Stochastic modelling in Mathematical Biology

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March 4th 2013

SIMBa

Seminari Informal
de Matemàtiques de Barcelona

Outline

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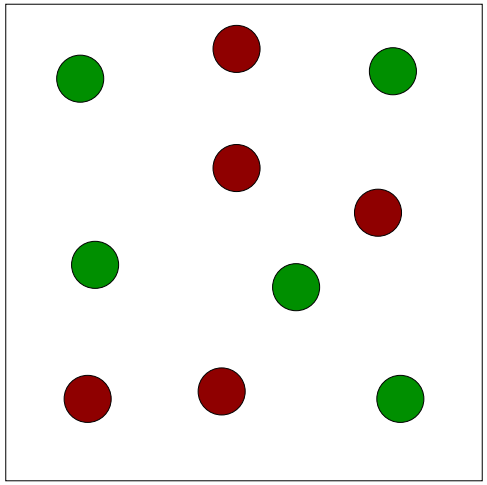
Motivation

- There exists the general idea that randomness and noise simply add an unsystematic perturbation to a well-defined average behaviour.
- I will present several examples of systems in which noise contributes to the behaviour of the system in a non-trivial manner and it is fundamental to understanding the system.
- From these examples I will extract rules of thumb for ascertaining when randomness plays a fundamental roles.
- I will show you how to modelize some natural process in a better way than using a continuous and deterministic approach.

The Moran Process

The Moran process, named after the australian statistician Pat Moran, is a widely-used variant of the Wright-Fisher model and is commonly used in population genetics.



- N individuals of two types. N is keep fixed.
- n: number of normal individuals. m: number of mutant individuals. N=m+n.
- At each time step:
  - $n \to n+1$ and $m \to m-1$ with probability rate $W_+(n) = \frac{n}{N}\left(1 - \frac{n}{N}\right)$.
  - $n \to n-1$ and $m \to m+1$ with probability rate $W_-(n) = \frac{n}{N}\left(1 - \frac{n}{N}\right)$.

The Moran Process

- Note that $W(n+1) = W(n-1)$, i.e. $\mathbb{E}[\Delta n] = \mathbb{E}[n(t+\Delta t) - n(t)] = 0$.
- This implies that with $m = \mathbb{E}[n]$:

$$\frac{dm}{dt} = 0 \tag{1}$$

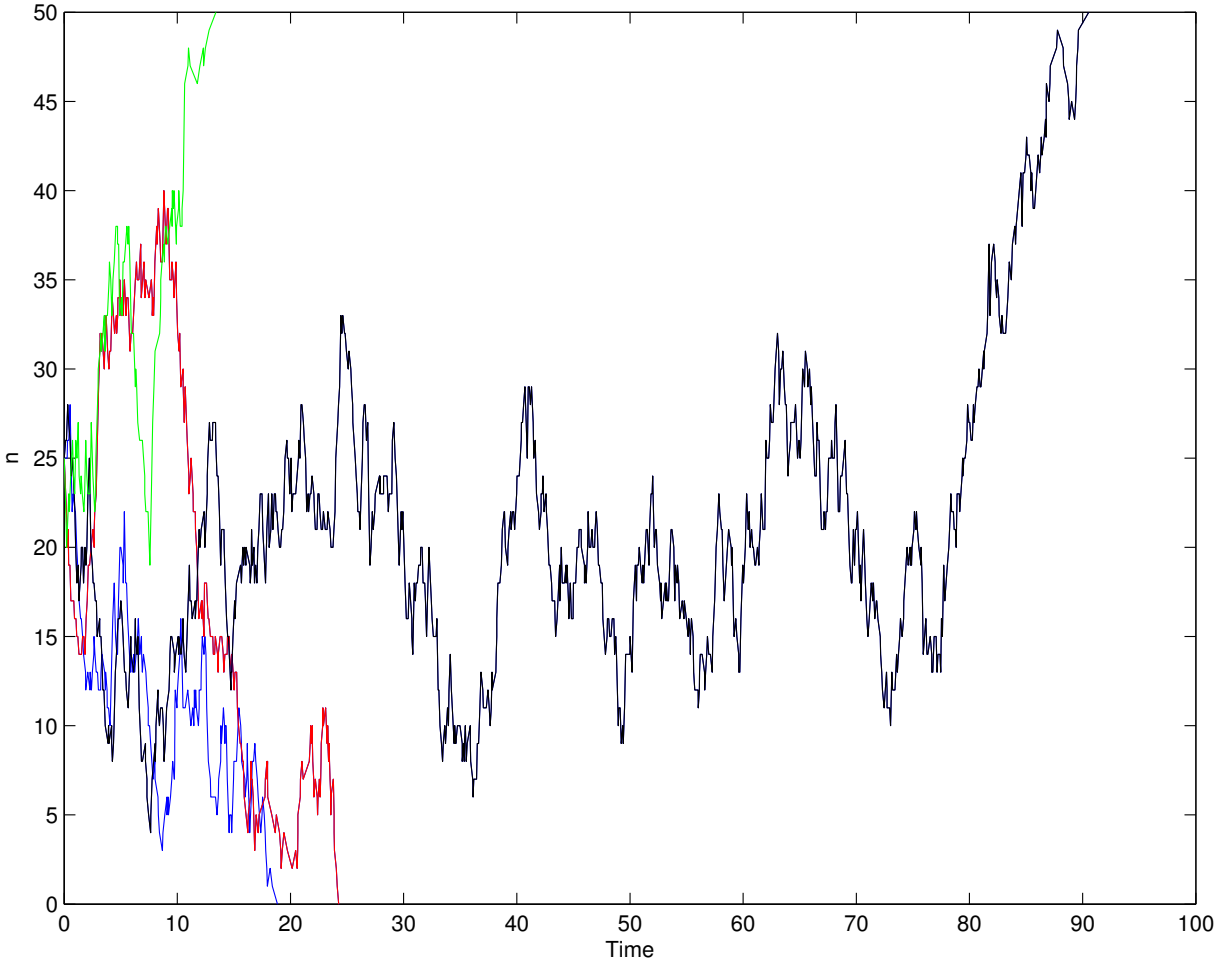
- *The system has two* ***absorving*** *states:*
  $W_+(n=0) = W_-(n=0) = 0$ and
  $W_+(n=N) = W_-(n=N) = 0$
- This means that

$$\lim_{t\to\infty} P(n(t) = 0 \quad \cup \quad n(t) = N) = 1 \tag{2}$$

- This behaviour is not at all captured by the deterministic equation, which predicts that the population will stay constant.

The Moran Process

Simulation results:



Logistic growth

- The logistic equation,

$$\frac{dm}{dt} = m\left(1 - \frac{m}{K}\right), \tag{3}$$

  has two steady states: $m = 0$ **unstable** and $m = K$ **stable**, i.e. regardless of the value of K and for any initial condition such that $m(t = 0) > 0$, $m(t)$ will asymptotically approach K.
- Consider now a continuous-time Markov process n_t whose dynamics are given by the following transition rate:
  - $n \to n + 1$ with probability rate n.
  - $n \to n - 1$ with probability rate $\frac{n(n-1)}{2}\frac{1}{K}$.
- This stochastic process has a unique absorbing state: $n = 0$, and therefore we expect the stochastic dynamics to show strong discrepancies with Equation (3) when randomness is dominant.

Logistic growth

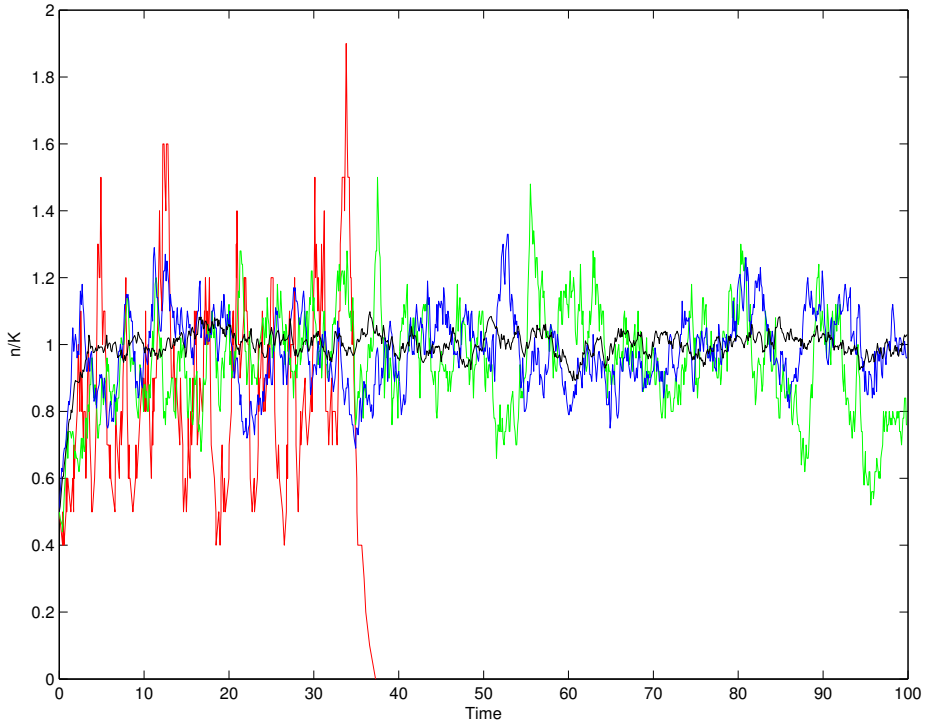


Figure: Red line K = 10, green K = 50, blue K = 100, black K = 1000

We observe that for small K fluctuations dominate the behaviour of the system. Extinctions are common for small K , in contradiction to the behaviour predicted by the logistic equation Eq. (3), and become rarer as K is allowed to increase.

Steady states vs Absorbing states

- The definition of equilibrium states in stochastic systems is a bit technical and there are several definitions of equilibrium.
- Consider again the stochastic logistic growth, i.e. a process n_t such that:
  - $n \to n+1$ with probability rate $W_+(n) = n$
  - $n \to n-1$ with probability rate $W_-(n) = \frac{n(n-1)}{2}\frac{1}{K}$
- Consider a state of system, n_s, is, roughly speaking, a state of the process such that $W_+(n_s) = W_-(n_s)$.
  - $W_+(n_s)$ is the number of births within a population of n_s individuals
  - Likewise, $W_-(n_s) =$ the number of deaths within a population n_s individuals
  - So an steady state of our population dynamics is reached when $n_t = n_s$, since death rate is balanced by birth rate and therefore the population stays roughly constant
- $n_s = K$ which coincides with the deterministic stable fixed point.
- Note that $W_+(n) - W_-(n) > 0$ if $n < n_s$ and $W_+(n) - W_-(n) < 0$ if $n > n_s$

Steady stats vs Absorbing states

- An absorbing state, n_0, is characterised by $W_i(n_0) = 0$ i.e. once the system has reached the absorbing state, it cannot leave anymore.
- Consider again, the stochastic logistic growth rate, we have:
  - Steady states are in general not absorbing states.
  - $W_+(n_s) \neq 0$ and $W_+(n_s) \neq 0$.
  - If $n = 0$ then $W_+(0) = W_-(0) = 0$ therefore $n = 0$ is an absorbing state.
- n_s belongs to the set of accessible states of $n = 0$, that means there is at least one consecutive set of transition that connects n_s and n_0. For Example: $K \to K - 1 \to K - 2 \to \cdots \to 1 \to 0$.
- However, if $K \gg 1$ the probability of such a chain of events is vanishingly small.

Summary

- n_s is an steady state in the sense that births and deaths are balanced. Moreover, $W_+(n) - W_-(n) > 0$ if $n < n_s$ and $W_+(n) - W_-(n) < 0$ if $n > n_s$. This is essentially equivalent to what happens in the deterministic logistic growth model.
- However, n_s is not an absorbing state of the stochastic dynamics. The only absorbing state is $n = 0$.
- Stochastic extinctions are relatively rare provided K is big. If this is the case, the deterministic system provides a reasonable approximation to the behaviour of the model.
- If, on the contrary, K is small stochastic extinctions are relatively common and the deterministic description is not an accurate one
- We have seen several examples of stochastic systems in which noise and randomness are the dominating factors. Their behaviours are not captured by their deterministic conterparts.
- In general, we should expect non-trivial random effects for small populations or dynamics with absorbing states.

Outline

The Master Equation

- The Master Equation is our fundamental mathematical description of an stochastic process and the starting point for any attempt to analyse a particular model.
- It is obtained as a probability balance for all the events that can occur during the time intertal $(t, t + \Delta t)$.
- Mathematically, it is a set of ordinary differential equations for the probability distribution $P(n, t)$ i.e. the probability that the number of individuals in the population at time t to be n.

The Master Equation II

Example: Birth and death process

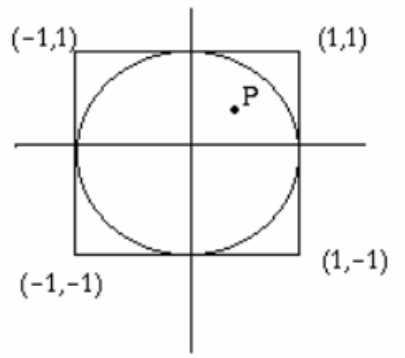
- Birth $n \to n+1$ with probability rate $W_+(n) = \lambda n$. Death: $n \to n-1$ with probability rate $W_-(n) = \sigma n$.
- Probability balance:
  $P(n, t+\Delta t) =$
  $\lambda(n-1)\Delta t P(n-1,t) + \sigma(n+1)\Delta t P(n+1,t) + (1-(\lambda n \Delta t + \sigma n \Delta t))P(n,t)$.
- When $\Delta t \to 0$:
  $$\frac{dP(n,t)}{dt} = \lambda(n-1)P(n-1,t) + \sigma(n+1)P(n+1,t) - (\lambda n + \sigma n)P(n,t)$$
- **Big Problem:** In general is not possible to get the analytical solution of the Master Equation, even a numerical solution of the Master Equation can be very hard.

Monte Carlo Simulations

- The first thoughts and attempts made to practice the Monte Carlo Method were suggested by a question which occurred in 1946 to Stanislaw Ulam was convalescing from an illness and playing solitaires. The question was what are the chances that a Canfield solitaire laid out with 52 cards will come out successfully?
- After spending a lot of time trying to estimate them by pure combinatorial calculations, he wondered whether a more practical method than "abstract thinking" might not be to lay it out say one hundred times and simply observe and count the number of successful plays.
- In 1950s Stanislaw Ulam and John von Neumann started a research in this topic founded by The RAND Corporation and the U.S. Air Force.
- Uses of Monte Carlo methods require large amounts of random numbers, and it was their use that spurred the development of pseudorandom number generators.

Monte Carlo Simulations

- There is no consensus on how Monte Carlo method should be defined.
- Example: Approximate the value of π
  - Consider a random point P in the unit square, which is the probability that P is in the unit circle?



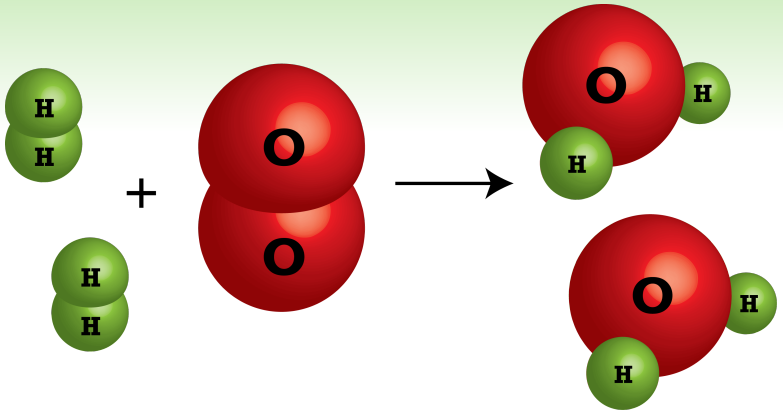
  - The probability has to be the quotinet of the areas, that is $\dfrac{\pi}{4}$.

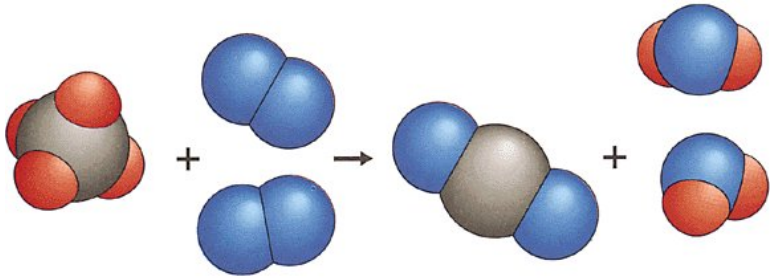
    a Set $Ok = 0$
    b Generate two random numbers $x, y \in [-1, 1]$ if $x^2 + y^2 < 1$, then $Ok = Ok + 1$
    c Repeat it N times. When $N \to \infty$, then $\frac{Ok}{N} \to \frac{\pi}{4}$

Outline

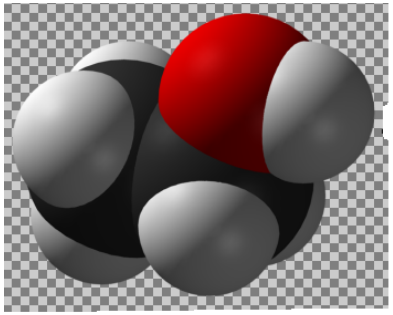
A Chemical Reacting System

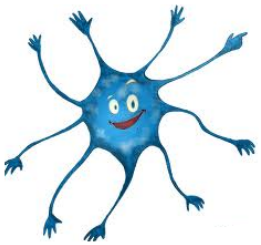
- Molecules of N chemical species $S_1, ..., S_N$
  - Inside some volume Ω, at some temperature T.
- Interacting through M elemental reaction channels $R_1, ..., R_M$.
- R_j is assumed to describe a single instantaneous physical event which changes the population of at least one species.





$$CH_4 + 2O_2 \longrightarrow CO_2 + 2H_2O$$





Deterministic vs Stochastic

The time-evolution of chemical systems has traditionally been analyzed using continuous, deterministic mathematics (ODEs, PDEs).
But in fact, chemical systems evolve

- Discretely, because molecules come in integer numbers
- Stochastically, for several reasons:
  - Even if all the molecules moved according to deterministic Newtonian mechanics, the system is so sensitive to initial conditions that is behaviour will be random.
  - Chemical systems of practical interest are NEVER isolated. The reason why a system is a temperature T is because it is having random exchanges of energy with its environment.
  - All unimolecular reactions $S \rightarrow$ anything are inherently stochastic.

Deterministic vs Stochastic

For the simplest chemical reaction: $S \to \emptyset$

- Traditional wisdom asserts that $X(t) \equiv$ the number of S molecules in the system at time t, evolves according to the ODE

$$\frac{dX(t)}{dt} = -cX(t). \tag{4}$$

- But **physics** $\implies$ the S molecules react independently of each other.
- The problem: There is no plausible physical mechanism that could give rise to such exquisitely coordinated deterministic behavior!
- The most reasonable mechanism for $S \to \emptyset$ is that the lifetimes of the individual S molecules are i.i.d. random variables. In that case (4) might describe how the average S population evovles in time:

$$\frac{dX_{avg}(t)}{dt} = -cX_{avg}(t). \tag{5}$$

- If the average S population evolves according to (5), then the lifetime of each S molecule must be an exponential random variable with mean $\frac{1}{c}$, or equivalently,

$$c \cdot dt = \text{Prob}\{\text{a given } S\text{−molecule will die in the next } dt\}$$

Proof of this result:

- With x_0 molecules at time 0, the ODE (5) implies

$$X_{avg}(t) = x_0 e^{-ct} \qquad (t > 0)$$

- Let $f(\tau)$ denote the cdf of the molecule lifetime. Then for any $t > 0$, $(1 - f(t)) =$ the probability that any particular one of the x_0 molecules at time 0 will stil be alive at time t.
- So the probability that exactly x moelcules will be alive at this t time is:

$$(1 - f(t))^x (f(t))^{x_0 - x} \frac{x_0!}{x!(x_0 - x)!}.$$

- From these expresions we obtain $f(t) = 1 - e^{-ct}$. This is the cdf of the exponential random variable with mean $\frac{1}{c}$.
- The corresponding pdf $p(t) \equiv df(t)/dt = ce^{-ct}$ is such that $p(t)dt = \text{Prob}\{$ the molecule will die in $[t, t + dt)\}$. Thus, $p(0)dt = c\ dt$. **QED**

This has some implications:

- The deterministic equation $\frac{dX}{dt} = -cX$ for $S \to \emptyset$ makes no sense physically unless there is an underlying stochastic dynamics for the S molecules.
- And not just any stochastic dynamics, but a stochastic dynamics of a very particular kind: Each S molecules must disappear in the next dt with probability $c \cdot dt$.
- If the S molecules don't behave in that way, then the equation $\frac{dX}{dt} = -cX$ will not correctly describe the reaction $S \to \emptyset$.
- No fundamental physical theory of chemical kinetics can be premised on a traditional ODE like $\frac{dX}{dt} = -cX$. Such an ODE can be, at best, a consequence of a more fundamental theory, and perhaps only an approximate consequence.

A tractable discrete-stochastic mathematical description of chemically reacting systems is possible if successive reactive collisions between molecules tend to be separated in time by very many non-reactive collisions.

- In that case, the many non-reactive collisions tend to randomize
  - the velocities of the molecules (Maxwell-Boltzmann distribution),
  - the positions of the molecules (randomly uniform inside Ω).
- Then, instead of having to describe the systems state by giving the position, velocity and species of every molecule in Ω , we can get away with specifying the much lower dimensional vector function.

$$X(t) = (X_1(t), ..., X_N(t)),$$

provided its ith component,
$X_i(t)$ the number of S_i molecules in Ω at time t ,
is treated as a random variable.

Each raction channel R_j can then be characterized by **two entities**:

- Its **propensity function** $a_j(x)$: If the system is currently in state x,

$$a_j(x) \cdot dt := \text{probability that one } R_j \text{ event will occur in the next } dt.$$

  The existence and form of $a_j(x)$ must come from molecular physics.
- Its **state change vector** $v_j \equiv (v_{1j}, ..., v_{Nj})$:

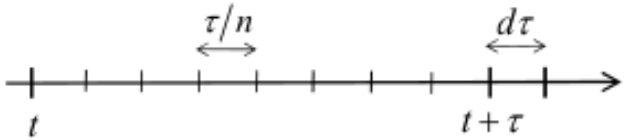
$$v_{i,j} = \text{the change in } X_i \text{ caused by one } R_j \text{ event.}$$

  R_j induces the state change $x \to x + v_j$.
- Examples:
  - $S_1 \to S_2$: $v_j = (-1, 1, 0, ..., 0)$; $a_j(x)dt = (c_j dt)x_1 \implies a_j(x) = c_j x_1$
  - $S_1 + S_2 \to 2S_2$: same v_j; $a_j(x)dt = (c_j dt)x_1 x_2 \implies a_j(x) = c_j x_1 x_2$

The Gillespie stochastic simulation algorithm (SSA)

A procedure for constructing sample paths or realizations of $X(t)$:

- Idea: Generate properly distributed random numbers for
  - the time τ to the next reaction
  - the index j of that reaction
- $p(\tau, j|x,t) \cdot d\tau \equiv$ probability, given $X(t) = x$, that the next reaction will occur in $[t+\tau, t+\tau+d\tau)$, and will be R_j.



$$\sum_{k=1}^{M} a_k(x) \equiv a_0(x)$$

$$p(\tau, j|x,t)d\tau = \left(1 - a_0(x)\frac{\tau}{n}\right)^n a_j(x)d\tau \to e^{-a_0(x)\tau} a_j(x)d\tau$$

- Therefore, $p(\tau, j|x,t)d\tau = e^{-a_0(x)\tau} a_j(x)d\tau = a_0(x)e^{-a_0(x)\tau} \cdot \dfrac{a_j(x)}{a_0(x)} d\tau$

  $\Longrightarrow$
  - τ is the exponenital r.v. with mean $\frac{1}{a_0(x)}$.
  - j is the integer r.v. with probability mass $\frac{a_j(x)}{a_0(x)}$.
  - τ and j are statistically independent.

The Gillespie stochastic simulation algorithm (SSA)

The following scheme is a Method of implementing the SSA

1. In state x at time t, evaluate $a_1(x), ..., a_M(x)$ and $a_0(x) = \sum_{k=1}^{M} a_k(x)$.
2. generate r_1 and r_2 random numbers in $[0, 1]$, and compute τ and j according to
   - $\tau = \frac{1}{a_0(x)} ln \left(\frac{1}{1 - r_1} \right)$,
   - $j =$ the smallest integer satisfying $\sum_{k=1}^{j} a_k(x) > r_2 a_0(x)$.
3. $t = t + \tau$ and $x = x + v_j$
4. Record (x, t). Go to 1 or end the simulation.

Outline

Examples

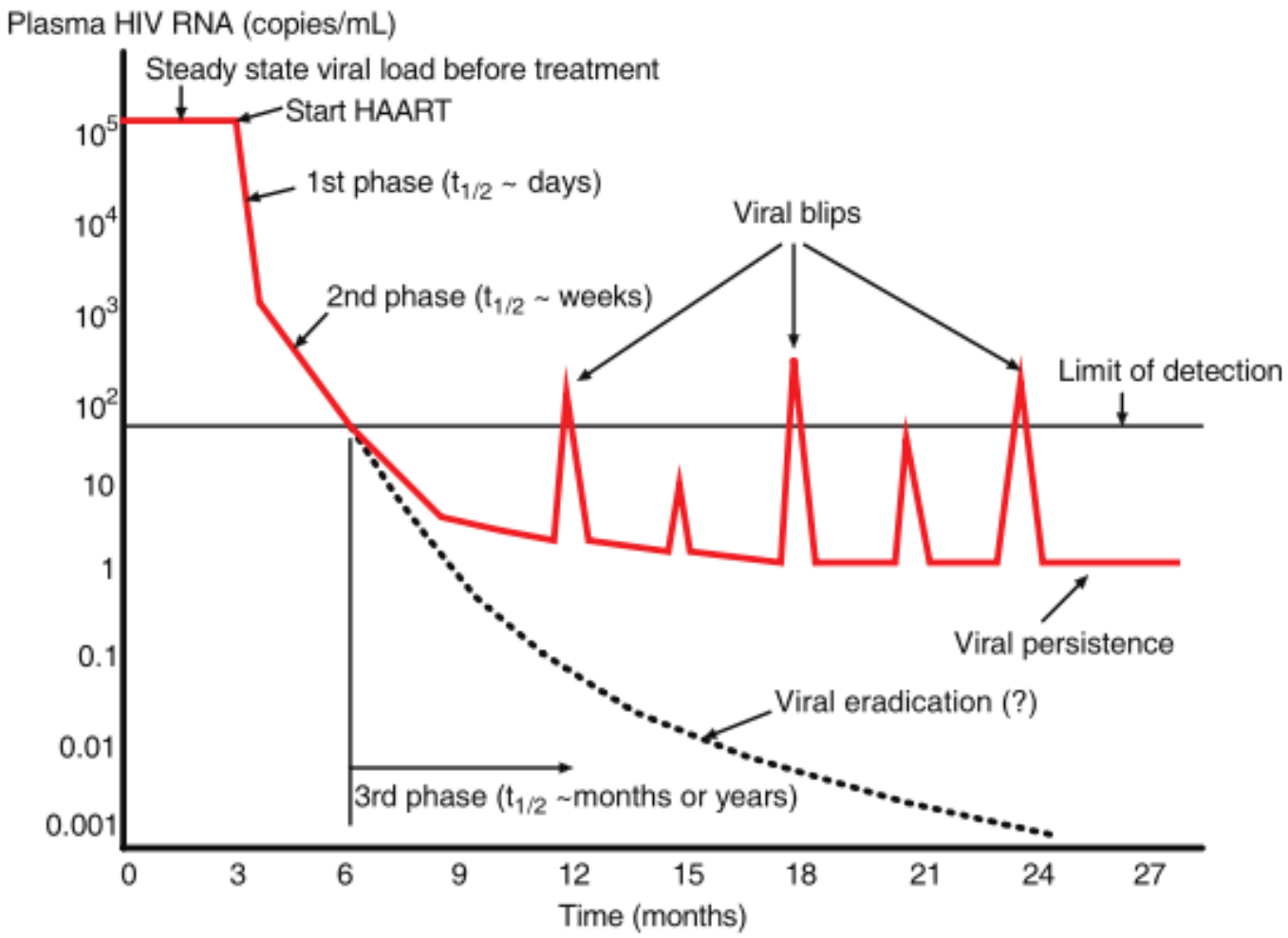
This kind of models can be used in a lot of situations:

- Chemistry, modelling chemical reactions.
- Ecology, for instance in prey predator systems:
  - Wolfs and rabbits.
  - Bougainvillea (Brazilian plant) and Lepidoptera (bug).
- Biological and medical problems:
  - Mutant invasions.
  - Populations of cells and virus.

HIV-1

- An HIV-1 infected person without any treatment has between 10^5 and 10^6 copies of virus per milliliter of blood.
- Following initiation of highly active antiretroviral therapy (HAART) the plasma viral load declines fast. After several months of treatment, most patients attain a level of plasma HIV-1 RNA below the detection limit (50 copies/mL).
- This does not imply that viral replication has been completely suppressed by therapy.
- Even in patients with "undetectable" plasma viral loads for many years, a low level of virus can be detected in plasma by supersensitive assays.
- An explanation is that HIV-1 establishes a state of latent infection in resting memory $CD4^+$ T cells, and virus is released when these cells encounter their relevant antigens and are activated.
- Observation of transient episodes of viremia ("blips") above the detection limit.

Summary



Rong L, Perelson AS (2009) Modeling HIV persistence, the latent reservoir, and Viral Blips in HIV-infected Patients on Potent Therapy. J Theor Biol 260: 308-31

Experimental results

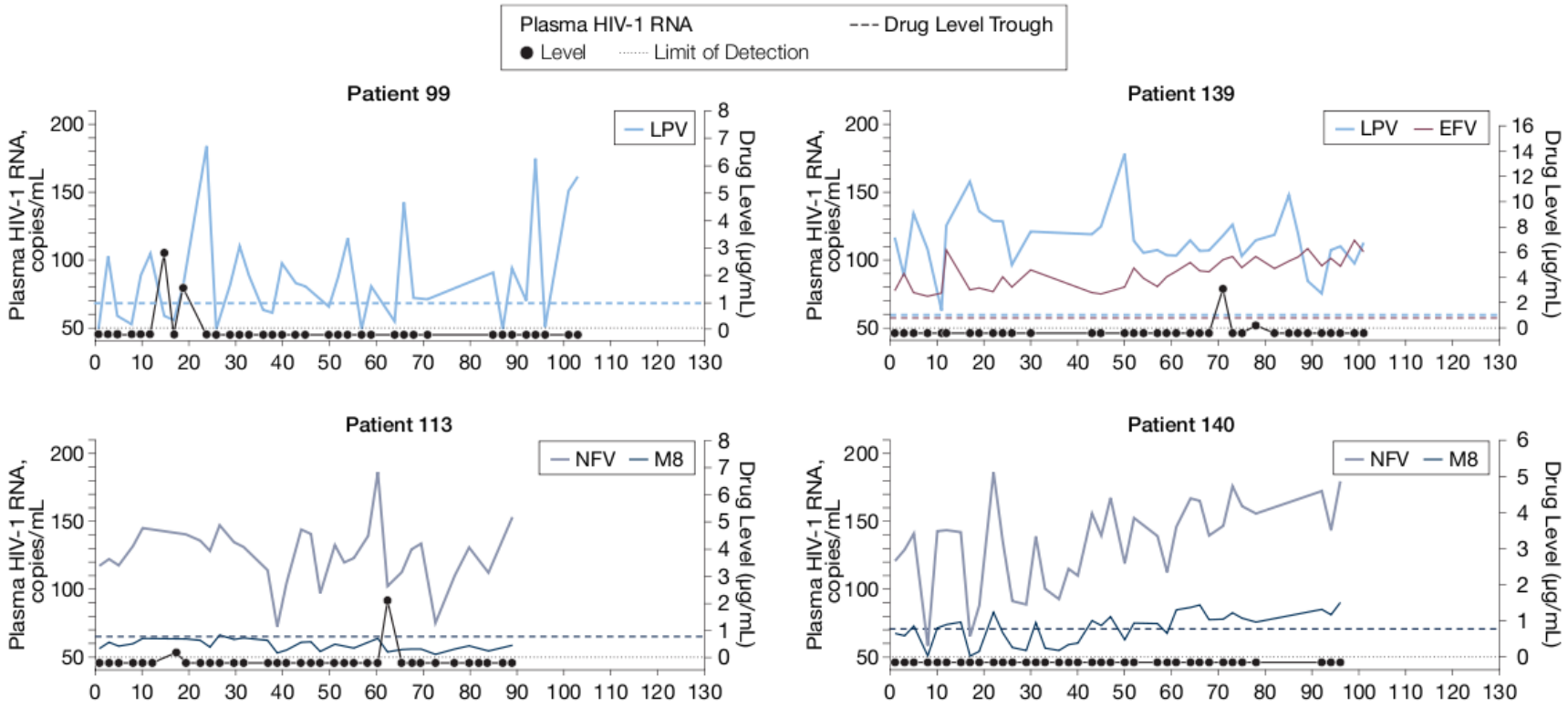
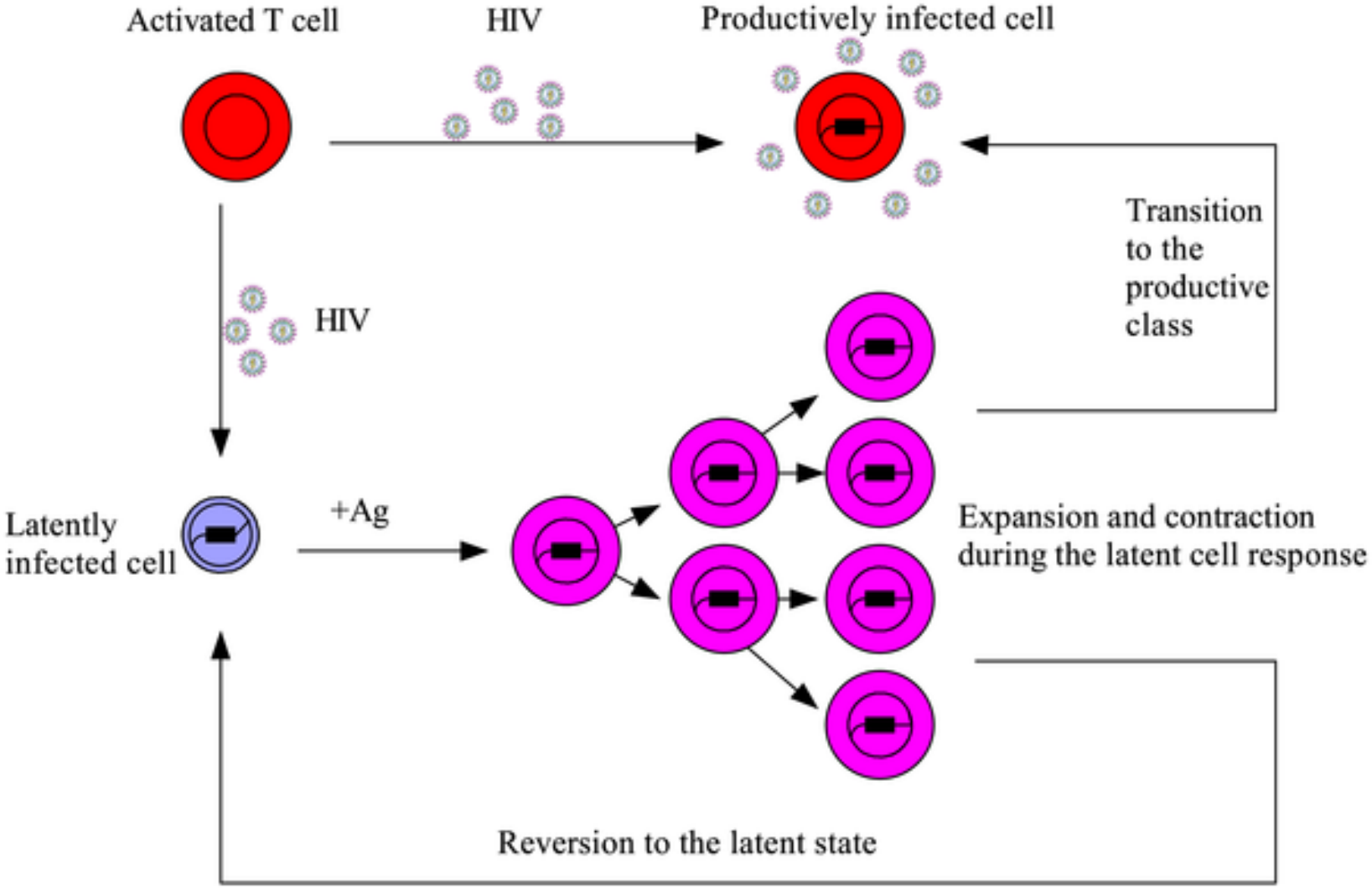


Figure: Experimental results from Nettles et. al

Nettles TE, Kieffer TL, Kwon P, Monie D, Han Y, et al. (2005) Intermittent HIV-1 viremia (Blips) and drug resistance in patients receiving HAART. JAMA 293: 817-829.

Mathematical Model



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Simulations

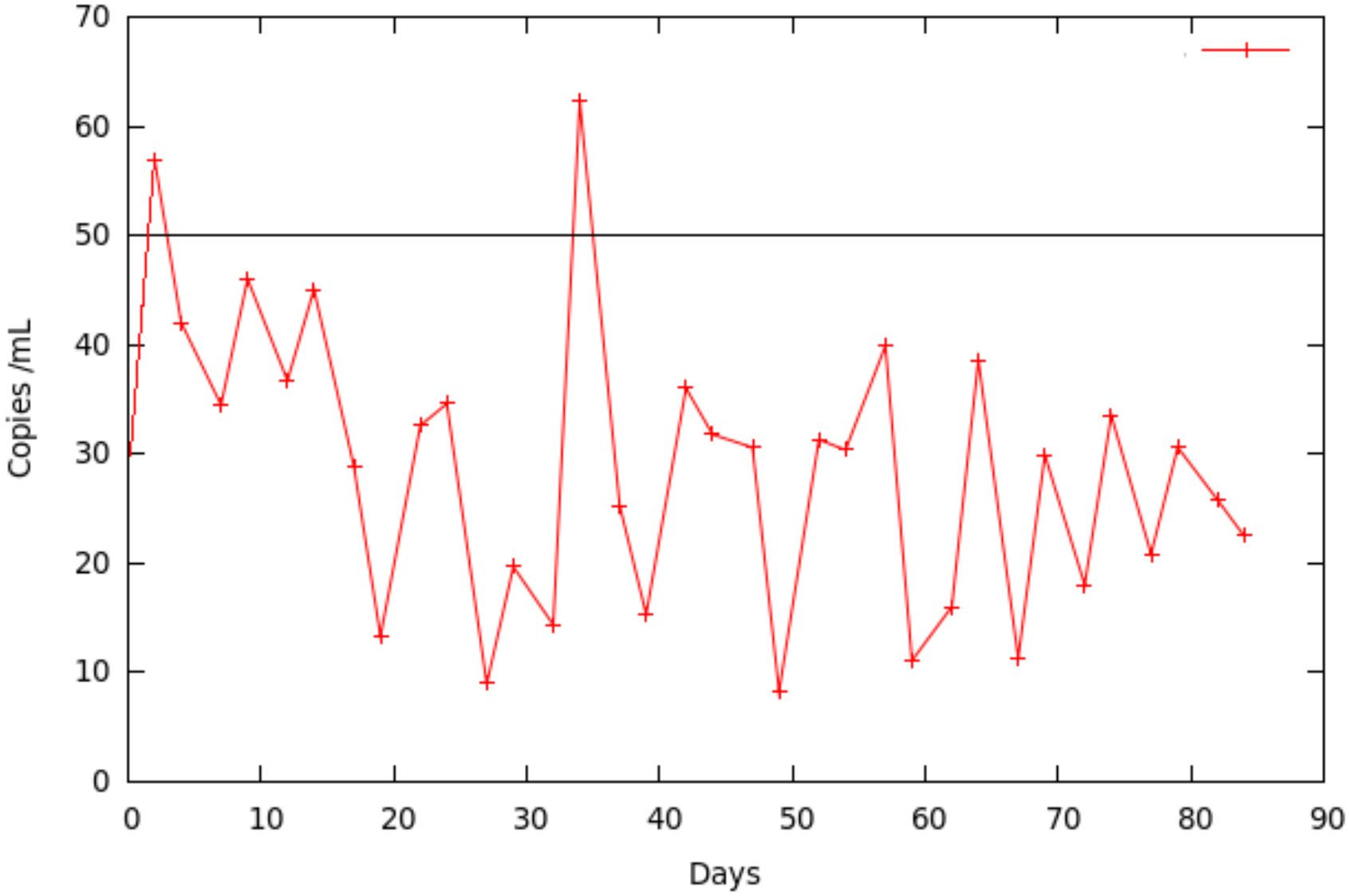

Figure: Gillespie Simulations of our system.

Simulations

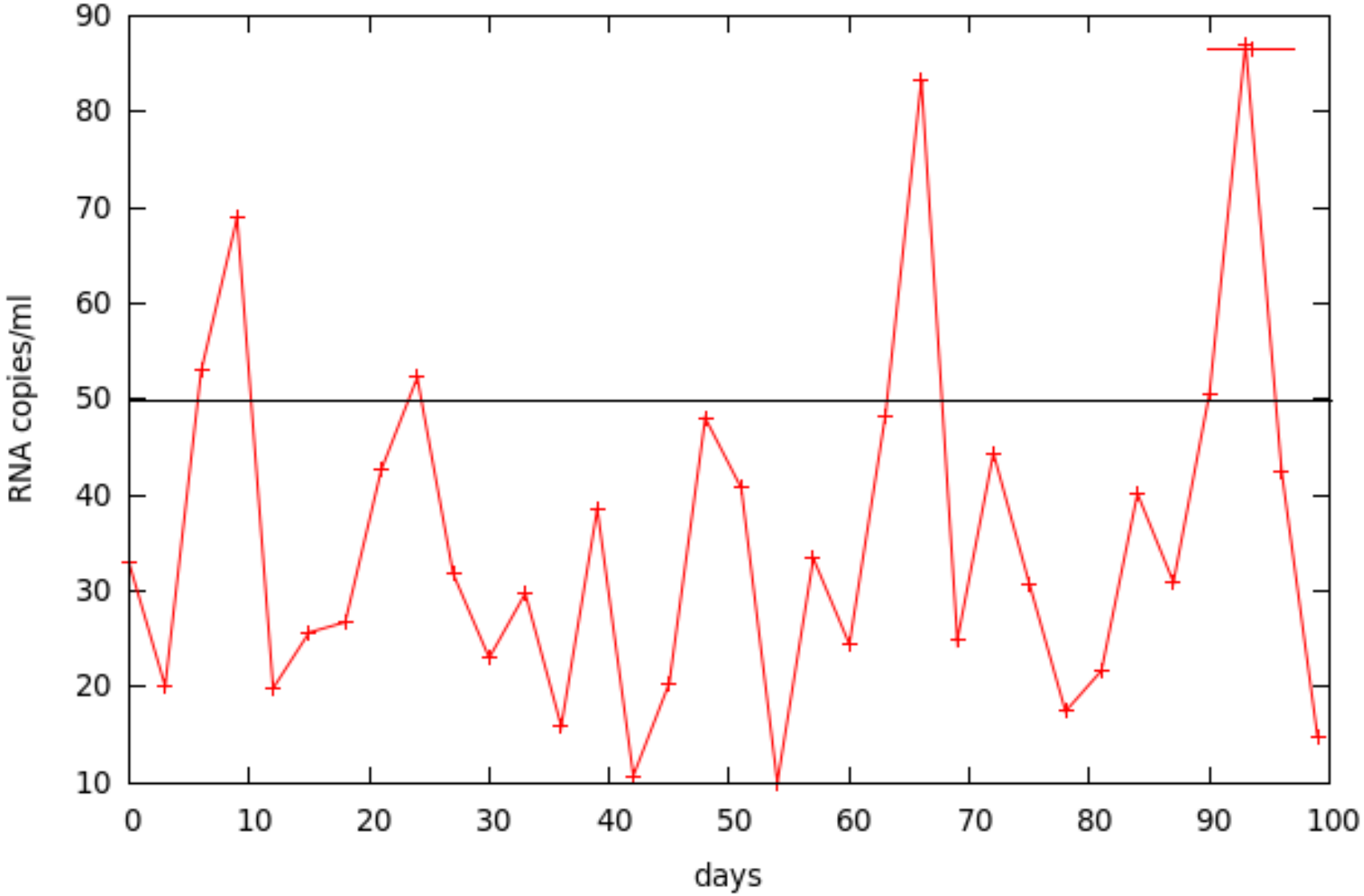

Figure: Gillespie Simulations of our system.

THANK YOU

FOR YOUR ATTENTION!!