Mathematical models of structured populations. Applications in Neuroscience.

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Introduction.

- By structured populations we mean a group of individuals that differentiate through some physiological characteristic e. g. age, size, genotype, etc.
- Examples: populations of humans, animals, plants, cells, viruses, etc.
- A mathematical model of a structured populations will not only track down the evolution in time of the number of individuals but also the evolution in structure of the considered population.

Age structured systems.

F.R. Sharpe, A. Lotka, A.G. McKendrick

$$\begin{cases} Dp(t,a) + \mu(a)p(t,a) = 0; & t > 0, a \in (0, A) \\ p(t,0) = \int_0^A \beta(a)p(t,a)\,\mathrm{d}a; & t > 0 \\ p(0,a) = p_0(a) \end{cases}$$

Notations:

- t denotes the time and a - the age; A - the maximal age;
- $p(t,a)$ - the population density of age a at time t;
- μ - the mortality rate;
- β - the natality rate;
- Dp - the directional derivative of p in the direction (t,a).

More general models

The total population

$$P(t) = \int_0^A p(a,t)\,\mathrm{d}a, \quad \forall t > 0$$

- the fertility and mortality rates are supposed to depend on the total population at each time t (M.E. Gurkin, R.C. MacCamy, F. Hoppensteadt);

Books on age-structured systems: F. Hoppensteadt, B. Charlesworth, J. Metz, O Dieckmann, J. Murray, N. Keyfitz, G. Webb

Control of age-dependent populations (books): S. Anița

Size structured population models.

N. Kato, H. Torikata

$$\begin{cases} \frac{\partial}{\partial t} p(t,s) + \frac{\partial}{\partial s}[v(t,s)p(t,s)] = -\mu(s, P(t))p(t,s) \\ P(t) = \int_0^l p(t,s)\,\mathrm{d}s \\ p(t,0) = C(t) + \int_0^l \beta(s, P(t))p(t,s)\,\mathrm{d}s \\ p(0,s) = p_0(s) \end{cases}$$

- v - the growth function; gives the evolution in time of the size of an individual of the population;
- l - the maximal size that can be achieved;
- $v \equiv 1$ - age-structured systems;
- μ and β are the vital rates;

Control problems associated with population models.

By control we mean a strategy that will influence the evolution of the population's behavior in time in a predictable manner.

- Stabilizability problems: finding a control function such that the corresponding solution to the considered model to have a specific large-time behavior.
- Optimal control problems - finding a control strategy such that the corresponding solution to maximize (minimize) a given functional that has a certain interpretation (e.g. maximize the harvest in population of plants or animals, minimize the costs, etc.)

Optimal control problems of size structured systems. A general model

The model

$$\max \left\{ \int_0^S l(p(T,s))\,\mathrm{d}s + \int_0^T \int_0^S L(t,s,p(t,s),y(t),u(t,s),v(t))\,\mathrm{d}s\mathrm{d}t \right\},$$

subject to

$$\begin{cases} \frac{\partial}{\partial t} p(t,s) + \frac{\partial}{\partial t}[g(t,s,y(t),v(t))p(t,s)] = f(t,s,u,p,y,v) \\ y(t) = \int_0^S h(t,s,x(t,s))\,\mathrm{d}s \\ p(t,0) = \varphi(t,y(t)) \\ p(0,s) = p_0(s) \end{cases}$$

Optimal control problems of size structured systems. A general model

- u and v are the control functions; u represents the harvest and v can be interpreted as food supplies , water or heat supply (in farming);
- the first term of the objective function represents the rest value of the population at the end of the planning horizon and the second term incorporates the aggregated over age and time “benefit” from x and “costs” of the controls u and v
- φ - the inflow of individuals of "size zero";
- $y(t)$ can represent one or more weighted means, e.g. the total population if $h = x$, the biomass if $h = sx$;

Optimal control problems of size structured systems

1. Optimal Control for a Class of Size-Structured Systems, C. O. Tarniceriu, V.M.Veliov , Lecture Notes in Computer Science, volume 4818, Springer Verlag, 2008.
   - an optimal control problem for size structured system where the inflow of population of size zero is not taken into account;
2. Numerical Optimal Control of Size-Structured Populations, K. Georgiev, C. O. Tarniceriu, V.M.Veliov, http://bis-21pp.acad.bg/results/results.htm
   - numerical method that applies to optimal control problems of both size - and age - structured systems ;
3. Optimal Control of Size-Structured Systems. Numerical simulations. C.O. Tarniceriu - in final stage;
   - Well-posedness of a general model for fixed controls. Numerical simulations for the optimal control problem.

Perspectives

- One of the limitation of the model is the form of the influx of the individuals of "size zero". In reality, not all the new born have the same size. In this direction, a more complex model has been proposed by J. Z.Farkas
- Optimal control problem for the more complex model.
- Stabilization control problems.

Physiology

A typical neuron can be divided into three functionally distinct parts: - *dendrites* (act as an input device);
- *soma* (processing unit);
- *axon* (output device).

If the total input exceeds a certain threshold value, an electrical signal is generated, which is taken by the output device and transmitted to other neurons.

The junction between two neurons is called *synapse*.

The transmitted signal - *spike* or *action potential*.

References for mathematical models of spiking neurons:

W. Gerstner and W. Kistler, Spiking neuron models, Cambridge university press

E.M. Izhikevich ,Dynamical Systems in Neuroscience: The Geometry of Excitability and Bursting,The MIT press

Membrane's potential

The membrane of a neuron separates the interior of the cell from the extracellular liquid and acts as a capacitor. The membrane's potential of a neuron is defined as the difference of electric potentials of the interior and exterior of the cell:

Membrane's potential

$$V = V_{int} - V_{ext}.$$

Ion channels are pore-forming membrane proteins whose functions include establishing a resting membrane potential, shaping action potentials and other electrical signals by gating the flow of ions across the cell membrane.

Ionic currents and conductances

Notations:

- V – potential of the membrane;
- E_{Na}, E_K, E_{Cl} – reversal potentials of each ion species;
- g_{Na}, g_K, g_{Cl} – corresponding conductances;
- I_{Na}, I_K, I_{Cl} – net current of each ion species;

Example

$$I_K = g_k(V - E_k)$$

Ionic currents and conductances

Kirchoff' law

$$I = C\dot{V} + I_{Na} + I_K + I_{Ca} + I_{Cl}$$

- $\dot{V} = \frac{\mathrm{d}V}{\mathrm{d}t}$;
- I – an external current ;
- C –membrane's capacitance.

The following dynamic system is obtained by replacing each current:

$$C\dot{V} = I - g_{Na}(V - E_{Na}) - g_{Ca}(V - E_{Ca}) - g_K(V - E_K) - g_{Cl}(V - E_{Cl})$$

Hodgkin-Huxley model.

In the typical Hodgkin-Huxley model, there are considered three types of ionic channels: Na^+, K^+ and a leakage channel. The probability that a channel is open is described by three aditional variables: m, n and h - the so called *gating variables*:

Hodgkin-Huxley model for giant squid axon neuron

$$
\begin{aligned}
C\dot{V} &= I - I_{Na} - I_K - I_L \\
\dot{n} &= \alpha_n(V)(1-n) - (\beta_n(V))_n \\
\dot{m} &= \alpha_m(V)(1-m) - (\beta_m(V))_m \\
\dot{h} &= \alpha_h(V)(1-h) - (\beta_n(V))_h
\end{aligned}
$$

Hodgkin-Huxley (H-H) model

- m, n, h - gating variables;
- $\alpha_n, \alpha_m, \alpha_h, \beta_n, \beta_m, \beta_h$ – empirical functions;
- $I_{Na} = g_{Na} m^3 h(V - E_{Na})$;
- $I_K = g_K n^4 (V - E_K)$;
- $I_L = g_L (V - E_L)$.

Reduced models

- H-H model remains one of the most accurate model to describe the internal mechanisms of the cell that lead to the initiation of action-potentials
- The very large number of neurons in the brain (10^{11}), the variability of the cell's physiological characteristics and the high number of the connections between them makes the realistic simulations of large networks of neurons very difficult to realize.
- By additional assumptions (eg. taking the conductances of the channels as being constant, etc), reduced models of the H-H models have been introduced. They do not offer all the complexity of the neural cell, but allow the simulations of large number of interconnected neurons.

Reduced models. Integrate-and-Fire model.

- a simplified model with threshold; when the potential of the membrane reaches the value of the threshold, it is considered that an action potential has been initiated and the membrane potential is reset to a reset value

Integrate-and-Fire

$$\dot{V} = -\gamma V + I, \quad V \in (v_r, \eta)$$

$$+ \text{ reset mechanism: if } V = \eta \text{ then } V = v_r$$

Reduced models. Quadratic Integrate-and-Fire model. The equivalent theta-neuron model.

Quadratic Integrate-and-Fire

$$\dot{V} = V^2 + I_b, \quad V \in \mathbb{R}$$

$$+ \text{ reset mechanism: if } V = +\infty \text{ then } V = -\infty.$$

- I - an external current. I is an important parameter of the model that dictates different behaviors of the solution.

By changing the variable $\theta = 2\arctan v + \pi$, the theta-neuron model is obtained:

Ermentrout-Kopell

$$\frac{d}{dt}\theta(t) = (1 + \cos\theta) + (1 - \cos\theta)I_b.$$

Interconnected neurons. Population density function for Integrate and Fire neurons.

For $N \to \infty$, the fraction of neurons having the membrane's potential in $[v_0, v_0 + \delta v]$ is:

$$\lim_{N \to \infty} \frac{neurons\ with\ v_0 \leq v(t) \leq v_0 + \Delta v}{\Delta v} = \int_{v_0}^{v_0+\Delta v} p(t, v')\,\mathrm{d}v'$$

- p(t,v) - membrane potential density

How does the membrane potential density function evolves in time?

Normalization:

$$\int_{v_r}^{\eta} p(t, v)\,\mathrm{d}v = 1.$$

- expresses the fact that all neurons have the membrane potential in the interval $[v_r, \eta]$.

Interconnected neurons. Population density function.

The population activity is defined as the fraction of the neurons that "flow" across the threshold, i.e.

$$r(t) = J(t, \eta)$$

Reinjection of neurons:

$$J(t, v_r) = J(t, \eta)$$

The flux is supposed to consists of two parts:

$$J(t, v) = J_{drift}(t, v) + J_{jump}(t, v)$$

Population density models for Integrate and Fire neurons

In the case of Integrate-and fire neurons, the drift flux is given by:

$$J_{drift}(t,v) = [-\gamma v + I]p(t,v)$$

It is supposed next that, every time a neuron of the population receives a signal, will have a jump in potential of magnitude h. Denoting by σ the average reception rate of a neuron, the jump-flux is given by:

$$J_{jump} = \sigma \int_{v-h}^{v} p(t,v')\,\mathrm{d}v'$$

The evolution in time of the density function is dictated by:

$$\frac{\partial}{\partial t}p(t,v) = -\frac{\partial}{\partial v}J(t,v)$$

Population density models for Integrate and Fire neurons

A population density model for integrate and fire neurons:

L. Sirovich

$$\begin{cases} \frac{\partial}{\partial t} p(t,v) + \frac{\partial}{\partial v}\left((-\gamma v) p(t,v)\right) = \sigma\left(p(t,v-h) - p(t,v)\right) \\ + \delta(v) r(t) \\ p(t,1) = 0 \\ r(t) = \sigma \int_{1-h}^{1} p(t,v)\,\mathrm{d}v = \frac{I}{h} \int_{1-h}^{1} p(t,v)\,\mathrm{d}v \\ p(0,v) = p_0(v). \end{cases}$$

Connected theta-neuron

Consider a population of interconnected quadratic integrate and fire neurons

$$\frac{d}{dt}v(t) = v^2(t) + I_b + h\sum_{j=1}^{+\infty}\delta(t-t_j)$$
$$\text{If} \quad v=+\infty \quad \text{then} \quad v=-\infty,$$

-t_j - firing times; The equivalent theta-neuron model:

$$\frac{d}{dt}\theta(t) = (1+\cos\theta) + (1-\cos\theta)I_b + s(\theta)\sum_{j=1}^{+\infty}\delta(t-t_j)$$

$$s(\theta) = \left(\theta - 2\arctan\left(h + \tan\left(\frac{\theta-\pi}{2}\right) + \pi\right)\right)$$

A population density model for theta-neurons

G. Dumont, J. Henry, C.O. Tarniceriu

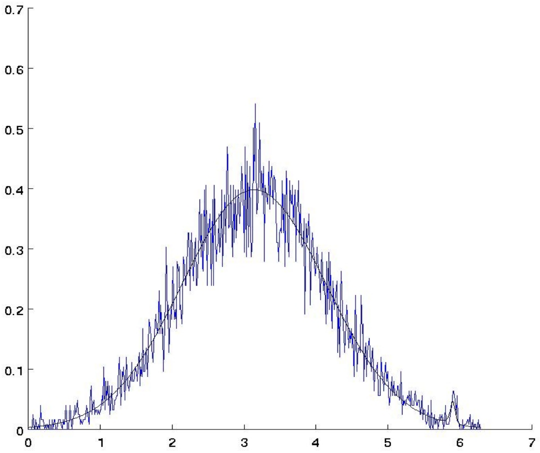
$$
\begin{cases}
\dfrac{\partial}{\partial t} q(t,\theta) + \dfrac{\partial}{\partial \theta}(f(\theta) q(t,\theta)) = \sigma(t)(s'(\theta) q(t, s(\theta)) - q(t,\theta)), \\
\sigma(t) = \sigma_0(t) + J \displaystyle\int_0^t \alpha(s) r(t-s)\, ds \quad \text{with conduction delay,} \\
\sigma(t) = \sigma_0(t) + J r(t) \quad \text{without conduction delay,} \\
r(t) = 2q(t, 2\pi), \\
q(t,0) = q(t,2\pi), \\
q(0,\theta) = q_0(\theta),
\end{cases}
$$

(with $\theta \in [0, 2\pi]$, $t \geq 0$).

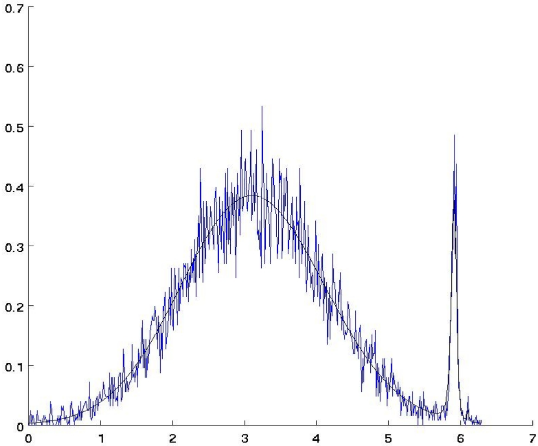
A population density model for theta-neurons

- well-posedness for the above introduced model in the case of both excitatory and inhibitory connections; global existence in the linear case;
- numerical simulations; comparison of the simulations to direct simulations via Monte Carlo method
- the stability of the stationary repartition
- synchronized solution?

Numerical simulations. Comparison with Monte Carlo direct simulations.



Numerical simulations. Comparison with Monte Carlo direct simulations.



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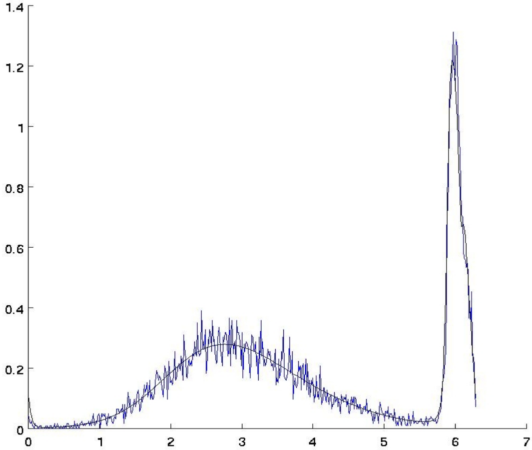

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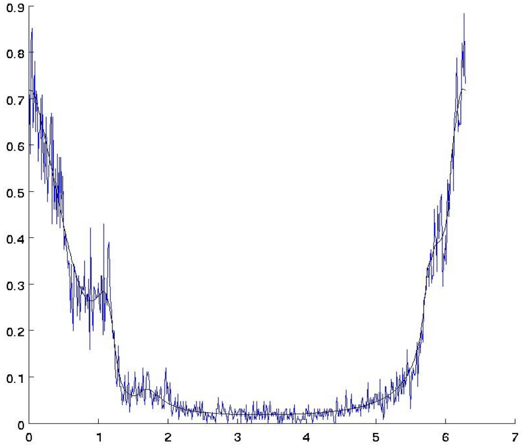

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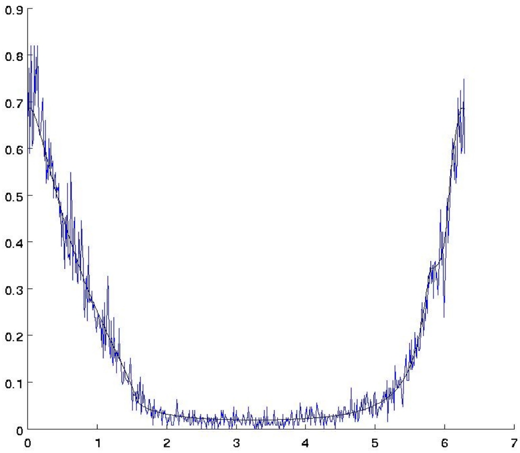
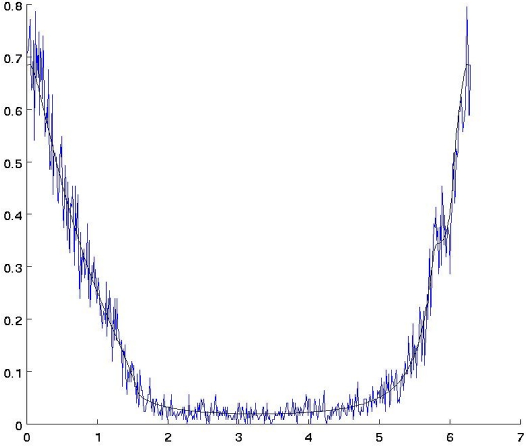


Numerical simulations. Comparison with Monte Carlo direct simulations.



Papers

1. Analysis of Synchronization in a Neural Population by a Population Density Approach, A. Garenne, J. Henry, C.O. Tarniceriu, Math. Model. Nat. Phenom. Vol. 5, No. 2, 2010, pp. 5-25
   - a population density model for a population of neurons individually described by the Izhikevich's bi-dimensional model
   - transition to phase-densities in the case of weak connections between neurons;
   - condition for stabilization towards the synchronized solution
2. Well-posedness of a density model for a population of theta neurons, G. Dumont, J. Henry, C.O. Tarniceriu, submitted to Journal of Mathematical Neuroscience
   - well-posedness
   - numerical simulations

Conclusions and perspectives

- The above models are obtained under the assumption of homogeneity of the population, i.e. there are considered populations of neurons with the same characteristics (parameters, same firing threshold etc.). Considering heterogeneous population will lead to more realistic results. A possible differentiation of neurons has been proposed by W. Gerstner and W. Kistler by supposing that not all neurons will fire at a fixed threshold value, rather than in an interval below a formal threshold value.
- The age-structured systems have been extensively studied in the last decades; we think that a passing from potential densities to a certain age-structure in neural populations may be done ("age" being the time elapsed since the last firing of a neuron). This will help reducing the density models to a more approachable form.

Conclusions and perspectives

- Once validated a model, the control problems for the considered model is the next natural step. In particular, the synchronized solution has been of great interest, since synchronization of neurons is a phenomena that is found both in physiological and pathological conditions. Controlling the mechanisms that lead to such a behavior is desirable.