0345 (0.0144, 0.0685)	0.0379 (0.0133, 0.0826)	0.4670 (0.3474, 0.5386)
Proportion of genes under NFDS prop_f	0.28835 (0.20115, 0.4566)	0.1614 (0.1077, 0.3611)	0.1708 (0.1584, 0.1967)
Migration rate m	0.0133 (0.0087, 0.0214)	0.0185 (0.0126, 0.0252)	0.0792 (0.0648, 0.0953)
Vaccination selection strength v	0.0814 (0.0627, 0.1046)	0.0905 (0.0759, 0.1055)	0.1766 (0.1405, 0.2159)

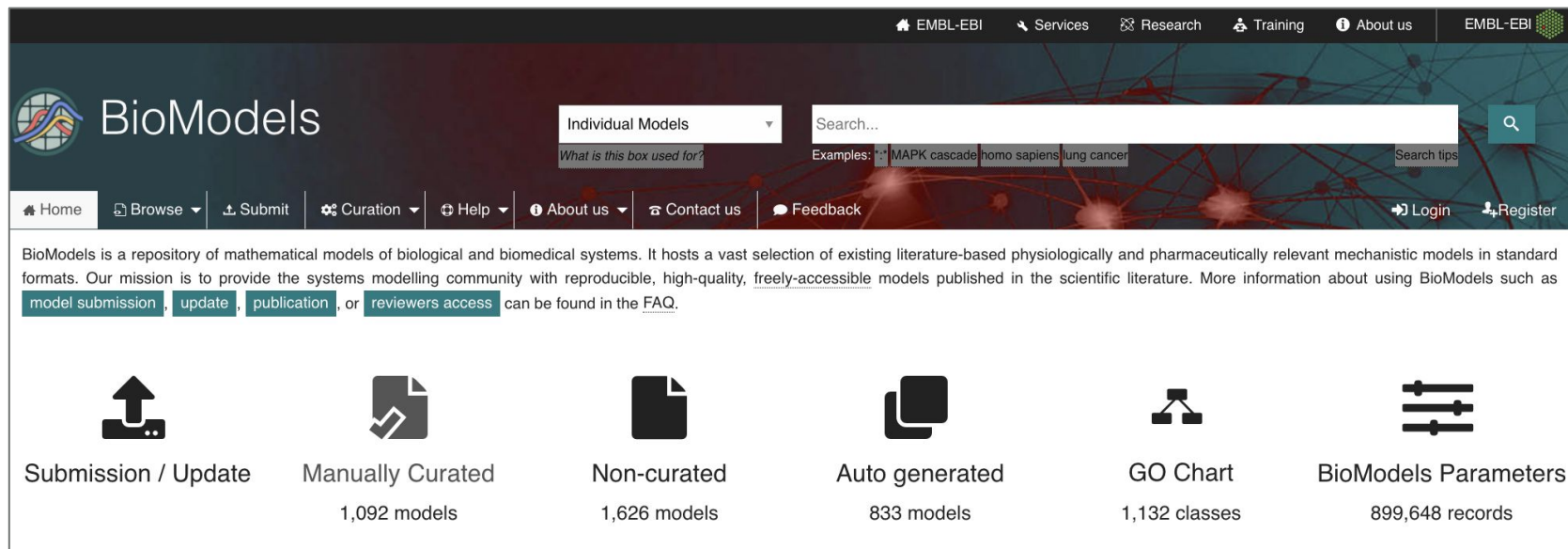
Benefits of implementing this model in odin

- Defining variables as vectors / matrices
- Readability of the model code (looks like equations)
- Reproducibility when fitting the model
- Having a likelihood and using MCMC
- It's fast

—> Reusability

Implementing a model translation and visualisation tool

Model Accessibility



The screenshot displays the BioModels website. At the top, there is a navigation bar with links for Home, Browse, Submit, Curation, Help, About us, Contact us, and Feedback. A search bar is prominently featured with a dropdown menu for 'Individual Models' and a search input field. Below the search bar, a list of model categories is shown, each with an icon and a count of models or records. The categories include Submission / Update (1,092 models), Manually Curated (1,626 models), Non-curated (833 models), Auto generated (1,132 classes), GO Chart (899,648 records), and BioModels Parameters (899,648 records).

EMBL-EBI Services Research Training About us EMBL-EBI

BioModels

Individual Models Search... Search tips

Examples: MAPK cascade homo sapiens lung cancer

Home Browse Submit Curation Help About us Contact us Feedback Login Register

BioModels is a repository of mathematical models of biological and biomedical systems. It hosts a vast selection of existing literature-based physiologically and pharmaceutically relevant mechanistic models in standard formats. Our mission is to provide the systems modelling community with reproducible, high-quality, freely-accessible models published in the scientific literature. More information about using BioModels such as [model submission](#), [update](#), [publication](#), or [reviewers access](#) can be found in the [FAQ](#).

Submission / Update	Manually Curated	Non-curated	Auto generated	GO Chart	BioModels Parameters
1,092 models	1,626 models	833 models	1,132 classes	899,648 records	

Model Accessibility

Elowitz2000 - Repressilator

[View the 2006-07 Model of the Month entry for this model >](#)



Overview Files History Components Curation

Model Identifier Short description

BIOMD0000000012

Elowitz2000 - Repressilator

This model describes the deterministic version of the repressilator system.

The authors of this model (see reference) use three transcriptional repressor systems that are not part of any natural biological clock to build an oscillating network that they called the repressilator. The model system was induced in *Escherichia coli*.

In this system, LacI (variable X is the mRNA, variable PX is the protein) inhibits the tetracycline-resistance transposon tetR (Y, PY describe mRNA and protein). Protein tetR inhibits the gene CI from phage Lambda (Z, PZ: mRNA, protein), and protein CI inhibits lacI expression. With the appropriate parameter values this system oscillates.

This model is described in the article:

[A synthetic oscillatory network of transcriptional regulators.](#)

Elowitz MB, Leibler S.

Nature. 2000 Jan; 403(6767):335-338

Abstract:

Networks of interacting biomolecules carry out many essential functions in living cells, but the 'design principles' underlying the functioning of such intracellular networks remain poorly understood, despite intensive efforts including quantitative analysis of relatively simple systems. Here we present a complementary approach to this problem: the design and construction of a synthetic network to implement a particular function. We used three transcriptional repressor systems that are not part of any natural biological clock to build an oscillating network, termed the repressilator, in *Escherichia coli*. The network periodically induces the synthesis of green fluorescent protein as a readout of its state in individual cells. The resulting oscillations, with typical periods of hours, are slower than the cell-division cycle, so the state of the oscillator has to be transmitted from generation to generation. This artificial clock displays noisy behaviour, possibly because of stochastic fluctuations of its components. Such 'rational network design' may lead both to the engineering of new cellular behaviours and to an improved understanding of naturally occurring networks.

The model is based upon the equations in Box 1 of the paper; however, these equations as printed are dimensionless, and the correct dimensions have been returned to the equations, and the parameters set to reproduce Figure 1C (left).

The original model was generated by B.E. Shapiro using Cellerator version 1.0 update 2.1127 using Mathematica 4.2 for Mac OS X (June 4, 2002), November 27, 2002 12:15:32, using (PowerMac, PowerPC, Mac OS X, MacOSX, Darwin).

Nicolas Le Novère provided a corrected version generated by SBMLeditor on Sun Aug 20 00:44:05 BST 2006. This removed the EmptySet species. Ran fine on COPASI 4.0 build 18.

Bruce Shapiro revised the model with SBMLeditor on 23 October 2006 20:39 PST. This defines default units and correct reactions. The original Cellerator reactions while being mathematically correct did not accurately reflect the intent of the authors. The original notes were mostly removed because they were mostly incorrect in the revised version. Tested with MathSBML 2.6.0.

Nicolas Le Novère changed the volume to 1 cubic micrometre, to allow for stochastic simulation.

Metadata information

is (2 statements)

BioModels Database [BIOMD0000000012](#)

BioModels Database [MODEL6615351360](#)

isDescribedBy (1 statement)

PubMed [10659856](#)

hasTaxon (1 statement)

Taxonomy *Escherichia coli*

isVersionOf (1 statement)

Gene Ontology [regulation of gene expression, epigenetic](#)

hasProperty (1 statement)

Mathematical Modelling Ontology [Ordinary differential equation model](#)

Curation status [Curated](#)

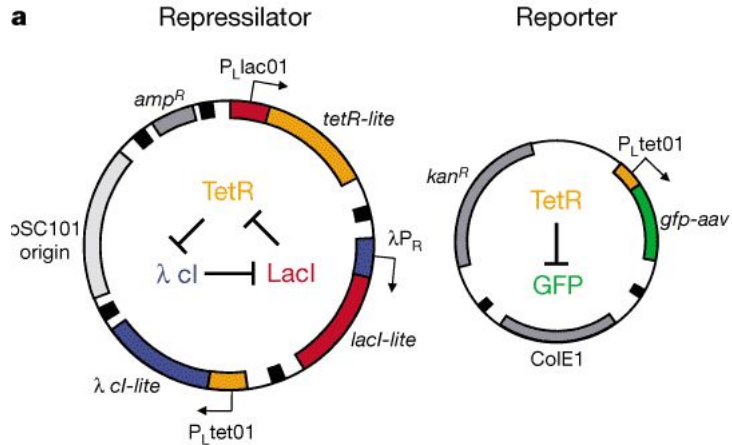
Modelling approach(es) [ordinary differential equation model](#)

Connected external resources

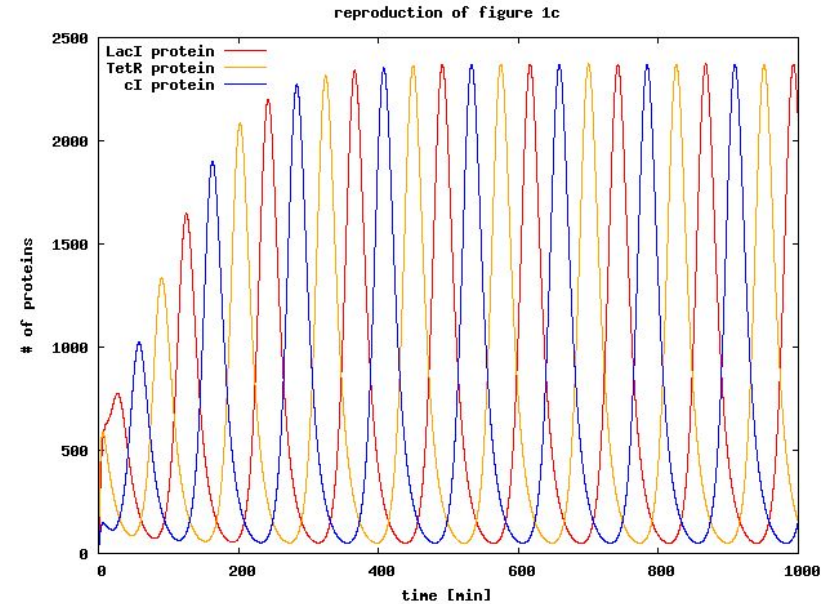


SBGN view in New Editor

System Biology Models



Adapted from Elowitz and Leibler (2000)
DOI: [10.1038/35002125](https://doi.org/10.1038/35002125)



Taken from BioModels
<https://www.ebi.ac.uk/biomodels/BIOMD0000000012#Curation>

The pipeline



BioModels

ODE Models in
SBML

 **Systems Biology
Markup Language**

```
</lambda>
</math>
</functionDefinition>
</listOfFunctionDefinitions>
<listOfUnitDefinitions>
  <unitDefinition id="length" name="length">
    <listOfUnits>
      <unit exponent="1" kind="metre" multiplier="1" scale="0"/>
    </listOfUnits>
  </unitDefinition>
  <unitDefinition id="area" name="area">
    <listOfUnits>
      <unit exponent="2" kind="metre" multiplier="1" scale="0"/>
    </listOfUnits>
  </unitDefinition>
  <unitDefinition id="volume" name="volume">
    <listOfUnits>
      <unit exponent="1" kind="litre" multiplier="1" scale="-3"/>
    </listOfUnits>
  </unitDefinition>
  <unitDefinition id="time" name="time">
    <listOfUnits>
      <unit exponent="1" kind="second" multiplier="86400" scale="0"/>
    </listOfUnits>
  </unitDefinition>
  <unitDefinition id="substance" name="substance">
    <listOfUnits>
```

Import BioModels into odin

SBML file

```
<math xmlns="http://www.w3.org/1998/Math/MathML">
  <lambda>
    <bvar>
      <ci> z </ci>
    </bvar>
    <bvar>
      <ci> beta_t </ci>
    </bvar>
    <bvar>
      <ci> S </ci>
    </bvar>
    <bvar>
      <ci> I </ci>
    </bvar>
    <bvar>
      <ci> N </ci>
    </bvar>
    <apply>
      <divide/>
      <apply>
        <times/>
        <ci> z </ci>
        <ci> beta_t </ci>
        <ci> S </ci>
        <ci> I </ci>
      </apply>
      <ci> N </ci>
    </apply>
  </lambda>
</math>
</functionDefinition>
</listOfFunctionDefinitions>
<listOfUnitDefinitions>
  <unitDefinition id="length" name="length">
    <listOfUnits>
      <unit exponent="1" kind="metre" multiplier="1" scale="0"/>
    </listOfUnits>
  </unitDefinition>
  <unitDefinition id="area" name="area">
    <listOfUnits>
      <unit exponent="2" kind="metre" multiplier="1" scale="0"/>
    </listOfUnits>
  </unitDefinition>
  <unitDefinition id="volume" name="volume">
    <listOfUnits>
      <unit exponent="1" kind="litre" multiplier="1" scale="-3"/>
    </listOfUnits>
  </unitDefinition>
  <unitDefinition id="time" name="time">
    <listOfUnits>
      <unit exponent="1" kind="second" multiplier="86400" scale="0"/>
    </listOfUnits>
  </unitDefinition>
  <unitDefinition id="substance" name="substance">
    <listOfUnits>
```

SBMLtoOdin



Automatically generated code by SBMLtoOdin

```
1 initial(Susceptible) <- Susceptible_init
2 Susceptible_init <- user(32680000)
3 initial(Infected) <- Infected_init
4 Infected_init <- user(728)
5 initial(Removed) <- Removed_init
6 Removed_init <- user(62.00000000000001)
7 delta <- Trigger_Stage_1 * 0.025 + Trigger_Stage_2 * 0.042 + Trigger_Stage_3 * 0.05
8 p <- Trigger_Stage_1 * 0.0784 + Trigger_Stage_2 * 0.045 + Trigger_Stage_3 * 0.0466
9 z <- Trigger_Stage_1 * 0.4374 + Trigger_Stage_2 * 0.3914 + Trigger_Stage_3 * 0.4047
10 N <- Infected + Removed + Susceptible
11 I_total <- Infected + Removed
12 beta <- beta_0 * (1 - p)^( t)
13 deriv(Susceptible) <- 0 - Malayasia * z * beta * Susceptible * Infected / N
14 deriv(Infected) <- 0 + Malayasia * z * beta * Susceptible * Infected / N - Malayasia * delta * Infected
15 deriv(Removed) <- 0 + Malayasia * delta * Infected
16 beta_0 <- user(0.4114)
17 Trigger_Stage_1 <- user(0)
18 Trigger_Stage_2 <- user(0)
19 Trigger_Stage_3 <- user(1)
20 Malayasia <- 1
```



odin

Import BioModels into odin

```
# SIR model example (Malaysia)
```

```
importSBMLfromBioModels("BIOMD0000000982", "../LawModel.R")
```

```
model_generator <- odin::odin("../LawModel.R") # creates model
```

```
LawModel <- model_generator$new() #creates object, with parameters if needed
```

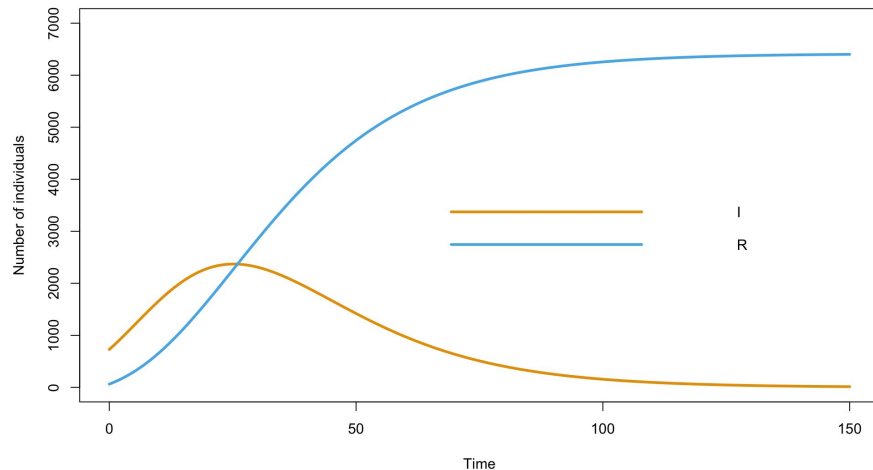
```
LawModel_res <- LawModel$run(0:150) # runs model forward in time, for specified time
```

```
# plot simulation
```

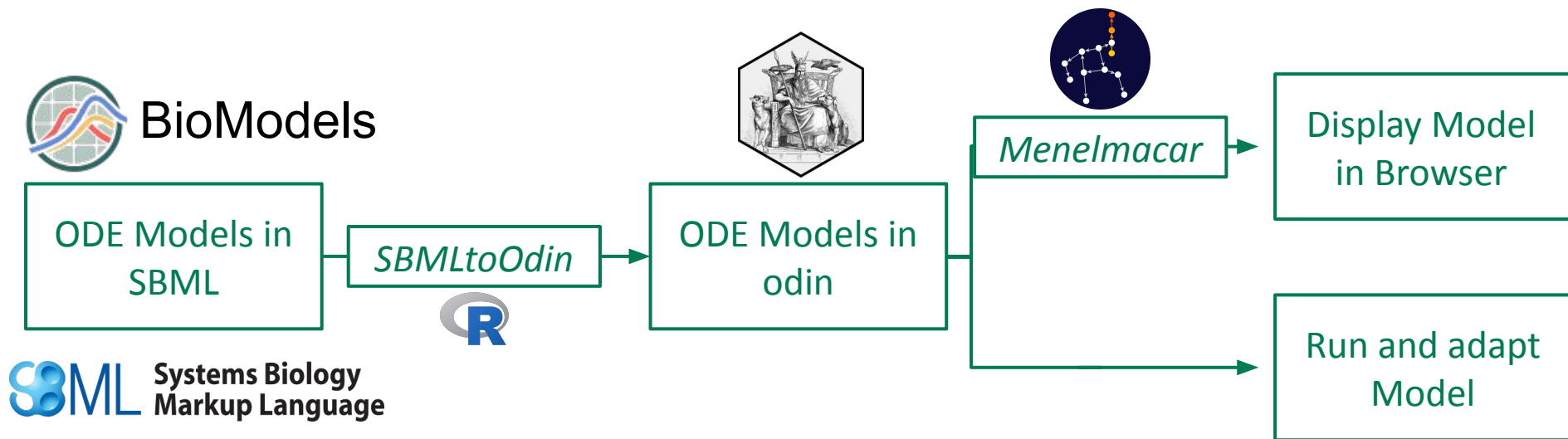
```
matplot(LawModel_res[, 1], LawModel_res[, c(3,4)], xlab = "Time", ylab = "Number of individuals",
```

```
type = "l", col = c(I = "#E69F00", R = "#56B4E9"), lty = 1, ylim = c(0,7000), lwd = 3)
```

```
legend(x = 50, y = 4000, lwd = 3, col = c("#E69F00", "#56B4E9"), legend = c("I", "R"), bty = "n")
```



The pipeline



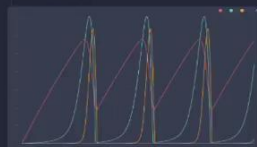
What is Menelmacar?

Menelmacar - Making Execution of (Nearly) Every Life-science Model ACcessible to All Researchers, helps to visualise models from the EMBL-EBI's BioModels database. You can investigate the models' development over time, change parameter values and observe changes in the model trajectory, and see the model graph.

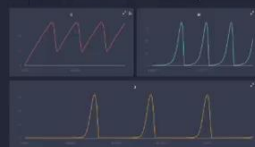
Example models: BIOMD0000000012 BIOMD0000000003



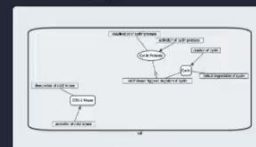
Plot a model



Plot each variable individually



Show as a graph



Frequently asked questions

- ✓ What is this website for?
- ✓ Who is this website for?
- ✓ How can I visualise a specific model?
- ✓ How do I know which models are available and how can I find models for a specific topic or organism?
- ✓ What information can be found in the different tabs of the website?

Noticed an error with a model? Report it here.

© 2025. All rights reserved.

Project idea and SBMLtoOdin: Leonie Lorenz and John Lees,

Code availability

- SBMLtoOdin: <https://github.com/bacpop/SBMLtoOdin>
- Menelmacar website:
 - Code: <https://github.com/bacpop/odinviewer>
 - Website: biomodels.bacpop.org
- NFDS Model: <https://github.com/bacpop/compartmental-models-odin-dust>

THANK YOU

Pathogen Informatics and Modelling Group

John Lees

Joel Hellewell

Jacqueline Toussaint

Hsueh-Chien (Raymond) Cheng

Samuel Horsfield

Johanna von Wachsman

Víctor Rodríguez Bouza

Tanushree Tunstall

Daniel Anderson

Daria Frolova

Gherard Batisti Biffignandi

Ines Sanchez-Hombria

Andrea Sanchez Serrano

Alireza Tajmiriahi



Collaborators

Nick Croucher

Henrik Salje

Stephanie Lo

Stephen Bentley

Rahuman S. Malik Sheriff

Gomoku Studio :

Andrea Epifani, Zeqing Lu