Mathematical Models in Neuroscience and their Applications
Lecture 3- Nerve Conduction and the Fitzhugh-Nagumo Equation

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Historical Introduction

Luigi Galvano (1737-1798, Bologna, Italy)

Discovered that muscles of dead frogs'legs can move when struck by an electrical spark (1780).
He founded bioelectricity (the part of Physics which studies electrical patterns and signals from tissues such as nerves and muscles).

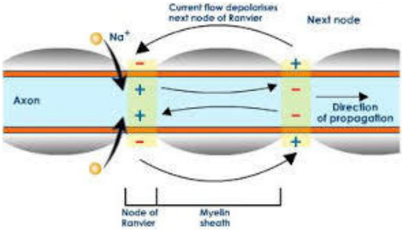
Myelinated and Unmyelinated Axons

The nerves work as electrical cables. They are bundles of nerve fibres called axons. Each axon is the extension of a neuron, so that it can send electrical signals from the central to the peripheral nervous systems; it can also receive signals from the peripheral nervous system.

- Unmyelinated axons For example, the squid giant axon (used by Hodgkin and Huxley in some of their experiments)
- Myelinated axons For example, in humans, the axons are covered with a substance called myelin, which makes the electrical conduction faster and more effective.

Discrete Fitzhugh-Nagumo Equation
Statement of Problem

The considered equation models conduction in a myelinated nerve axon in which the myelin completely insulates the membrane, except at the nodes of Ranvier, so that the potential change jumps from node to node (pure saltatory conduction).



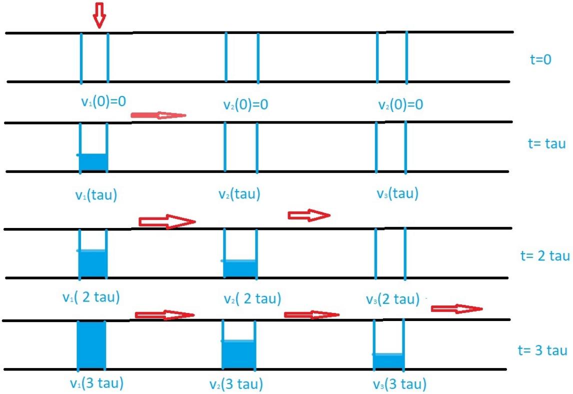
Stimulus Propagation

How does a nervous stimulus propagate?
In the first moment no node in the axon is active.

- A certain node is stimulated (by an external signal) so that its transmembrane potential reaches a certain threshold level.
- local ionic currents are generated which excite the neighbouring node.
- the electric potential at the neighbouring node increases and reaches the threshold.
- local ionic currents are generated at the neighbouring node and its transmenbrane potential increases.

After a certain time all the nodes in the axon were activated.

Stimulus Propagation

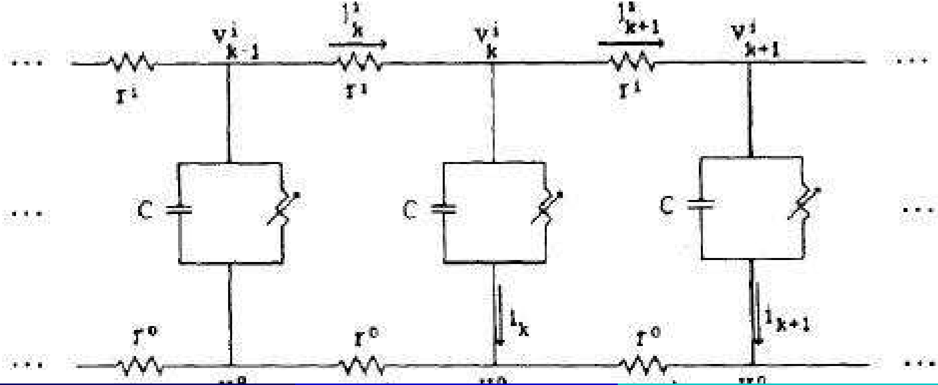


$$v_{k+1}(t) = v_k(t-\tau), \quad v_{k-1}(t) = v_k(t+\tau).$$

Discrete Fitzhugh-Nagumo Equation

Circuit Model

Impulse conduction in a myelinated axon can be simulated using a circuit model: the nodes of Ranvier correspond to capacitors and the space between them, to resistances.



Assumptions of the Nerve Conduction Model

- the nodes are uniformly spaced and electrically identical,
- the axon is infinite in extent,
- the cross-sectional variations in potential are negligible,
- The electrical processes at the nodes satisfy the Fitzhugh-Nagumo dynamics without a recovery term
- a supra-threshold stimulus begins a signal which travels down the axon from node to node.

Discrete Fitzhugh-Nagumo Equation

At an arbitrary Ranvier node, the transmembrane potential statisfies the equation

$$RCv'(t) = F(v(t)) - 2v(t) + v(t-\tau) + v(t+\tau). \qquad (1)$$

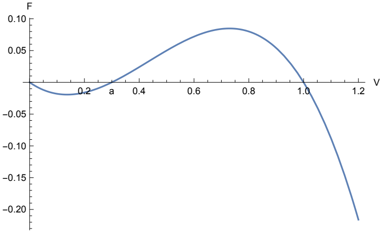
We are interested in a solution of (1), increasing on $]-\infty, \infty[$, which satisfies the conditions

$$\lim_{t \to -\infty} v(t) = 0, \qquad \lim_{t \to +\infty} v(t) = 1, \qquad v(0) = 1/2. \qquad (2)$$

Such a solution exists for certain values of τ which must be computed.

- $v(t)$ represents the transmembrane potential at the given node;
- τ is the time required by the electrical signal to move from a node to the following one.
- $v(t-\tau)$ and $v(t+\tau)$ represent, respectively, the electrical potential at the previous and following node.
- F is a nonlinear function (activation function) which reflects the current-voltage model.
- R and C are respectively axiomatic nodal resistivity and nodal capacity.

Discrete Fitzhugh-Nagumo Equation



The current-voltage relation (activation function)has the form

$$F(v) = bv(v - a)(1 - v),$$

where a is the threshold potential $(0 < a < 1/2)$;
b is related with the strength of the ionic current density $(b > 0)$.
Moreover, F must satisfy

$$\int_0^1 F(v)dv > 0.,$$

which means $a < 0.5$.

Numerical Methods

Specific features of this nonlinear problem:

- The functional equation contains both advanced and delayed terms
- The BVP is given on $\boldsymbol{R}$
- The value of τ (inverse of propagation speed) is unknown

Method of Steps

Suppose that all the needed derivatives of f and v exist in $(a-2\tau, a]$. We obtain the following expressions for the solution on the intervals $(a, a+\tau]$ and $(a+\tau, a+2\tau]$: Assume, for simplicity, that $R = C = 1$.

$$v(t+\tau) = v'(t) - v(t-\tau) + g(v(t)), \tag{3}$$

$$v(t+2\tau) = v'(t+\tau) - v(t) + g(v(t+\tau)) \tag{4}$$

where $g(u) = 2u - F(u)$, $t \in (a-2\tau, a]$.

Continuing this process, we can extend the solution to any interval $(a+k\tau, a+(k+1)\tau], k = 1, 2, \ldots$.

Method of Steps

On the other hand,differentiating (3),

$$v'(t+\tau) = v''(t) - v'(t-\tau) + g'(v(t))v'(t). \tag{5}$$

Replacing in the right-hand side of (4),

$$v(t+2\tau) = v''(t) - v'(t-\tau) + g'(v(t))v'(t) - v(t) + g(v(t+\tau)) \tag{6}$$

We see that the solution at any sub-interval $(a+k\tau, a+(k+1)\tau]$ can be constructed knowing only the solution and its derivatives
(up to order $k+1$) at $(a-2\tau, a]$.
However, the solution constructed in this way may not be continuous at the breaking points $a+k\tau$, $k=1,2,...$ (this depends on the initial conditions).

Asymptotic Behaviour of Solution

The study of the asymptotic behaviour of solution at $-\infty$ and $+\infty$ is essential to implement the numerical scheme. When $t \to -\infty$, we have $v(t) \to 0$ and $F(v(t)) \to 0$. Use the Taylor expansion of F for x close to zero,

$$F(x) = F'(0)x + \frac{F''(0)}{2}x^2 + \frac{F^{(3)}(0)}{3!}x^3 + O(x^4).$$

For $t \leq -L$, where L is sufficiently large, search for v in the form of a series of powers of ϵ:

$$v(t) = \epsilon u_1(t) + \epsilon^2 u_2(t) + \epsilon^3 u_3(t) + O(\epsilon^4).$$

Asymptotic Behaviour of Solution

We recall that

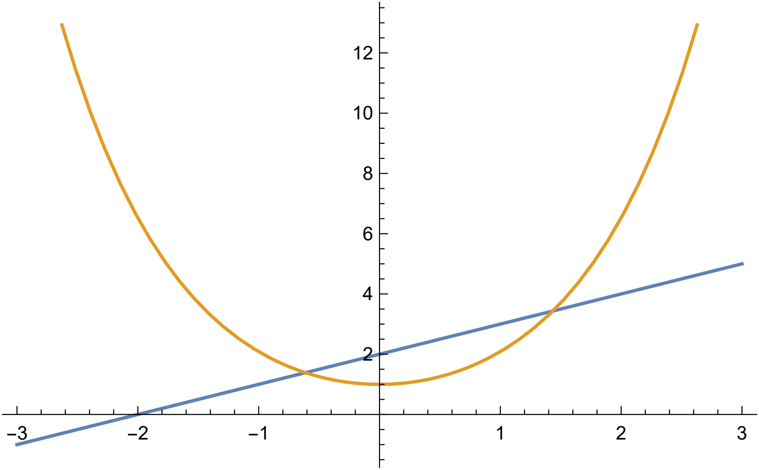
$$v'(t) = F(v(t)) - 2v(t) + v(t-\tau) + v(t+\tau). \tag{7}$$

Linearizing this equation as $t \to -\infty$, we replace $F(v(t))$ by $F'(0)v(t)$. Assuming that $u_1(t) = Ce^{\lambda(t+L)}$, where C is a constant, and replacing in (7), we obtain the following characteristic equation:

$$\lambda + 2 - F'(0) - 2cosh(\lambda\tau) = 0 \tag{8}$$

Knowing that $F'(0) < 0$, the characteristic equation has exactly two roots, one positive λ_+ and one negative λ_-; since $\lim_{t\to-\infty} u_1(t) = 0$, we choose the positive root.

Characteristic Roots



yellow : $y_1(x) = 2\cosh(x) + F'(0)$
blue: $y_2(x) = x + 2$
$y_1(x) = y_2(x)$ - roots of the characteristic equation.

Asymptotic Behaviour of Solution

On the other hand, when $t \to +\infty$, we have $v(t) \to 1$ and $F(v(t)) \to 0$. Using the Taylor expansion of F for x close to 1,

$$F(x) = F'(1)(x-1) + \frac{F''(1)}{2}(x-1)^2 + \frac{F^{(3)}(1)}{3!}(x-1)^3 + O((x-1)^4).$$

For $t \geq L$, where L is sufficiently large, search for v in the form of a series of powers of ϵ_+:

$$v(t) = 1 - \epsilon_+ w_1(t) + \epsilon_+^2 w_2(t) + \epsilon_+^3 w_3(t) + O(\epsilon_+^4).$$

Assuming that $w_1(t) = C' e^{\lambda(t-L)}$, where C' is a constant, we obtain the following characteristic equation:

$$\lambda + 2 - F'(1) - 2cosh(\lambda\tau) = 0. \tag{9}$$

Since $F'(1) < 0$, the characteristic equation has again 2 roots. In this case we choose the negative root of the characteristic equation.
The higher order terms of the expansions $(u_2, w_2, u_3, w_3, \text{etc.})$ can be obtained in a similar way.

Newton Method

Once we know the approximate solution of the equation for $t \geq L$ and $t \leq -L$, the problem is reduced to a BVP on $[-L, L]$, where L is a multiple of τ.

The nonlinear problem can be reduced to a sequence of linear problems. by the Newton Method.

In the i-th iteration of the Newton method, we have to solve a linear equation of the form:

$$\begin{aligned} v'_{i+1}(t) - F'(v_i)(v_{i+1}(t) - v_i(t)) - M(v_{i+1}(t)) = \\ = F(v_i(t)), \qquad t \in [-L, L], \end{aligned} \tag{10}$$

where

$$M(v(t)) = v(t+\tau) + v(t-\tau) - 2v(t).$$

We search for a monotone solution v_{i+1} which satisfies the boundary conditions

$$\begin{aligned} v_{i+1}(t) &= \phi_0(t), \qquad t \in [-L-\tau, -L]; \\ v_{i+1}(t) &= \phi_1(t), \qquad t \in [L, L+\tau]. \end{aligned} \tag{11}$$

where ϕ_0 and ϕ_1 are the obtained asymptotic expansions for v.

In order to compute an initial approximation v_0, we need the values λ_-,λ_+,τ, ϵ and ϵ_+.
These values are obtained by solving a system of five nonlinear equations:

$$\begin{array}{l} \lambda_- + 2 - F'(0) - 2cosh(\lambda_-\tau) = 0 \\ \lambda_+ + 2 - F'(1) - 2cosh(\lambda_+\tau) = 0 \\ \lim_{t\to 0-} v(t) = 1/2; \\ \lim_{t\to 0+} v(t) = 1/2; \\ \lim_{t\to 0-} v'(t) = \lim_{t\to 0+} v'(t). \end{array} \tag{12}$$

The values of v in this system are computed, using the method of steps, and assuming that v satisfies the obtained asymptotic expansions, when $t < -L$ and $t > L$. This system is solved again at each iterate of the Newton method, in order to update the parameter values.

Initial Approximations

τ - inverse of the propagation speed

First Estimate

$$\tau \approx \tau_0 = \frac{\sqrt{2}}{(1-2a)\sqrt{b}}.$$

Second Estimate

$$\tau_1 = \frac{1}{\lambda_+} arccosh\left(\tfrac{\lambda_+ + 2 - f'(0)}{2}\right),$$

where $\lambda_+ = 4f\left(\frac{1}{2}\right)$.

Third Estimate

τ_2 is obtained from the solution of a system of equations.

Numerical Results

a	τ_0	τ_1	τ_2	τ
0	0.3651	0.2987	0.3101	0.38029
0.05	0.4057	0.3318	0.3461	0.43511
0.2	0.6086	0.4978	0.5250	0.7300
0.3	0.9129	0.7467	0.7917	1.2515
0.4	1.825	1.4934	1.588	5.68

Table: Estimates of τ for different values of a, with $b = 15$

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Numerical Results

b	τ_0	τ_1	τ_2	τ
1	1.571	1.540	1.652	1.626
11	0.4738	0.4034	0.4325	0.50078
15	0.4057	0.3318	0.3461	0.43511
21	0.3429	0.2666	0.2656	0.3744
51	0.2200	0.1443	0.1216	0.2554

Table: Estimates of τ for different values of b, with $a = 0.05$

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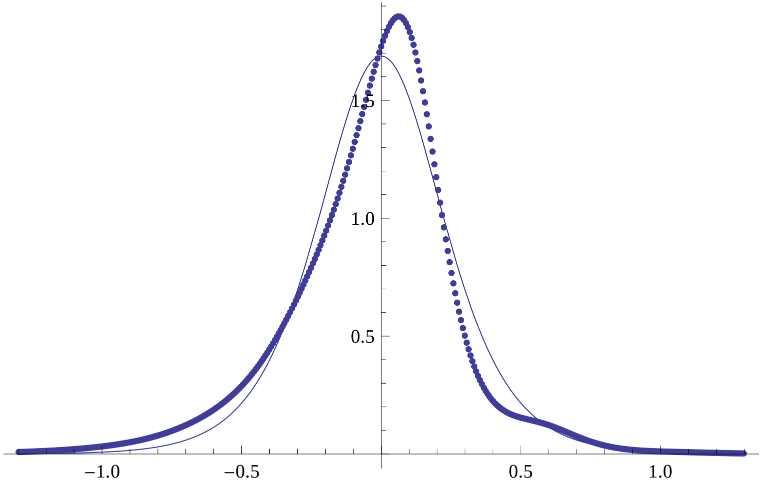
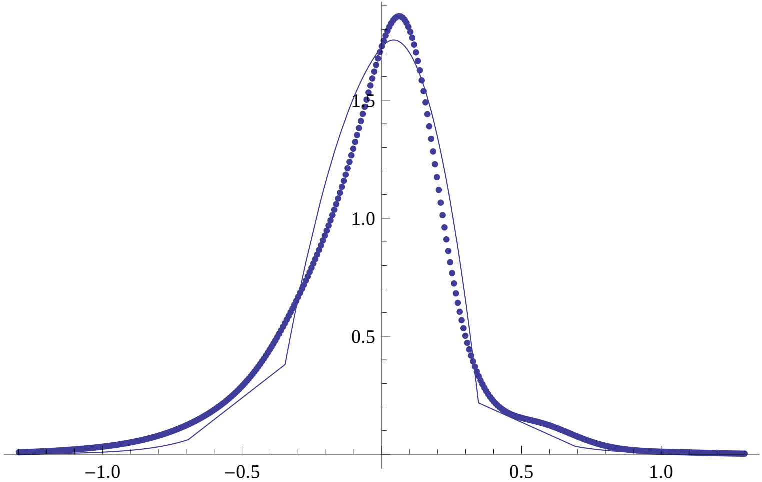
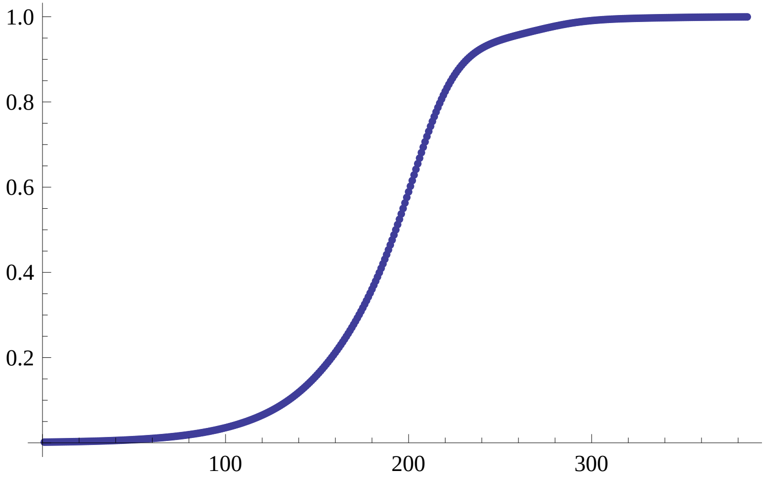


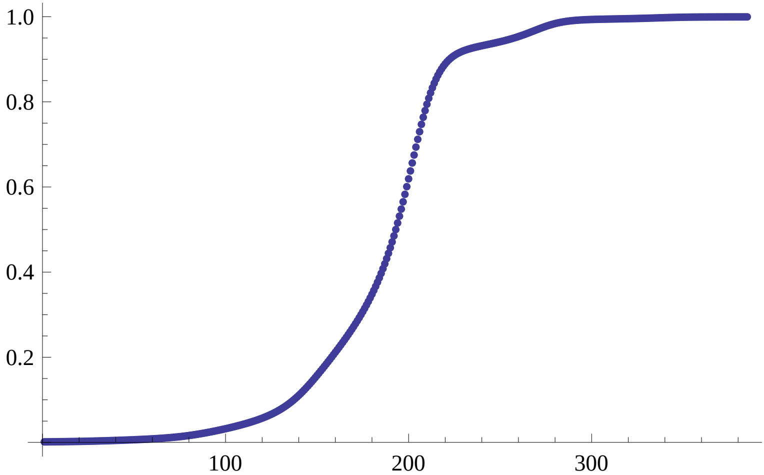
Approximation v_1' of the solution derivative versus finite-difference approximation (dotted line) in the case $a = 0.3$, $b = 15$



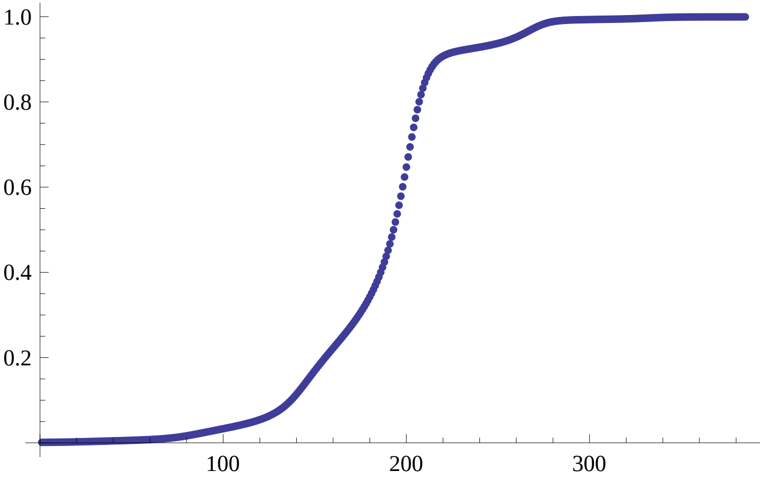
Approximation v_2' of the solution derivative versus finite-difference approximation (dotted line) in the case $a = 0.3$, $b = 15$



Finite-difference approximation of solution in the case $a = 0.1$, $b = 15$, with $N = 64$.



Finite-difference approximation of solution in the case $a = 0.3$, $b = 15$, with $N = 64$.



Finite-difference approximation of solution in the case $a = 0.35$, $b = 15$, with $N = 64$.

Conclusions about the Deterministic Case

- For the nonlinear case the Newton method provides a fast iterative scheme and the convergence is guaranteed, provided a good initial approximation is given.
- Besides the collocation methods, a fourth-order finite difference scheme has been implemented.
- The finite difference method has a good performance for different parameter values, except in the case when a is greater 0.3.

Stochastic equation

We recall the deterministic equation:

$$v'(t) = A\left[v(t+\tau) - 2v(t) + v(t-\tau)\right] + Bf(v(t)), \tag{13}$$

where

$$f(v) = v(v-1)(\alpha - v).$$

We assume that the term f (current-voltage function) can be affected by noise:

$$\tilde{f}(v) - f(v) = (\tilde{\alpha} - \alpha)v(v-1); \tag{14}$$

therefore, we introduce a stochastic term of the form

$$\Gamma(t) = \gamma v(t)(v(t)-1)W(t), \tag{15}$$

where γ is a positive constant and $W(t)$ is a stochastic process with normal distribution, zero expectation and standard deviation 1, that is $W(t) \sim N(0,1)$.

Stochastic equation

We obtain the following SDE:

$$dv(t) = \left(A\left(y(t+\tau) - 2v(t) + v(t-\tau)\right) + Bf(v(t))\right)dt + \gamma v(t)(v(t)-1)dW(t). \tag{16}$$

To simplify, we assume that

$$W(t) = 0, \qquad \text{if} \quad t < -2\tau \quad \text{or} \quad t > 2\tau, \tag{17}$$

that is, the solution is not affected by noise outside of $[-2\tau, 2\tau]$.
To solve the mixed-type functional differential equation, we need to set some initial data on intervals $[-3\tau, -2\tau]$ and $[2\tau, 3\tau]$.
As in the deterministic case, we use the information on the asymptotic behaviour of the solution at infinity. So we set

$$v(t) = \epsilon_1 e^{\lambda_+(t+3\tau)}, \qquad t \in [-3\tau, -2\tau] \tag{18}$$

and

$$v(t) = 1 - \epsilon_2 e^{\lambda_-(t-3\tau)}, \qquad t \in [2\tau, 3\tau]. \tag{19}$$

Discretization of the stochastic equation

Note: the discretization scheme used in the deterministic case cannot be directly applied to the stochastic equation .
We start by introducing a uniform mesh on $]-3\tau, 3\tau[$ with stepsize $h = \tau/N$, for a given N. Then we have

$$t_i = -3\tau + ih, \quad i = 0, ..., 6N.$$

If we apply the explicit Euler method to the deterministic equation, we get:

$$\frac{v_{i+1} - v_i}{h} = A\left(v_{i+N} - 2v_i + v_{i-N}\right) + Bf\left(v_i\right), \qquad i = N+1, ..., 5N. \tag{20}$$

If we try to solve this equation with respect to v_{i+N} (assuming that all the other entries of v are known) we get a very unstable scheme. Instead, we try to solve (20) as a system of nonlinear equations.
With this purpose, we use an iterative procedure (similar to the Gauss-Seidel method).

Discretization of the stochastic forward equation

Suppose that an intial approximation $v^{(0)}$ to the solution of (1) is known on the interval $[-3\tau, 3\tau]$ (this initial approximation is obtained from our numerical results for the deterministic case.
Then we can compute a new approximation $v^{(1)}$ from the explicit formulae

$$\frac{v_{i+1}^{(1)} - v_i^{(1)}}{h} = A\left(v_{i+N}^{(0)} - 2v_i^{(1)} + v_{i-N}^{(1)}\right) + Bf(v_i^{(1)}), \qquad i = N+1, ..., 5N. \tag{21}$$

The solution is computed forwards , with the advanced term v_{i+N} replaced by the previous iterate. Iterating this scheme we obtain the following iterative method:

$$\frac{v_{i+1}^{(k+1)} - v_i^{(k+1)}}{h} = A\left(v_{i+N}^{(k)} - 2v_i^{(k+1)} + v_{i-N}^{(k+1)}\right) + Bf(v_i^{(k+1)}), \quad i = N+1, N+2, .., 5N; \qquad k = 0, 1, ... \tag{22}$$

Stopping criterion:

$$\|v^{(k+1)} - v^{(k)}\| < \epsilon.$$

Discretization of the stochastic forward equation

The latter scheme can be easily adapted to the stochastic case. With this purpose, we use the Euler-Maruyama method. In this case, we write the equation

$$v_{i+1}^{(k+1)} = v_i^{(k+1)} + h\left(A\left(v_{i+N}^{(k)} - 2v_i^{(k+1)} + v_{i-N}^{(k+1)}\right) + Bf(v_i^{(k+1)})\right) + \gamma\sqrt{h}v_i^{(k+1)}(v_i^{(k+1)} - 1)w_i, \qquad i = N+1, N+2, \dots \tag{23}$$

where w_i represents a random variable with standard normal distribution $N(0,1)$.

Discretization of the backward stochastic equation

In the same way, we can construct a discretization scheme which builds the solutions backwards:

$$v_{i-1}^{(k+1)} = v_i^{(k)} - h\left(A(v_{i+N}^{(k+1)} - 2v_i^{(k+1)} + v_{i-N}^{(k)}) - Bf(v_i^{(k+1)})\right) + \gamma\sqrt{h}v_i^{(k+1)}(v_i^{(k+1)} - 1)w_i, \quad i = 3N, 3N-1, \dots, 0 \tag{24}$$

To avoid instability, we use the following algorithm:

- We apply the forward scheme on $[0, 3\tau]$, assuming that the solution is known on $[-3\tau, 0]$;
- We apply the backward scheme on $[-3\tau, 0]$, assuming that the solution is known on $[0, 3\tau]$;

Numerical results for the stochastic equation

1. Perturbation of a constant solution $v(t) \equiv \alpha$ - constant solution of the deterministic equation; (unstable equilibrium point of this equation).
The equation has the stable equilibrium points $v(t) \equiv 0$ and $v(t) \equiv 1$.
question: how does the constant solution $v(t) \equiv \alpha$ change if the deterministic equation is perturbed by noise?
Deterministic equation:

$$v'(t) = A\left(v(t+\tau) - 2v(t) + v(t-\tau)\right) + Bf(v(t)) \tag{25}$$

Boundary conditions: $v(t) \equiv \alpha$, if $t \in [-3\tau, -2\tau]$; $v(t) \equiv 0$ or $v(t) \equiv 1$, if $t \in [2\tau, 3\tau]$.
Stochastic equation:

$$dv(t) = \left(A\left(v(t+\tau) - 2v(t) + v(t-\tau)\right) + Bf(v(t))\right)dt + \gamma v(t)(v(t)-1)dW(t). \tag{26}$$

Boundary conditions: $v(t) \equiv \alpha$, if $t \in [-3\tau, -2\tau]$;
$v(t) \equiv 0.5$, if $t \in [2\tau, 3\tau]$.

Numerical Results - perturbation of a constant solution

For the deterministic equation, we have two different situations:

- $\gamma > 0$ (the threshold potential is increased under the effect of noise); then the perturbed solution is less than α . Hence it will approach $v(t) \equiv 0$ (stable equilibrium point).
- $\gamma < 0$ (the threshold potential is decreased under the effect of noise); then the perturbed solution is greater than α . Hence it will approach $v(t) \equiv 1$ (stable equilibrium point).

If we consider the stochastic equation with a certain value of γ, it is expected that the trajectories of its solutions are located between $v(t) \equiv 0$ and $v(t) \equiv 1$.

Numerical Results - perturbation of a constant solution

$$v_{min}(t) = \min_{i=1,..,ns} v_{(i)}(t), \quad v_{max}(t) = \max_{i=1,..,ns} v_{(i)}(t), \tag{27}$$

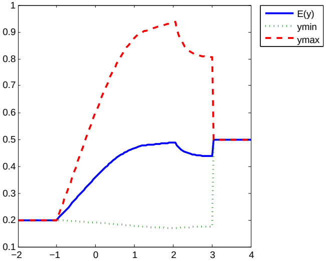


Figure: Solutions of the stochastic equation (16), with constant boundary conditions, $\alpha = 0.2$ and $\gamma = 0.001$. The trajectories were obtained with $N = 20$ and $ns = 100$.

Numerical Results - dependence of the solution on α

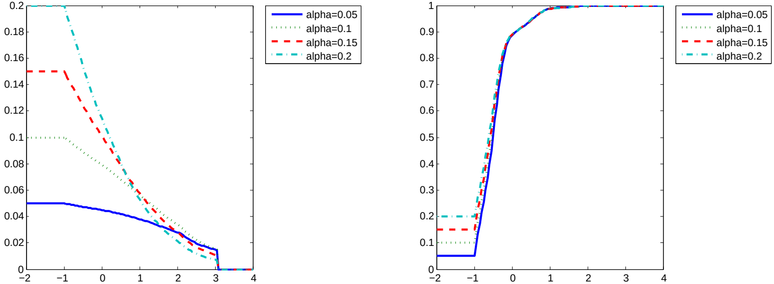
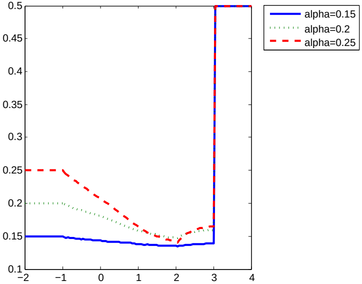


Figure: Solutions of the deterministic equation with $\gamma = 0.001$ (left) and $\gamma = -0.001$ (right), with different values of α.

Numerical results- dependence on α.

- the graphs of v_{min} are decreasing and their slopes become steeper, as α increases.
- the graphs of v_{max} are increasing and they become less steep, as α increases.



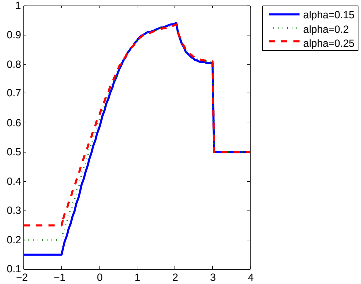


Figure: Graphs of v_{min} (on left) and v_{max} (on right), for the stochastic equation in the case $\gamma = 0.01$ with different values of α.

Numerical Results - dependence on α.

How do the expected values of v change with α ?

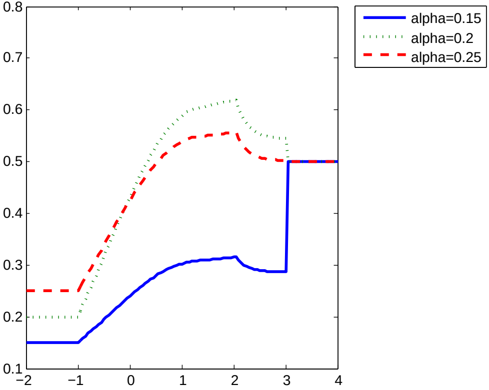


Figure: Graphs of $E(v(t))$, for the stochastic equation, in the case $\gamma = 0.01$, with constant boundary conditions and different values of α.

Numerical Results - convergence issues

Do the numerical results indicate that the expected value of the solution $E(v_N(t))$ converges to a certain function, as N tends to ∞?

Numerical experiment: $N = 8$, $N = 16$, and $N = 32$;

$E(v(s))$ is computed based on $ns = 50000$ trajectories;

$$r = \frac{|E(v_{16}) - E(v_8)|}{|E(v_{32}) - E(v_{16})|}, \tag{28}$$

α	0.2	0.25	0.3
$\gamma = 0.001$	1.254	2.2920	2.3099
$\gamma = 0.01$	2.2969	2.4412	2.5088
$\gamma = 0.1$	2.4391	1.3179	1.9850

Table: values of the coefficient (**??**), indicating weak convergence of order one in the case of constant boundary conditions

Numerical Results - Expected values of the growth rate

local growth rate

$$E(\Delta v)(t_i) = \frac{E(v(t_{i+1})) - E(v(t_i))}{h}$$

α	0.2	0.25	0.3
$\gamma = 0.001$	0.4032	0.3456	0.2752
$\gamma = 0.01$	0.4038	0.3392	0.2688
$\gamma = 0.1$	0.4096	0.3392	0.2688

Table: Estimated expected values of the local growth rate at $t = -23/16$, in the case of constant boundary conditions

Numerical Results - Solution with non-constant boundary conditions

Comparison of v_{min}, v_{max} and $E(v(t))$.

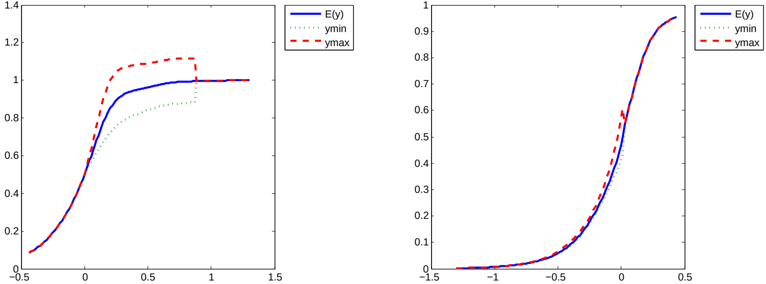
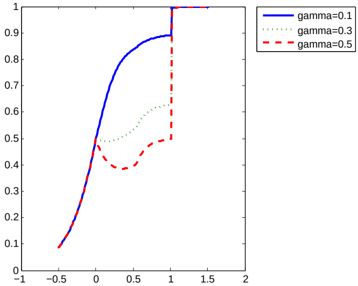


Figure: Graphs of $E(v(t))$, v_{min} and v_{max} for the stochastic equation on $[-\tau, 3\tau]$ (left) and $[-3\tau, \tau]$ (right), in the case of asymptotic boundary conditions, with $\gamma = 0.1$, $\alpha = 0.1$

Numerical Results - Solution with non-constant boundary conditions

How do v_{min} and v_{max} depend on γ?



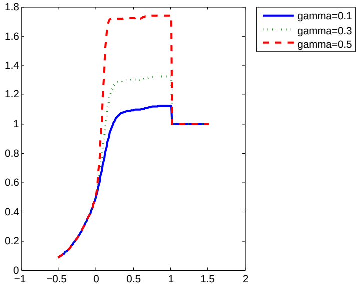


Figure: Graphs of v_{min} (left) and v_{max} (right) for the stochastic equation on $[-\tau, 3\tau]$ in the case of asymptotic boundary conditions, with $\gamma = 0.1$, $\alpha = 0.1$

Conclusions about the Stochastic Case

- The convergence of the discretisation method has been tested experimentally and the obtained estimates of the weak convergence rate (close to 1) are in agreement with the known theory about the Euler-Maruyama method.
- When the stochastic equation is solved with constant boundary conditions $y(t) \equiv \alpha$, which is an unstable equilibrium point for the deterministic equation, we observe that the solutions are very sensitive to the stochastic noise.
- We have analysed the properties of the solutions separately on the intervals $[-2\tau, 0]$ and $[0, 2\tau]$. An important conclusion is that the solutions are much more sensitive to stochastic noise in the second case than in the first one.
- The expected solutions of the stochastic equation $E(y(t))$ are smooth and increasing, and even when $\gamma = 0.5$ they don't strongly differ from the solutions of the corresponding deterministic equation (when $\gamma = 0$).

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