H1. FULL DESCRIPTION

1. Objectives

(scientific problem aimed to be solved by the proposed project, project scientific hypotheses)

Many biological and social processes can be modeled by systems of interacting objects. One may then try to derive their global behavior from individual interactions between their basic entities such as RNA and protein molecules in biochemical reactions of gene expression and regulation, animals in evolutionary and ecological processes, and people in social processes. Usually such systems are described by differential equations such as kinetic rate equations describing changes of concentrations of substrates and products in chemical reactions, and replicator dynamics describing evolution of frequencies of various strategies in evolutionary games. However, many cells are very small and the numbers of protein molecules present in them might be very low [33, 34, 59, 65, 67]. Also populations of interacting individuals in evolutionary games are often finite and not very large [45, 54]. If the number of interacting objects is small, to describe and analyze time evolution of such systems we should take into account stochastic fluctuations.

Moreover, it was usually assumed that reactions in biochemical systems take place instantaneously, and their effects are immediate. In reality, all biochemical processes take a certain time, there is a substantial time delay between the beginning of a reaction and the appearance of new products in the system. Similarly, in ecological and evolutionary models, results of interactions between individuals may appear in the future, and in social models, players may act, that is choose appropriate strategies, on the basis of the information concerning events in the past. It is very important therefore to incorporate time delays and stochasticity in the construction of mathematical models of biological and social processes.

The main goal of this project is to investigate joint effects of time delays and stochastic perturbations in deterministic dynamical systems. It is well known that time delays may cause oscillations in solutions of ordinary differential [5, 6, 21, 24, 35], systems may change their stabilities through the Hopf bifurcation.

We will investigate conditions satisfied by mathematical models of interacting objects which are responsible for the appearance of oscillations and cycles in stochastic systems with time delays – how their evolution, position and stability of their stationary states depend on types of time delays and stochastic perturbations. We will be dealing with general dynamical systems such as Markov chains, Markov jump processes (birth and death processes), and stochastic differential equations with time delays. We will obtain rigorous and approximate formulas for probabilistic stationary distributions, expected value and variance of the number of various types of proteins in living cells, and frequencies of various strategic behaviors in evolutionary games. We will investigate how stochastic perturbations affect systems with bifurcations and cycles caused by time delays [47]. Usually time delays change stability of stationary states. We will check in what circumstances time delays may actually change stationary states themselves.

Our project has an interdyscyplinary character. Our goals are inspired by specific problems in evolutionary and molecular quantitative biology. We will construct or modify mathematical models of negative and positive feedback in gene expression, toggle switches of two competing proteins, and gene expression models and evolutionary games with multiple delays. Then various mathematical techniques will be developed to analyze these models and to provide answers to mathematical questions related to biological problems. In particular, the objective of this project is a systematic development of a mathematical theory of stochastic dynamics with time delays and construction of effective mathematical techniques applicable in stochastic biological systems with time delays. We will develop new mathematical theories and techniques: 1) Theory of singular perturbations of Markov jump processes, 2) Low-noise expansions in non-equilibrium states (stationary probability distributions of stochastic processes which do not satisfy detailed balance conditions) appearing in random perturbations of deterministic systems as discussed in [18], 3) Mathematical foundations of self-consistent mean-field approximations viewed as optimization problems in spaces of probability measures.

2. Significance

(justification for tackling specific scientific problems by the proposed project, pioneering nature of the project, the impact of the project results on the development of the research field and scientific discipline, economic and societal impact)

As we have already mentioned, time delays may cause oscillations in solutions of ordinary differential [5, 6, 21, 24, 35]. Very often time delays are introduced in a rather arbitrary way, without any fundamental microscopic modeling of interactions between objects and individuals of given populations. When one models biological and

social processes it is very important to take into account particular reasons of time delays. In this project we will investigate microscopic foundations of classic models with time delay and construct new ones. In finite (and also infinite) populations, combined effects of time delays and stochastic perturbations may result in a novel behavior. For example, in deterministic systems we may have multiple stationary states with certain basins of attraction, in corresponding stochastic models, some of these states may disappear. We will now briefly review two examples which will illustrate the state of knowledge, and point out to problems we would like to address in our project.

Our first example concerns gene expression. It was argued recently in [8] that combined effects of time delay of protein degradation and stochastic fluctuations may cause an oscillatory behavior in a simple model of gene expression. We showed in [48] that if one assumes that a process of degradation is consuming, that is molecules which started to degrade cannot take part in other processes (including another degradation as it is allowed in [8]), then oscillatory behavior is no longer present in such systems. The key point here is that although a protein molecule will completely degrade at some time in the future, it has already changed the state of the system at an earlier time. In [48], we constructed two stochastic Markov jump processes, for active particles and for all particles of the system. We would like to extend our innovative approach to other models of gene regulation with time delays such as auto-regulated genes with delayed production, and various models of toggle switches with bi-modal probability stationary distributions.

The second example concerns evolutionary games [26, 27, 42, 45]. In [66], the effect of a time delay on the stability of interior stationary points of the replicator dynamics was investigated. The authors considered a two-player game with two strategies and a unique asymptotically stable interior stationary point (a mixed evolutionarily stable strategy). They proposed a certain form of a time-delay differential replicator equation and showed that the interior stationary point is stable if a time delay is small, and for sufficiently large delays it becomes unstable. In [1], we discussed discrete-time replicator dynamics and introduced a time delay in two different ways. In both cases we begun with microscopic difference equations for numbers of individuals using particular strategies. In the so-called social model, we assumed that players imitate a strategy with the higher average payoff, taking into account time-delayed information. In the so-called biological model, we assumed that the number of players born in a given time is proportional to payoffs received by their parents in a certain moment in the past. In the first model, we proved results analogous to those in [66]. However, in our second model, we showed the stability of the interior point for any value of the time delay. Moreover, in this case the system cannot be described by one differential time-delayed equation, one needs another equation for the size of the population. In both cases, we proved our results in a direct way (using various inequalities), that is without any reference to the theory of time-delay equations. It is clear now that evolution and stability of stationary states depend on the type of the time delay. It is one of the goals of this project to extend the direct and novel approach of [1] to other evolutionary games, especially with multiple stationary points.

A special attention in our project will be devoted to systems with small time delays. In such systems one sometimes expands terms including delays into Taylor series [22]. Comparison of the dynamics of delay differential equations for small delays with the corresponding ordinary differential equations that arise by the Taylor expansion with respect to the time delay seems to be important and not obvious. In [14–16, 63, 64] some results were proven for linear and weakly non-linear equations. On the other hand, it was shown (see e.g. [16]) that the behavior of a simple linear delay differential equation may be qualitatively different from the equation that is constructed by a second order Taylor expansion with respect to a time delay. Therefore, such approximations need to be done with care, in particular if some stochastic effects are involved.

Approximations of Fokker-Planck equations with time delays were proposed in [22]. We will extend small-time-delay approximations presented in [22] to systems with variance which depends on the state of the system at earlier times. Some partial results concerning small-delay approximations were obtained by the author of this grant proposal in gene expression model with delayed degradation [46] and in systems with strategy-dependent delays in [52]. We will analyze such and other systems subject to stochastic perturbations. Especially, we will be concerned with systems with multiple delays, strategy dependent time delays in evolutionary games, and time delays of various biochemical processes in cellular regulatory systems. In this project we would like to explore possibility of adapting methods employed in [29, 60] for stochastic differential equations to Markov jump processes describing auto-regulated genes. Specifically, we will investigate time evolution and stationary states of self-regulated systems in the limit of zero time delay and an infinite frequency of gene switching.

In many evolutionary games, it is natural to introduce strategy-dependent delays. In biochemical systems, all reactions take time and are naturally delayed. Therefore it is very important to study systems with multiple time delays. It is one of the goals of this project to investigate effects of random perturbations on systems with multiple time delays.

The general goal of this project is to contribute to a general theory of stochastic dynamics with time delays, develop appropriate techniques to deal in a constructive and effective way with such systems.

On the other hand, specific formulas obtained in the project will be very useful in quantitative biology, to infer various parameters of biochemical reactions and to speed up calculations and numerical simulations of large bio-systems. In evolutionary games our goal will be to see how the presence of time delays changes standard results concerning stability of stationary states and extinction of strategies.

Stochastic processes studied in this project describe various biological phenomena. Biological systems are open, they are connected to external reservoirs and heat baths. Usually in such systems, even in stationary states, there exist fluxes and currents. Therefore stationary probability distributions are time irreversible (they do not satisfy detailed balance conditions present in equilibrium statistical mechanics of interacting particles [12, 39, 40]). The breaking of the detailed balance allows other than equilibrium distributions and more specific kinetic tuning can favor greater abundance of the required end products. Such kinetic amplification introduces irreversible steps in reaction pathways and makes essential use of differences in time scales. It will be interesting to confront these issues with new developments in non-equilibrium statistical mechanics concerning the role of dynamical activity in nonlinear response. We have in mind recent programs on the glass transition, jamming and negative differential response which ought to have important analogues in bio-stochastic systems.

3. Work plan

(outline of the work plan, critical paths, state of pre-existing research indicating feasibility of research objectives)

We will explore joint effects of time delays and stochastic perturbations in particular models of gene regulation and evolutionary games. We will simultaneously investigate mathematical problems arising in molecular biology (biochemical stochastic processes) and evolutionary game theory (random perturbations of finite populations of players). This will allow to transport ideas and techniques between these two domains. We will examine mathematical foundations and applicability of various approximation schemes in recently studied models and use their modifications in various mathematical settings.

In particular, this will analyze self-consistent mean-field theories and other procedures which enable a closure of hierarchical infinite chains of equations for moments of stationary probability distributions [2, 9, 58, 68]. It is well known for example, that the mean-field approximation used in the ferromagnetic Ising model can be seen as a result of minimizing the free energy functional within a class of factored probability distributions [30]. We would like to explore the possibility of such an approach in biological models and in other closure procedures. Our goal here is to provide all relevant approximation procedures with a precise mathematical structure. This will allow an application of approximation analytical schemes in a controlled and efficient way in various biological and social models, especially with time delays.

Another concept and technique which will be explored here is that of stochastic stability. In particular we refer here to the tree lemma [18, 19]. We will study rigorously zero-noise limits of stationary probability distributions for various types of random perturbations and specifically in the presence of time delays. Some partial results were obtained in [47, 51], where we showed that for three-player games with two mixed and one pure Nash equilibrium, that is with two asymptotically stable stationary points (a boundary and an internal one) and an unstable internal stationary point of discrete replicator dynamics, stability of asymptotically stable points depends on the magnitude of time delay and the presence of stochastic perturbations. We showed that for any time delay smaller than the size of the basin of attraction of the interior stationary point, the stationary point loses its asymptotic stability, an asymptotically stable cycle appears. There is a critical time delay, beyond which, the cycle loses stability and a pure Nash equilibrium becomes globally asymptotically stable. We will check the possibility of such a behavior in other models of evolutionary games and gene regulation, in particular in time-continuous dynamical systems, where the time delay can be arbitrarily small.

We will investigate small-time delay limits in conjunction with other time scales approaching zero, for example in the adiabatic limit of infinitely fast switching genes in auto-regulatory systems. To deal with such systems we will develop of a theory of singular perturbations in Markov jump processes with various small parameters describing time scales in biological processes, time delays and frequency of switching gene states.

Research tasks:

1. **Effects of time delays in genetic systems with feedbacks**

a) In the simplest model of gene expression that is protein production, protein molecules are produced directly from DNA (transcription and translation processes are lumped together). Protein molecules may bind to special promoter regions of DNA, to either activate or repress its own production. States of the cell are characterized by the number of protein molecules and one of two states of DNA promoter: unoccupied and occupied one. Stochastic models of such self-regulated genes are represented by four coupled Markov jump processes (birth and death processes) of production and degradation of proteins, binding and unbinding of DNA promoter [28, 37, 38, 49, 68]. Formulas for the variance in the number of protein molecules were derived in various approximations (fast and slow DNA switching, self-consistent mean field). In [31], in the fast-switching case, two switching processes were replaced by appropriate probabilities (depending on the current number of protein molecules) for states of DNA. Then the evolution of the number of protein molecules is governed by the standard birth and death process and one can write formulas for the stationary state. In [36], such an approximation was the starting point of models with time delay. The goal of this task is to treat the general case (with explicit jump processes between two states of the gene as in [49]) with time delays and get formulas for the expected value and the variance of the number of protein molecules in the stationary case.

b) In the self-activation case we have to deal with a possible bi-stability [2, 38, 55, 56]. In deterministic approximations, time evolution of concentration of various types of protein molecules is described by systems of ordinary differential equations (the so-called chemical kinetic equations). In the self-activated genes, for a certain range of parameters, such equations may have multiple stationary points (for example two stable ones and one unstable) [31]. In the corresponding birth and death processes, only one of these points may survive, that is a stationary probability distribution assigns to it a high probability (one in an appropriate small-noise limit). For other range of parameters, it may happen that two such points are stochastically stable, that is the stationary distribution is bi-modal). In toggle switches, we have two types of proteins which repress each other. The goal of this task is to obtain formulas for expected values of protein molecules for the above models to see what is the state of the cell in the uni-modal case. For bi-modal cases, the goal is to construct appropriate variables describing bi-stability [2, 38].

2. **Detailed balance in stochastic biological systems**

The simplest stochastic model of gene expression without regulation is described by the standard birth and death process which satisfies the so-called detailed balance condition [12]. In the stationary probability distribution there are no currents, there is no time arrow. Both self-regulation and time delays brake the detailed balance.

a) One of the goals of this task is the construction of an effective expansion of the stationary probability distribution around the detailed balance for various systems with small parameters, in particular small time delays in production and small differences in rates of production in two gene states in gene expression models with self-regulation. We will try to modify the expansion recently proposed in [12].

b) We will analyze effects of kinetic elements on dynamics which do not satisfy the detailed balance condition in the context of mathematical problems which arise in the rigorous construction of non-equilibrium statistical mechanics [39–41]. In such systems, the jump rates of appropriate continuous-time Markov chains depend exponentially on the inverse of the temperature. In equilibrium statistical mechanics satisfying detailed balance, in the limit of zero temperature, equilibrium states are concentrated on configurations with minimal energy, on the so-called ground states. We would like to derive a systematic low-temperature expansion for systems without detailed balance in analogy with the low-temperature expansions in the Ising models or in general in the the lattice-gas models (Pirogov-Sinai theory [43,44,61]). Concepts of stochastic stability and the tree lemma might be useful here. Some preliminary results were obtained in [39–41].

3. **Singular perturbations of Markov jump processes**

The general goal of this task is to develop a singular perturbation theory for Markov jump processes analogous to the theory of perturbed stochastic differential equations presented in [29, 60]. The theory will be applied to a model of a self-repressed gene (discussed in Task 1) in the adiabatic limit (infinitely fast switching gene) and in the limit of small time delays.

a) The goal here is to develop an expansion around the adiabatic limit. We will try to adapt an approach of singularly perturbed generators developed in [29] for stochastic differential equations describing motion of

physical particles in the limit of the small particle mass. In the adiabatic limit, the stationary state distribution satisfies the detailed balance condition and we will compare our results to those obtained in Task 2 by a different approximation.

b) [60] studies the scaling behavior of stochastic differential equations (describing a voltage in an electric circuit) involving a small time correlation of a colored noise and a small time delay of a feedback. One of the goals of this task is to develop an analogous theory for Markov jump processes describing self-regulated genes, replacing the driving Poisson proccess by its (Markovian) perturbation. We will also investigate the scaling behavior of systems of auto-regulated genes in limits of small time delays and fast switching genes.

c) We will check the mathematical correctness of the small-time approximations of Fokker-Planck equations which were presented in [22]. We will extend the construction of such approximations to systems with a time delay in the variance of a stochastic perturbation and systems with multiple time delays.

4. **Stability of stationary states in systems with multiple delays**

a) So far in all known evolutionary games, time delays may change stability of stationary states. We will explore the possibility of a shift of a stationary state as a result of time delays or a joint effect of time delays and stochasticity. Preliminary results were obtained by the author of this grant project in [52]. A two-player game was studied with a unique interior stationary point (a mixed Nash equilibrium) with strategy-dependent delays. We showed that the original stationary point is no longer stable, the system approaches a limit point whose location depends on the relative size of both delays. We will show how such system behaves in the presence of stochastic perturbations.

b) It is well known that the number and stability of stationary states in multi-player evolutionary games depend on the number of players; cf. e.g. [10, 20, 45, 53]. In models with multiple delays this is expected to give rise to interesting evolution patterns with jumps of trajectories between basins of attraction of stable stationary states if delay-induced oscillations become large enough [47, 53]. We shall investigate systematically the influence of the magnitude of time delays in models of populations that play multi-player games on the macroscopic characteristics of the evolution. We shall study the influence of various types of stochastic perturbations. Such models are also of interest for self-activated genes with bi-stabilities and toggle switches (cf. Task 1). Both systems (evolutionary and genetic ones) are characterized by the presence of two asymptotically stable and one unstable stationary points in the deterministic approximation.

4. Methodology

(underlying scientific methodology, data reduction and treatment schemes, type and degree of access to the equipment to be used in the proposed research)

General methodology. Inspired by questions from biological and social sciences, we will construct and investigate specific mathematical models of stochastic dynamics with time delays. Similar tools and approaches will be used for models in micro-scale and macro-scale biology which should be fruitful for both classes of models. Guided by particular examples we will formulate and prove general mathematical theorems. We will develop of a theory of singular perturbations in Markov jump processes with various small parameters describing time scales in biological processes, mathematical foundations of mean-field methods in biological models and the theory of stochastic stability in non-equilibrium stationary systems without detailed balance conditions.

Mathematical tools and techniques. Biochemical and evolutionary processes were usually modeled by systems of ordinary differential equations describing time evolution of concentrations of various substances in reactions (in micro-scale biology) or frequencies of various behaviors (in macro-scale biology). When the number of bio-molecules or individuals in evolutionary, ecological or social processes is low we resort to stochastic modeling. We will construct and analyze appropriate Markov chains in discrete time and continuous time birth and death (jump) processes.

In dynamical systems with time delays, one has to specify initial conditions not only at a specific time, as in ordinary differential equations, but on the time interval of the length equal to the time delay. It means that such systems are in fact infinite-dimensional, their dynamics may be represented by functionals on certain spaces of functions on the time interval. Stochastic perturbations make such systems non-Markovian. However, in the case of bounded delays,

one may enlarge the space of states in such a way that a resulting process is Markovian. Models with transition probabilities depending upon the finite history are known as high-order Markov chains [11, 47, 51, 62]. One may also introduce an auxiliary random variable and an auxiliary Markov process as it was done in [48]. Our technique was already generalized in [36]. Here we would like to extend this approach to apply it in auto-regulatory genetic systems with a delayed production.

It is well known in statistical physics that it is difficult or impossible to effectively construct equilibrium states (probability measures on appropriate probability spaces) of systems of many interacting objects such as particles or spins. In the classical mean-field approximation, interactions of a given object with other objects of the system are replaced by an interaction of the object with the mean interaction field generated by the whole population. The mean field is then found by solving an equation for its self-consistent value. This led for example to a spectacular solution of the ferromagnetic Ising model [30, 50]. Such an approach was used recently by the author of this grant project in models of self-repressed genes [49], see also [2, 9, 58, 68] for other schemes of self-consistent approaches. We will modify these techniques to use them in other models with feedbacks (enabling self-consistency to work) such as self-activated genes, toggle switches, and systems with time delays.

The general framework of our project is that of stochastic stability in randomly perturbed dynamical systems [18, 19]. Systems of interacting objects can be described on a deterministic level by a difference or differential equations. Such equations may have multiple stationary states (critical points) with basins of attractions of various sizes. Then such systems are subject to stochastic perturbations of various types. In this way we obtain stochastic dynamics described by ergodic Markov chains or birth and death processes with unique stationary probability distributions. A state of the system is stochastically stable if the stationary distribution assigns to it a nonzero probability in the limit of zero stochastic perturbation. Such limit may usually depend upon the type of the stochastic perturbation. For example, in models of auto-regulated genes, one may consider biological regimes (rates of reactions or intensities of corresponding stochastic processes) where either stochastic fluctuations caused by gene switching (switching noise) or those of production and degradation are dominant [31]. The concept of stochastic stability was recently applied by the author of this grant proposal to systems with cycles [51]. Markov chains with time delays still can be considered as Markov systems with enlarged set of states and are called high-order Markov chains. We will apply the concept of stochastic stability to analyze systems of time delays perturbed by various types of stochastic perturbations.

We will develop theory of singular perturbations of Markov jump processes. We will be guided by results obtained in [29, 60] for Brownian processes.

The mathematical studies of models and phenomena described in the project will be augmented by numerical simulations. The role of computer simulations is two-fold: to discover an interesting behavior and to support results obtained by various approximation schemes.

Some specific models

Self-regulated gene

In the stochastic model of a self-regulated gene, the gene (DNA) can be in two discrete states: unbound one denoted by 0 or bound one denoted by 1. The protein degradation rate is denoted by γ. We consider a monomer binding and thus we assume that the binding rate is given by βn, where n is the number of proteins in the system, and the rate of switching the gene on (unbinding) is denoted by α.

We denote by $f_i(n,t)$, $i = 0,1$ the joint probability that there are n protein molecules in the system at time t and the gene (DNA) is in the state i. The standard Master equations can be written as:

$$\frac{d}{dt}f_0(n,t) = k_0[f_0(n-1,t) - f_0(n,t)] + \gamma[(n+1)f_0(n+1,t) - nf_0(n,t)] - \beta n f_0(n,t) + \alpha f_1(n,t), \tag{1}$$

$$\frac{d}{dt}f_1(n,t) = k_1[f_1(n-1,t) - f_1(n,t)] + \gamma[nf_1(n+1,t) - (n-1)f_1(n,t)] + \beta n f_0(n,t) - \alpha f_1(n,t),$$

for $n \geq 1$ and for $n = 0$ we have $\frac{d}{dt}f_0(0,t) = -k_0 f_0(0,t) + \gamma f_0(1,t)$ and $f_1(0,t) = 0$.

If $k_0 = k_1$, then the stationary state of the above equations can be analytically calculated, the Markov jump process satisfies the so-called detailed balance conditions which are equivalent to time reversibility. If $k_0 \neq k_1$, then detailed balance conditions are not satisfied and in principle it is difficult or impossible to obtain simple expressions for the stationary state and even for its moments (but see [28] for an expression involving special functions). The self-consistent mean-field approximation is to replace n in the switching terms of Master equations by its unknown expected value allows to get analytical solutions for moments of the stationary state [49] in the case of the self-repressing gene

($k_0 = 0$). For the self-activated gene ($k_1 > k_0$), in the appropriate model, we replace βn by $\beta_0 + \beta_2 n^2$. Then for some range of parameters we expect a bi-modal stationary state. Such and other biological systems with a broken symmetry (like toggle switches of two genes which repress each other) will require a nontrivial modification of mean-field techniques (Task 1). Especially in the presence of time delays we have to extend standard Master equations by appropriate equations for time-correlation functions.

One of the goals of this project is to develop a systematic expansion around stationary states satisfying detailed balance conditions, an appropriate small parameter in the case of a self-repressed gene can be $k_0 - k_1$ (Task 2).

The above system of Master equations can be written as $\frac{df}{dt} = Lf$, where L is a generator of the Markov process. Another goal of the project is to develop a method of singularly perturbed generators for jump Markov processes (Task 3). Such approach was used so far for continuous processes like Brownian motion [29, 60].

Replicator dynamics of evolutionary games

The basic deterministic equations describing infinite populations are those of replicator dynamics [26]. For games with two strategies, the time evolution of the fraction of the population using the first strategy and the strategy-dependent time delays can be written as

$$\frac{dx}{dt} = x(1-x)(f_1(t-\tau_1) - f_2(t-\tau_2)), \tag{2}$$

where f_1 and f_2 are averaged payoffs of corresponding strategies.

In finite populations, we propose the following equations:

$$p_i(t+\varepsilon) = (1-\varepsilon)p_i(t) + \varepsilon p_i(t-\tau_i)U_i(t-\tau_i);\ \ i = 1,2, \tag{3}$$

where $p_i(t)$, $i = 1,2$, be the number of individuals playing at the time t the strategy 1 and 2 respectively. It can be shown that (3) do not lead to (2) in the limit of $\varepsilon \to 0$ [1].

We will study effects of time delays and stochastic perturbations on stationary states in such and other dynamics involving multiple time delays (Task 4).

Organization of the project. The leader and the co-investigator of the proposed grant are members of the Faculty of Mathematics, Informatics, and Mechanics of the University of Warsaw. Co-investigator is Marek Bodnar, a specialist in differential equations with time delays (see [5,6]). Recently he started to work with deterministic models with time delay applied to biochemical systems showing that some models are not well constructed [17], proving global stability of the steady states [3,7], and existence and direction of the Hopf bifurcations [4].

It is the main idea of the project to concentrate effectively our strengths and expertise on a systematic study of stochastic dynamics with time delays. At the same time, we would like to engage young people in the specific tasks of this project. We would like to support financially four master students for one year each and one PhD students for two years. Prospective candidates will be chosen in a recrutation process supervised by a committee consisting of two investigators of the proposed project and a third person chosen by us.

Obtained results will be disseminated in appropriate scientific meetings (European Congress on Mathematical and Theoretical Biology, Meetings of Society of Mathematical Biology, and smaller mathematics meetings). Results will appear in papers published in international journals.

Our efforts will be supported by an international collaboration. Task 2 will be done in close cooperation with Christian Maes (a specialist in rigorous construction of non-equilibrium statistical mechanics) from Katholieke Universiteit Leuven. Task 3 will be done in close cooperation with Jan Wehr (a specialist in stochastic differential equations and their applications) from University of Arizona. It is worth to mention that both mathematicians were invited recently by the author of this grant proposal to give a series of lectures (intensive courses in spring 2012 and 2014) in our Faculty on rigorous construction of non-equilibrium statistical mechanics, and mathematics and physics of diffusion respectively. We are also planning to invite Tobias Galla from Univeristy of Manchester and Ofer Biham from Hebrew University in Jerusalem to collaborate with us on Task 1, and Jorge Pacheco from University of Lisbon to collaborate with us on Task 4. International collaboration will involve our trips abroad and visits of foreign investigators to Warsaw.

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