PROGRAMME INTERNATIONAL DE COOPERATION SCIENTIFIQUE (PICS)

FRANCE - RUSSIE

Modélisation des Structures et des Processus en Biologie

I. Partie générale

1. Objectifs du projet
2. Structure du projet, repartition géographique
3. Collaborations déjà établies

II. Thématiques scientifiques

1. Coagulation du sang
2. Croissance de plantes
3. Dynamique des populations biologiquement structurées
4. Analyse de biomolécules
    - 4.1. Structure atomique de macro-molécules
    - 4.2. Modélisation de "fingerprint" d'ADN
    - 4.3. Transport de charge dans les molécules ADN
5. Analyse mathématiques des modèles biologiques
    - 5.1. Hydrodynamique des écoulements biologiques
    - 5.2. Cinétique chimique et thermodynamique des processus biologiques

I. PARTIE GENERALE

1. Objectifs du projet

Le but de ce projet est de réunir des mathématiciens, des biologistes et des médécins autour des questions où la modélisation mathématique peut donner un avancement important et où la cooperation entre les deux pays, la France et la Russie peut etre particulièrement utile. Ce projet repond à une forte demande de coopération entre les deux pays en biologie mathématique. Il est orienté vers la structuration de cette coopération et il reste ouvert pour d'autres thématiques et pour de nouveaux participants.

Le projet est consacré à la modélisation des structures biologiques et des processus qui menent à l'apparition des ces structures. L'analyse des structures biologiques, soit au niveau moléculaire, comme l'analyse des molécules ADN ou des protéines, soit au niveau cellulaire (organismes biologiques) ou au niveau de la dynamique des populations est importante pour la compréhension des phénomènes biologiques.

Les mécanismes d'apparition des structures biologiques dans la plupart de cas ne sont pas connus. L'origine de la diversité de formes biologiques, leur emergence au cours d'évolution et leur réalisation pendant le développement d'un organisme ne sont pas actuellement comprises.

Nous allons appliquer, dans le cadre de ce projet, l'analyse mathématique et la modélisation numérique d'emergence et d'évolution de structures pour étudier

- coagulation du sang et maladies sanguines,
- croissance de plantes,
- dynamique de populations biologiquement structurées,
- structure des biomolécules,
- propriétés mathématiques des modèles biologiques

Ces études théoriques et expérimentales seront effectuées en étroite collaboration entre les mathématiciens, biologistes et médécins. Nous proposons d'eťudier des questions fondamentales qui auront des applications pour la santé public et pour l'environnement.

2. Structure du projet, répartition géographique

Le projet est structuré autour de la modélisation mathématique en biologie où les méthodes mathématiques comme l'analyse de stabilité et la théorie de bifurcations, les développements asymptotique et l'analyse multi-échelle, theorie des équations aux dérivées partielles et des systèmes dynamiques, des modéles statistiques de traitement de données, ainsi que les mathématiques discrètes et les simulations numériques seront appliqués pour étudier l'emergence et l'évolution des structures en biologie.

Ces outils mathématiques seront utilisés pour étudier les équations de la cinétique chimique, les systèmes de réaction-diffusion et les systèmes de réaction-diffusion avec hydrodynamique, des modèles matriciels.

Les résultats mathématiques et numériques seront appliqués dans les contextes biologiques variés mais pour lequels les outils mathématiques sous-jacents, les modèles et les résultats sont souvent liés. Certaines thématiques de ce projet sont complémentaires, comme par exemple, l'analyse de biomolécules ou de la cinétique chimique pour les études de la coagulation du sang ou de la croissance de plantes.

Les thématiques du projet étant décrites dans les sections suivantes avec le contexte scientifique, la nécessite de la coopération, les travaux déjà effectués et les étapes du travails, nous donnons ici leur brèfs résumés avec la répartition géographique des activités de recherche.

1. *Coagulation du sang.* Ce processus est très complexe avec trois niveaux d'interaction : protéine-protéine, protéine-cellule, cellule-cellule dont la première est assez bien étudiée tandis que les autres reste peu connues. On peut les décrire avec les équations de la cinétique chimique, avec des systèmes de réaction-diffusion et avec les systèmes de réaction-diffusion avec hydrodynamique.

La coagulation du sang avec les effets d'écoulement répresente un problème extremement complexe et pratiquement pas étudié. C'est un des sujets principaux de ce projet.

Cependant, même les systèmes de réaction-diffusion sans hydrodynamique où les méthodes mathématiques sont bien développées pourront être appliqués pour diagnostiquer des maladies sanguines. Les expériences montrent que le processus de coagulation répresente une onde qui se propage et se stabilise vers une structure stationnaire. Les caractéristiques de l'onde et de la structure sont différente pour les cas normal et hémophilique. La modélisation mathématique des systèmes de réaction-diffusion permettrait de mettre en évidence l'origine de cette différence et préciser les diagnos-

tiques.

Répartition géographique :

National Research Center for Hematology (Moscou)
Institute of Mathematical Problems in Biology (Puschino)
Semenov Institute of Chemical Physics (Moscou)
Hémophilie et maladies hémorragiques, Universite Lyon 1 (Lyon)

2. *Croissance de plantes.* La croissance de plante est déterminée par l'interaction de flux des nutriments et des métabolites avec les cellules du méristeme en prolifération. Les flux évoluent avec le changement de taille et de forme de la plante en fonction de temps, et la prolifération de cellules en dépend, ainsi que des phénomènes complèxes à l'interieur des cellules.

Nous proposons des modèles mathématiques ou ces phénomènes sont pris en considération. Les premiers résultats montrent que cette approche peut permettre de proposer quelques éléments d'explication de la variété de formes, tailles et durée de vie de plantes.

Les modèles et les résultats doivent etre justifiés et comparés avec les expériences biomoléculaires et mésures biométriques prevues également dans ce projet.

Les modèles mathématiques sont basés sur des systèmes de réaction-diffusion avec hydrodynamique. Leur analyse mathématique et numérique est liée à celle dans la section précédente et à la section 5.

Répartition géographique :

Laboratoire de mathématiques appliquées (Lyon 1 - ECL - INSA)
MIP (Toulouse)
Institute of Mechanical Engineering Problems (Saint Petersbourg)
Komarov Botanical Institute (Saint Petersbourg)

3. *Dynamique de populations biologiquement strucutrées.* Les populations biologiques sont souvent structurées par rapport à l'age, le cycle de vie ou par rapport à d'autres paramètres. Leur structuration peut influencer la dynamique spatiale et temporelle, ainsi que les interactions avec les autres éspeces biologiques et l'environnement.

Dans ce projet on va développer l'analyse basée sur les matrices de Leslie et leur généralisation pour les populations doublement structurées pour étudier des populations des plantes et des insectes. Des outils informatique seront développés pour des

organismes publiques et privés afin de prédire le développement forestier et l'influence des produits chimiques sur les invertébrés.

La structuration des populations par rapport aux resources consommees sera étudiée sur des modèles de réaction-diffusion avec des termes non locaux et un nouveau mécanisme d'emergence de structures sera discuté.

Répartition géographique :

Biométrie et Biologie Evolutive (Lyon 1)
Laboratoire de mathématiques appliquées (Lyon 1 - ECL - INSA)
MIP (Toulouse)
Laboratoire d'Ecotoxicologie (CEMAGREF - Lyon)
Laboratory of Mathematical Ecology (Moscou)
Biological Department, Moscow State University (Moscou)

4. *Analyse de biomolécules.*

4.1. Structure atomique de macro-molécules. Le but du projet est de développer une nouvelle approche pour la détermination de la structure atomique et la répartition de la densité électronique dans des macro-molécules biologiques en utilisant des donn´-ees d'une expérience de diffraction des rayons X, une modélisation probabiliste de l'objet des recherches et la technique de la vraisemblance maximale. Dérivation des formules asymptotiques et développement des méthodes Monte Carlo de calculs de la fonction de vraisemblance seront effectués.

Répartition géographique :

Institute of Mathematical Problems of Biology (Puschino)
Institute of Problems in Mechanics (Moscou)
Université de Nancy

4.2. Modélisation de "fingerprint" d'ADN. Cette modélisation sera basée sur l'analyse des génomes complets des prokaryotes, chloroplastes et mitochondria avec l'utilisation des oligonucleotides correspondants à certaines séquences comme les fragments surreprésentés, fragments répétitifs non codant, etc. Le modèle proposé donnera des outils bio-informatiques pour développer des méthodes diagnostiques biomoléculaires et pour expliquer les mécanismes de diversité chez les prokaryotes.

Répartition géographique :

Department of Mathematics and Mechanics, Moscow State Universtity (Moscou)

Centre of Bioengineering (Moscou)
Biométrie et Biologie Evolutive (Lyon 1)

4.3. Transport de charge dans les molécules ADN. L'influence des effets spatiaux, du couplage des paramtrès et du caractère non linéaires du problème sur la dynamique de trous et sur le transport des éléctrons dans les molécules ADN.

Répartition géographique :

Laboratory of Mathematical Methods in Mechanics, Institute for Problems in Mechanics (Moscow)

5. *Analyse mathématiques des modèles biologiques*

5.1. Hydrodynamique des écoulements biologiques. Des méthodes asymptotiques et des outils numériques seront développés pour étudier des écoulements des liquides micro-polaires dans un système de vaisseaux et appliqués pour les écoulements sanguins.

Repartition geographique :

Equipe d'Analyse Numerique, l'Universite de Saint-Etienne
Laboratoire de Mathematiques Appliquees (Lyon1 - ECL -INSA)
Department of Mathematics and Mechanics, Moscow State University

5.2. Cinétique chimique et thermodynamique des processus biologiques. La cinétique chimique et la thermodynamique de certaines processus biologiques seront décrites avec des méthodes probabilistes.

Répartition géographique :

Laboratory of large random systems, Moscow State University
Probablity chair of Moscow State University
Institute of Information Transmission (Moscow)
INRIA - Rocquencourt

3. Collaborations déjà établies

Cette question sera développée pour chaque thématique dans les sections suivantes. Cependant, il nous semble important de souligner ici que toutes les thématiques du projet, sauf une, sont basées sur les collaborations franco-russes déjà éxistantes. La thématique coagulation du sang était développée indépendamment à Moscou-Puschino et à Lyon. La coopération entre ces groupes, établie pendant la préparation du projet, nous semble très prometteuse.

II. THEMATIQUES SCIENTIFIQUES

II - 1. Blood Coagulation

Russian participants:

Laboratory of Physical Biochemistry, National Research Center for Hematology (Moscow)

Laboratory of Applied Mathematics, Institute of Mathematical Problems in Biology (Puschino)

Laboratory of Mathematical Methods for Chemical Physics, Semenov Institute of Chemical Physics (Moscow)

French participants:

Hemophilie et maladies hemorragiques, Université Lyon 1 (Lyon)

1. Scientific Context

The process of blood coagulation is characterized by a complex time and spatial organization. To stop bleeding the damaged area must be quickly and completely sealed with a clot. It is equally dangerous for an organism to form an insufficiently sized clot or to form a clot accidentally in another area or at a wrong time. Studying the mechanisms of blood coagulation is among the most important problems of modern biology and medicine. In about 50humans, its direct cause is a disruption of these mechanisms resulting in a condition called disseminated intravascular coagulation [1]. This lethal complication arises in various cancers, renal insufficiency, various blood disorders and other pathologies. During disseminated intravascular coagulation the spatial organization of clotting is impaired. It is no longer localized to a site of injury; instead numerous clots emerge at different places within the vascular system [1].

Despite the significance of the problem, spatio- temporal dynamics of clot formation remains poorly understood. Clot's size, shape, and structure are usually studied by static methods, e.g. histological [2]. Such methods cannot answer important dynamic questions, such as the rate of clot growth, nature of the factors determining this rate and controlling size of the clot, and how the clot growth is terminated.

There are two pathways by which blood coagulation can take place: the extrinsic and intrinsic pathways [1]. Unlike clots that are studied in the in vitro stirred systems, clots that occur under natural conditions in circulating blood are always compact and localized, i.e., only a small fraction of blood immediately adjacent to the site of injury is involved in the local formation of a solid clot. This means that in addition to the kinetics of clotting reactions, the spatial distributions of activated factors should also be considered to achieve a more complete view of the clotting processes in vivo. The molecular mechanisms and kinetics of both extrinsic and intrinsic pathways in the in vitro stirred systems are known quite well (reviewed in [2-4]). Both enzymatic pathways lead to the production of thrombin, which is a key clotting factor. Thrombin cleaves the fibrinogen to produce fibrin monomers, which polymerize into fibrin fibers [4]. Thrombin is also a key regulator of the clotting cascades, because it is involved in many positive and negative feedbacks [2]. The prominent feature of the kinetics of clotting is its threshold behavior in response to activation [3,5]. The kinetics of production of active factors change dramatically when activation threshold is exceeded. Thrombin concentration increases exponentially by 1,000 - 10,000 times and becomes comparable with the prothrombin concentration. After reaching its maximum, the concentration of thrombin falls rapidly to its original level due to the initiation of the negative feedback via activation of protein C by thrombin and due to the inhibitors of thrombin constantly present in plasma. Thus, suprathreshold activation of blood or plasma via the extrinsic and the intrinsic pathways causes the impulse of thrombin concentration with amplitude, which is sufficient for rapid formation of a solid clot. Simulation analysis of these cascade pathways and their positive feedbacks predicts similar amplitudes of thrombin impulses for both pathways and that this amplitude is almost independent of the amplitude of activating signals above threshold. However, the time, which takes thrombin concentration to reach its maximum, depends strongly on both the amplitude and nature of activating signal [5]. The clotting cascade is, therefore, characterized by the threshold behavior and strong positive feedbacks. A theory of such biochemical cascades predicts its complex spatial behavior, e.g. propagation of the self-sustained "autowaves" [6]. This aspect of clotting, however, until recently has not been examined, and detailed description of the distribution and kinetics of the activity of clotting factors is not

known. The significance of this investigation is of vital importance because many pathological conditions in humans are associated with different abnormalities in spatial organization of clotting. For example, many pathological disorders, such as acute renal insufficiency, extensive bleeding, sepsis, shock, etc. often lead to a disruption of normal clotting mechanisms resulting in disseminated intravascular coagulation [1]. The mechanisms, which link these diseases and pathologies to the spatial coagulation disorders are not known. Clearly, deeper understanding of the regulatory mechanisms determining spatial dynamics of clotting is a key to understanding its pathological aberrations, and may pave the way for new generations of drugs.

2. Research Objectives

We propose a novel approach to study blood clotting by direct examination of the spatial dynamics of growing clot and of the activated clotting factors in flowing blood plasma. Our previous experimental work [8-10, 12,14,16,17] and theoretical analysis [7, 11,13,15] of the spatial aspects of blood clotting have lead to a view of the clotting process as consisting of three distinct phases: initiation, elongation, and termination. Each of them could be influenced by blood flow in different extent. In this work we will directly test a hypothesis, which specifies the blood flow effects on each of these phases. According to this hypothesis: (i) the reactions of both, the intrinsic and extrinsic pathways, are initiated on the foreign (or damaged) surface and do not depend on blood flow. (ii) the elongation phase is determined by a balance between thrombin generation via the intrinsic pathway and the reactions that terminate thrombin generation (the protein C pathway) and inactivate thrombin (the antithrombin). These reactions could be affected mostly by flux of platelets. (iii) the termination phase of clot growth involves reactions on the surface of undamaged vessel wall downstream of damage zone. These reactions could switch thrombin conformation to generate thrombin in an anticoagulant form. Such switching for example may be induced by thrombomodulin. Specifically, we will focus on the following aims: 1. to study the spatio-temporal dynamics of clot growth initiated by extrinsic and intrinsic pathways as a function of the speed of blood flux by examining the propagation of activated clotting factors in normal plasma and in plasmas of patients with different diseases.

2. to design a correct mathematical description of clotting in the blood flow.

3. Role of Mathematical Modelling

Blood clotting is a very complex process, so it is highly unlikely that understanding of this process as a whole is possible without mathematical modelling. An additional complexity of blood clotting is its spatial dynamics: a "clotting wave" starts from the site of injury and propagates into the bulk of blood. Normal blood contains all molecular and cellular components required for clot formation. So, blood is an active media for blood clotting and mathematical description of this process is naturally given by partial differential equations of "reaction-diffusion" type. The process of mathematical modelling of blood clotting can be viewed as a hierarchy of several levels: 1. Ordinary differential equations to describe biochemical reactions without diffusion. 2. One-dimensional partial differential equations to find out ranges of parameters where autowave solutions exist. 3. Partial differential equations with two space variables. These models should explicitly take into account the biochemical reactions on a vessel wall. To take into account a blood flow, we should add the hydrodynamic equations to the "reaction-diffusion" system. Calculations should be done for flow in a domain, shape of which changes with time. As it is usual for modelling in biology and chemistry, the values of the reactions rates are not known well, so we have to vary them. Because characteristics of the solutions depend on parameters, we have to use an approach based on the qualitative theory of differential equations and bifurcations theory to achieve an understanding of spatial dynamics of blood clotting. At the same time, numerical calculations should be the main source of information for two-dimensional models.

4. Experimental Design

The spatial dynamics of clot growth will be monitored using the microscope-based experimental device with CCD camera, which was constructed in Ataullakhanov's lab specifically for these studies. The first results obtained with this device have been published [9]. Clot growth is monitored by the red-light scattering, and the spatio-temporal dynamics of the clotting factors is registered using fluorogenic substrates. The fluorescent and light-scattering images are recorded with the CCD camera at 1-2 frames/min. To process and analyze the images we developed the software, which

corrects the spatial non-uniformity and illumination fluctuations. The corrected data are used to determine the rate of clot growth, clot size and the spatial dynamics of clotting factors. We also can use a temperature controlled stage with a flow-through chamber to register clot growth in plasma flow. A new modification of our device allows us to measure the clot growth in plasma flow as a function of flow rate.

5. Justification of Necessity of Cooperation

France-Russian cooperation could have a mutual advantage for both teams, because we can use a new device designed in the National Research Center for Hematology, Russia to study a spatial dynamics of coagulation of the blood for patients of L'Hopital Edouard Herriot (Lyon). Acquaintance of young Russian researchers with achievements of the French hematology would be very useful.

6. Work Planning and Schedule

The team of researchers from National Center for Hematology studies the spatio-temporal dynamics of blood clotting using both theoretical and experimental approaches. The point of view on the clot growth as an autowave propagation was developed in the lab of Prof. F. Ataullakhanov. Using mathematical modelling as a tool is typical for this team. The team from Institute of the Mathematical Problems of Biology, Russian Academy of Science has a wide experience in developing new mathematical methods and software to solve the biological problems. A number of special software packages were created in this Institute for qualitative analysis of differential equations. We are planning the following works and dates.

First Year: A comparative study of spatial dynamics (1D problem) of several simple models of blood clotting (2-3 variables) with a detailed mathematical model of biochemical network of blood coagulation (more than 25 variables) developed recently in the National Research Center for Hematology, Russia.

Making a new device for study a spatial dynamics of clotting in flowing blood plasma for French team and fitting it

Second Year: A theoretical study of spatial effects of biochemical reactions connected with a blood vessel wall on clot growth in flowing blood plasma. Computer experiments with 2D mathematical models using a simplified biochemistry (3-5 variables). An experimental study of spatial dynamics of coagulation of the blood for

patients of L'Hopital Edouard Herriot and Russian - Hematology Center with blood diseases.

Third Year: Elaboration of 2D mathematical models of blood clotting taking into consideration a complicated biochemical information. Computer experiments with such models and comparison of their results with experimental data.

7. Other Financial Sources

National Research Center for Hematology, Russia has a grant from Russian Foundation for Basic Research for 2003-2005 No. 03 04-48338.

8. Participating of Young Researches

Two graduate students of National Research Center for Hematology, Russia will participate in the project (supervisor - prof. F.Ataullakhanov): 1. Panteleev Michail, 2. Tokarev Alexey

9. References

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II-2. Modelling of Plant Growth

French participants:
Laboratoire de Mathematiques Appliquees (Lyon 1 - ECL - INSA)
MIP (Toulouse)

Russian participants:
Institute of Mechanical Engineering Problems (Saint Petersbourg)
Laboratory of Plant Embryology, Komarov Botanical Institute (Saint Petersbourg)

1. Scientific Context

The mathematical modeling of biological processes is a very important instrument for the investigation and prediction of their possible development. There are several lines of investigation in the plant growth modeling, existing for today. The main of them could be grouped as following:

1. Geometrical theory of plant growth and phyllotaxis. This is mostly phenomonelogical approach, the main core of which is that the finite number of cells in a given structure are taken and a geometrical algorithm of their proliferation is described. Among the most interesting works in this field we could mark:

a) A simulation-based model for growth and cell divisions described by the growth tensor. Here the growing organ is characterized by the continuous field of the displacement velocity, V. From the knowledge of V, the growth tensor (GT) is calculated. It follows directly from the definition of the relative elemental rate of growth, RERG (Richards and Kavanagh, 1943). The GT generates the field of growth rates in the organ. Inherent characteristics of the field are principal directions of growth, PDGs. Using the tensor analysis of the organ growth it was shown that if the pattern of PDG trajectories is steady over time, then segments joining recognizable points of the wall mesh-work and chosen so as to be tangent to the PDG trajectories, maintain their orthogonality during growth. (Hejnovich and Romberg, 1984).

b) A "cellworks" algorithm which presents a 3-dimentional L-systems which generate 3D network of cell walls within a tissue. In the latest model cellworks are

characterized by a double labeling of cell walls, a table of cell contacts and specify how cells types are derived one from another. It pretends to generate the plant-like patterns, and explains how cell families may be organized.(H. Luck, J. Luck, 2000, P.W. Barlow, 2001).

c) Creating a specific computer program allows to make a plant apical meristem of any shape and size from a small group of initial cells. Their contribution to the circumference of developing apex is investigated by this way. It appears that it is very different depending upon the initials quantity, size, shape, number of contacts etc. In one of these computer programs its postulating, that the cell cycle itself might be the key to some limited autonomy of dividing cells. It is possible that before new equilibrium is reached some irregularities may appear along the apex circumference. These changes in apex geometry, called discountinuous, could be shown by the computer simulation. (B. Zagorska-Marek, 2001). In others pattern formation processes are characterized in terms of the number of morphological agents, the computing capability of each agent, and the forms of information transfer between the agents and their environment. This computational analysis can be applied to a wide range of patterns. It gives the computational theory of morphogenesis on the basis of the theory of algorithms. (P. Prusinkiewicz, 2001).

All these models are created without taking into consideration the biochemistry and molecular biology processes, maintaining the pattern formation of the growing organism.

2. Biochemical models, mostly based on A. Turing reaction-diffusion model, developed for two chemical species, activator and inhibitor. For today there are a grate number of very similar works in this area for animal or plant models. Although it can explain the production of some complex structures and give predictions that are in a good agreement with the real ones, these models are very restricted and cant explain the complex process as a plant growth.

2. Research Objectives

The adult plant organism, growing from zygote, is realizing the number of programs, according to which it obtains the spatial form and specific function of each cell, typical for the given specie.

Thus, ontogenesis is a spatial-temporal process, involving sub-cellular mechanisms and leading eventually to morphological changes on the tissue level and on the level of the whole organism. Obviously, that requires strict regulation of an entire set of

processes, such as a) cell proliferation b) differentiation, c) growth d) movement of cells, including tissue movement.

Here we suggest the general model of plant growth, which is developed taking into account the basic phenomenological features of plant growth as well as the basic underlying growth mechanisms.

It allows to study the kinetics of growth, depending on the essential physiological and biochemistry parameters of the cells.

The main processes which are suggested to be taken into account for the model are:

1. Cell proliferation

2. Transport of nutrients.

3. Concentration of the specific factors, essential for the growth. (Salts, sugars, plant hormones, glycoproteins, proteins-markers, cyclins and cyclin-dependent kinases).

The main positions we should put in the model:

1.The growing part of the plant, apex, contains a narrow exterior part, meristem where cells proliferate. We should consider, that this is the main factor providing the plant growth. This layer has a constant width and consists of an approximately the constant number of cell layers specific for this plant.

2.The appearance of new cells implies that old cells exit this layer after some time. They differentiate, that is change their function. They cannot divide any more and serve as different plant tissue, in particular to transport nutrients to the meristem.

3.The proliferation rate is determined by the concentration of nutrients and metabolites in the meristem.

We describe plant growth as a free boundary problem where the motion of the interface corresponds to the displacement of the apical meristem. The speed of the growth, that is of the interface motion is determined by diffusion and convective fluxes of nutrients in the plant and by a self-accelerating production of plant growth factors in the meristem.

The model possesses a continuous family of stationary solutions that differ from each other by the length of the interval, i.e., by the plant height. If we suppose that the plant type is determined by the values of parameters, then for fixed values of the parameters the final height of a given plant, where its growth stops, is approximately the same and almost independent of its initial height. On the other hand, it strongly depends on the value of parameters. This can explain why plants are so different in size. The preliminarily work shows that we observe two qualitatively different modes

of growth. One of them remains almost linear in time while the plant reaches its final height and stops growing. Another one is periodic in time where the intervals of growth are separated by the intervals of rest. In the first growth mode the final height depends on parameters weakly, in the second case this dependence is strong. The final height is basically determined by the number of intervals of growth that can vary from one to probably infinity. The number of periods of growth and the final height depend on available nutrients provided through the root boundary condition.

The periodicity of growth observed in the model corresponds to the endogenous rhythms where the exterior conditions are constant. However, it can be difficult to distinguish exogenous and endogenous rhythms in nature. For example, annual endogenous rhythms of plants, if we assume that they exist, would coincide with the exogenous rhythms. Endogenous rhythms are well known for short time intervals.

Another interesting question is related to plant branching. In the proposed model we impose the place and time of branching, as well as its mode, in other words, how many branches appear at each node. In the subsequent work we should incorporate other conditions of branching in the model.

To have a well-posed problem in the case of branching, we need to find out some additional conditions which should be determined from the plant morphology.

The next stage in the development of these works is related to the two-dimensional modelling. One of the key questions arising here is whether the model can describe emergence of patterns and variety of plant forms.

The first simulations show that indeed we can obtain various and sometimes complex forms of growing plants. It is a new mechanism of pattern formation that is completely different in comparison with Turing structures.

3. Work Planning

1. To develop the model of plant growth taking into consideration the main morphological parameters.

2. To discover the real biological meaning of the growth factor, which have according to the prediction of the proposed mathematical model, the self-accelerating production. This will be done with the help of laboratory experiments in botanical, biochemistry and plant molecular biology.

3. To study kinetics of plant growth and emergence of spatial patterns in relation

with various biological mechanisms incorporated in the model.

4. Necessity of Cooperation

We suggest a complex multi-disciplinary investigation of plant growth where elaboration of new mathematical models based on the available biological information (Laboratoire de Mathematiques Appliquees de Lyon, Komarov Botanical Institute) will be followed by mathematical analysis and numerical simulations (Institute of Mechanical Engineering Problems, Laboratoire de Mathematiques Appliquees de Lyon, MIP), and then the results will be tested by measurements and experiments (Komarov Botanical Institute).

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the XIIIth Eucarpia Congress, 1992, Angers, France. p.363-364

II - 3. Biologically Structured Population Dynamics: a Stage-Duration Based Approach

French participants:
Biometrie et Biologie Evolutive (Lyon 1)
Laboratoire de mathematiques appliquees (Lyon 1 - ECL - INSA)
MIP (Toulouse)
Laboratoire d'Ecotoxicologie (CEMAGREF - Lyon)

Russian participants:
Laboratory of Mathematical Ecology, IFA (Moscow)
Biological Department, Moscow State University (Moscow)

1. Scientific Context

Among numerous ways to describe and formalize biological population dynamics, of particular interest are those amenable to verification versus empirical data/theoretical knowledge. In the terms of population structure, it means, at least, classifying individuals of the species population into some categories which should correspond to known biology of the species and which can be observed/measured in practice. The resulting mathematical models should reproduce the population dynamics in time or/and space, admit calibration on data available and serve a tool for population research, control or/and management.

Conceptions of age or size classes and of life-cycle stages are among the simplest and most natural ones in population biology. The reputation of a mathematical object such as matrices is, on the contrary, esoteric outside mathematics, appalling even by the fact ABBA, unlike with usual numbers. But it is however the matrices which formalize such a natural idea that the age (respectively size or stage) structure of a population causes the population dynamics, thus giving rise to the population projection matrix perhaps, the most urgent and efficient tool of population modelling.

Leslie matrix was historically the first form of the projection matrix proposed about 60 years ago for a population of single-species individuals classified, according to their ages, into a finite number of sequential discrete (e.g., yearly) age classes. The ensuing models of population dynamics were soon recognized to have quite limited applications as the time-table of aging was strictly fixed in such models. Also, there are many species, perennial grasses, for instance, where the age of an individual is hard to determine. Lefkovitchs expansion of the Leslie formalism was therefore logical and pragmatic: classifying individuals by developmental stage rather than by chronological age and it expanded drastically the range of ecological applications. Nowadays, stage-classified matrix models, with the stages understood in a generalized sense: either as the life-cycle stages, or multiple habitats of the population, or stages of ecological succession which the habitat of a given species may have reached, etc., feature a wide range of applications (see e.g. Caswell, 2001).

Meanwhile, an applied case study may still motivate certain mathematical problems to be solved for a particular class of models isomorphic (in the pattern of the projection matrix) to a given life cycle graph, or more general, to a known (or partly known) biology of the species under study.

For example, the French group has succeeded in constructing classical Leslie-type models for the population dynamics of the midge Chironomus riparius (an insect widely spread in aquatic environments) based on a series of laboratory experiments. It was found (Charles et al., 2004) that the amount of food, Q, serves the major parameter which determines both the size of the Leslie matrix (varying from 17?17 to 29?29) and the corresponding set of vital rates as certain saturating functions of Q derived from other, energy-based models. The qualitative pattern of birth rates at several reproductive ages was changing with Q, which generated either oscillating or monotone growth of the population size, yet the exact bifurcation value of Q has not been quantitatively determined.

At the Russian party, there is a unique dataset gained from field and laboratory studies on population biology of Calamagrostis spp., perennial clonal grasses colonizing open plots in forest areas after gap-forming disturbances (like clear-cuts or wind-throws) by Dr. Nina G. Ulanova (and her group at Dept of Geobotany, Moscow State University). These data and knowledge posed a number of new mathematical problems after a specific matrix formalism for a double-structured population (with both chronological ages and ontogenetic stages of individuals) had been developed and the standard problems inherent in application of the classic PerronFobenius theorem for nonnegative matrices had been solved (Ulanova et al., 2002). Those problems non-standard but motivated by the ecological application include examination of

whether any single-dimension classification be sufficient for an adequate description of the population dynamics (the exact-aggregation problem), whether a calibration of the projection matrix be possible on the shortest time-series of empirical data (the equilibrium calibration problem), and whether there exists an indicator of population growth easy calculable for a given set of vital rates (the potential-growth indicator problem, see Logofet, 2002).

Matrices, in the form of the transition probability matrix, work also in Markov-chain modelling, in general, and Markov-chain modelling of vegetation successions, in particular. The Moscow team has developed and applied an original, stage-duration-based method of Markov-chain modelling of forest successions (Logofet and Lesnaya, 2000; Korotkov et al., 2001; Logofet and Korotkov, 2002). Unlike traditional methods of landscape statistics, the method does not require a bulk of data from landscape surveys for the transition probability matrix to be estimated, but it does rely upon (expert-given) ranges for the duration of stages and for the likelihood ratio of alternative transitions (if any). Although a certain analogy between the projection matrix and the transition probability one was already noticed in the literature (Caswell, 2001, and references therein), the analogy is not complete because of the birth rates of the projection matrix, which can hardly be considered as probabilities when exceeding 1. However, using the analogy in variable duration of stages might open a new dimension in elaborating stage-structured models of population dynamics.

A fundamental problem that remains open in general is to recognize, given a set of observations, whether the population dynamics is or is not affected by intra- or/and interspecific competition, predation, and other environmental pressures (pollution, etc.). Here is the niche for various models, both linear and non-linear ones, to be developed testing hypotheses specific for a given case study. Adequacy of the models is of crucial importance at this stage of model development, and our studies have revealed the models developed so far to be qualitatively adequate to the data/knowledge available, i.e. the models reproduce the type of dynamic behaviour which the modeller expects for, under the assumption of unlimited growth, the behaviour being robust to local variations in quantitative values of model parameters. Further efforts are needed which would concentrate on the choice of the environmental impact(s) to be incorporated into the further models, on the development of qualitatively adequate types of the model formalism, on posing and solving calibration problems for a short time-series of data based on optimization techniques for under- and over-determined

formulations.

2. Research Objectives

General:

To verify or/and to make quantitatively certain the hypotheses about dynamic behaviour of plant and insect populations under concern by means of adequate mathematical models to be developed.

Specific:

In the Chironomus study, our specific aim will be to propose a modelling approach to assess the effects of various environmental pressures (chemicals, food,) on the population dynamics. Of particular interest would be the formulation and solution of the exact-aggregation problem to see whether a double-structured formalism is necessary. We first plan to work with laboratory populations, and second to infer results in situ. The final goal is to choose relevant end-points to predict population dynamics in field. In the Calamagrostis*) study, appropriate models will be developed and specific issues will be addressed, such as whether the outcome of the early stage of forest succession can be viewed as the outcome of competition between a dominating clonal grass (like Calamagrostis or other spp.) and small-leaved tree spp.; what is the quantitative level of vegetation cover disturbances that results in grasses suppressing tree seedlings, thus blocking up the normal course of forest succession?

3. Interdisciplinary Aspects

The project is inherently interdisciplinary, covering certain areas of population biology of insect and perennial grass species, ecotoxicology of aquatic environments, data processing, modelling population dynamics by means of matrix models, and mathematical theory of matrices and graphs applied to the dynamics and stability issues in the models.

4. Applications

Among the expected results of the Project, there are recommendations to be made

on experimental designs for the case studies of the species under concern or/and predictions of future population dynamics under given environment/management scenarios (whenever applicable). We plan to develop a computer program to assess risk of chemicals on benthic invertebrates from results obtained with sediment toxicity tests. This tool will be designed for public organizations involved into environmental issues or/and private managers. Of applied value is also predicting an outcome of the early stage of forest succession as a function of the initial population structure in the dominant clonal grass species or of the kind of initial disturbance induced by forest management actions.

5. Justification of the Necessity of the Cooperation

The French team is experienced in biological studies of the midge Chironomus riparius by means of energy-based models (Pry et al., 2003; Ducrot et al., 2004) and age-structured matrix models of the classical Leslie type (Charles et al., 2004), and it has reached a point where the research practice requires a stage-structured formalism to describe the population dynamics. With certain temperature and water controlled exposure systems for pelagic and benthic species, image analysing system, HPLC and GC/MS, the team is also well equipped to perform long toxicity tests. The Russian team is experienced in modelling stage-structured plant populations and even double (i.e., age-stage)-structured populations of perennial plants (Logofet and Klochkova, 2002, Ulanova et al., 2002) as well as in solving certain relevant mathematical problems in a general form (Logofet and Klochkova, 2002; Logofet, 2002). Also, there is an analogy between the variable duration of stages found in the Chironomus case study and the original, stage-duration-based method of Markov-chain modelling developed by the Moscow team. Further development and usage of this analogy in population modelling looks potentially perspective. The experiences of the groups are thus complementary, so that an exchange of ideas about, and cooperative work on, both mathematical apparatus and biological applications looks promising.

6. Joint Works Already Done

the 1st attempt in a joint project, yet a mutual understanding has been achieved on the preferable type of population models, and a similarity has been found between stage-duration-based Markov-chain modelling and stage-structured population

models with variable duration of the stages.

7. Work Planning and Schedule

Task 1. Conceptualizing biology, ontogenesis and the age-stage structure of the populations:

Task 1.1 . involved into Chironomus Case Study

Task 1.2. involved into Calamagrostis Case Study

Task 2. Modelling single-species age-stage-structured population dynamics with linear formalisms:

Task 2.1. in Chironomus Case Study

Task 2.2. in Calamagrostis Case Study

Task 3. Studying population dynamics affected by abiotic pressures:

Task 3.1. Modelling age-stage-structured dynamics affected by toxicant(s) in Chironomus Case Study

Task 3.2. Modelling age-stage-structured dynamics affected by abiotic pressures in Calamagrostis Case Study??

Task 4. Studying population dynamics affected by competition/predation:

Task 4.1. Modelling age-stage-structured dynamics affected by competition/ predation in Chironomus Case Study*)

Task 4.2. Modelling age-stage-structured dynamics affected by competition in Calamagrostis Case Study

Task 5. Holding a workshop on Project findings

8. Other Financial Sources

part of the Russian team activity (modelling double-structured populations of perennial plant species) is being supported by the INTAS (Reference : INTAS-2001-0527), yet at the former rates, which are two times lower than the INTAS rates for the later accepted projects.

9. Participating of Young Researches

the Russian team includes 1 post-doctor, 4 PhD-students, and an undergraduate

student might also be affiliated. The French team includes 1 master-student, 1 PhD-student, 1 ingnieur IGREF, 1 matre de conference.

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3. Ducrot V., A.R.R. Pry, R. Mons, and J. Garric. 2004. Energy based modelling as a basis for the analysis of reproduction data with the midge Chironomus riparius. Environmental Toxicology and Chemistry, 23:225-231.

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II - 4. Analyse de Biomolécules

4.1. Structure Atomique de Macro-Molécules

Russian participants:
Laboratory of Macromolecular Crystallography, Institute of Mathematical Problems of Biology (Puschino)

French participants:
UMR 7036 CNRS LCM3B, Université de Nancy
UMR 7503 LORIA, Université de Nancy

1. Contexte Scientifique

Actuellement, les methodes, qui se basent sur des modeles probabilistes et application de vraisemblance statistique pour choisir des modeles, sont largement utilisees dans la cristallographie macromoleculaire. Plusieurs chercheurs y compris les auteurs du projet ont bien developpe la theorie ainsi que les aspects pratiques et des logiciels correspondants. Neanmoins, dans la plupart des approches, seulement le schema le plus simple qui se base sur la distribution uniforme des coordonnees atomiques est utilise. Ce schema ne reflet pas correctement la realite de la cristallographie macromoleculaire ou une grande partie de la maille (parfois, plus qu'une moitie) est occupee par le solvant desordonne dont les proprietes sont tres differentes de celles des macromolecules. L'elimination de ce desaccord est un des buts du projet. L'autre probleme important est que toutes les methodes actuelles de calcul de vraisemblance se basent sur le Theoreme Centrale de Limite dans l'hypothese d'une faible correlation des facteurs de structure ce qui n'est pas toujours justifiee.

Les auteurs du projet sont les premiers qui ont propose d'utiliser les approches sur la base de la vraisemblance maximale pour identifier des modeles dans la cristallographie macromoleculaire. La forme proposee par les auteurs il y a 20 ans reste

essentiellement une seule utilisee actuellement pour la resolution des problemes pratiques, dans le phasage et dans l'affinement des modeles atomiques. Les auteurs ont propose l'approche pour eliminer des erreurs systematiques dans des facteurs de structure calcules a partir d'un modele atomique apres un affinement. Ils ont propose et verifie une procedure de type Monte Carlo pour calculer la vraisemblance. L'approximation de la fonction de vraisemblance developpee par les auteurs a permit d'analyser theoriquement ce critere et deriver des tendances de l'affinement effectue avec des modeles probabilistes.

2. Objectifs

Le but du projet est de developper une nouvelle approche pour la determination de la structure atomique et la repartition de la densite electronique dans des macromolecules en utilisant des donnees d'une experience de diffraction des rayons X, une modelisation probabiliste de l'objet des recherches et la technique de la vraisemblance maximale.

Le choix des classes de repartition de la probabilite pour interpreter des resultats d'une experience de diffraction des rayons X par des cristaux macromoleculaires dans de differentes etapes de l'analyse d'une structure. Derivation des formules asymptotiques et developpement des methodes Monte Carlo de calculs de la fonction de vraisemblance. Developpement des algorithmes numeriques de la maximisation de vraisemblance dans des problemes de la radiocristallographie macromoleculaire.

3. Methodes et Approches Proposees

La radiocristallographie macromoleculaire est une methode principale pour obtenir une information sur la structure de macromolecules biologiques (proteines, acides nucleiques, virus) et leurs complexes au niveau atomique. En fonction de details demandes, cette information peut etre la fonction de la repartition des electrons dans la maille cristalline (autrement dire, le carre du module de la fonction d'onde) soit les coordonnees des centres de tous les atomes de la macromolecule (qui correspondent, dans le cas ideal, aux maximums de la repartition de densite electronique). Une experience de diffraction des rayons X par un cristal macromoleculaire permet a mesurer, pour la fonction de la repartition de la densite electronique qui est une fonction periodique dans l'espace tridimensionnel, les modules de ces coefficients complexes de

Fourier, appeles en cristallographie 'facteurs de structure'. La procedure classique de la determination d'une structure atomique contient de plusieurs etapes: reconstruction des valeurs de phases des facteurs de structure (arguments de valeurs complexes des coefficients de Fourier), calcul d'une approximation a la repartition de la densite electronique, son interpretation en termes d'atomes, affinement des parametres atomiques effectue par une minimisation locale d'une fonction, ayant de nombreux minimums locaux, dans un espace de tres grande dimensionnalite.

La reconstruction des phases de facteurs de structure est faite grace a l'utilisation d'une information complementaire sur le cristal macromoleculaire concerne. Dans le cadre du projet actuel, nous allons utiliser la composition atomique d'une molecule comme une telle information complementaire. La structure particuliere est consideree comme un element de l'ensemble de structures composees d'un nombre necessaire d'atomes generes au hasard dans la maille cristalline. Ce modele permet d'obtenir quelques repartitions probabilistes de certaines combinaisons de phases, dites invariantes de phases, et estimer leurs valeurs. Initialement, on utilise le modele le plus simple de la distribution uniforme d'atomes dans la maille ce qui donne les estimations de phases assez faibles. L'utilisation des modeles plus sophistiques de la distribution d'atomes peut ameliorer la qualite des phases obtenues dans la premiere etape. Le probleme central est qu'une telle distribution atomique n'est pas definie a priori mais doit etre choisie parmi une classe de distributions. La vraisemblance statistique, definie comme une probabilite de reproduire des donnees experimentales dans le cadre de l'hypothese probabiliste a verifier, peut etre utilisee comme critere pour choisir cette distribution.

Le calcul efficace de la fonction de la vraisemblance dans le cadre d'un modele probabiliste d'une structure macromoleculaire est un probleme numerique tres complique. Nous pensons developper et comparer de differentes approches pour le calculer: celle sur la base du Theoreme Centrale de Limite dans l'hypothese d'une correlation assez faible des facteurs de structure ; l'autre, sur la base de simulation Monte Carlo ; la troisieme, sur la presentation explicite des formules pour la methode de col, developpees par nous-memes.

Outre du probleme de l'estimation de phases des facteurs de structure, la modelisation probabiliste et le choix d'un modele sur la base de vraisemblance seront utilises pour la derniere etape d'une recherche structurale macromoleculaire, l'affinement de parametres atomiques. Dans ce cas, l'objet a modeliser est la partie inconnue du modele disponible, par exemple les coordonnees d'atomes absents. L'incompletude d'un modele ne permet pas resoudre le probleme direct, savoir predire les resultats hypothetiques de l'experience a partir d'un modele donne. Par consequent, le cal-

cul des facteurs de structure a partir d'un modele incomplet ne permet pas de les comparer avec les valeurs experimentales et d'effectuer l'affinement macromoleculaire correctement.

4. Resultats Attendus

De differentes classes des modeles probabilistes, utilises pour l'affinement macromoleculaire, seront etudiees. En particulier, ces classes incluent des modeles incomplets ainsi que des modeles avec des erreurs dans des parametres atomiques. La construction d'un modele optimale applicable dans des situations pratiques est un des interets principaux. Les resultats de l'affinement avec la vraisemblance seront compares avec les resultats d'affinement obtenus avec un analogue de la methode des moments. Une revue commune avec des partenaires francais sera preparee pour presenter l'etat actuel de recherches dans le domaine de l'identification des modeles sur la base de vraisemblance maximale.

5. Publications

Publications principales (y compris celles avec des partenaires francais) en liaison avec le projet propose :

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2. Afonine P., Lunin V.Y. , Urzhumtsev A. (2003). "MLMF: least-squares approximation of likelihood-based refinement criteria" J. Appl. Cryst., 36, 158-159

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15. Lunin V.Yu. (1989). "The Calculation of the Second Moments for the Values of Fourier Syntheses with Random Structure Factors". Acta Cryst. A45, 501-505.

16. Lunin V.Yu., Urzhumtsev A.G. (1984) "Improvement of protein phases by coarse model modification". Acta Cryst., A40, 269-277

4.2. Modelling of DNA Fingerprints

Russian participants:
Department of Mathematics and Mechanics, Moscow State Universtity (Moscou)
Centre of Bioengineering (Moscou)

French participants:
Biometrie et Biologie Evolutive, UIniversité Lyon 1

1. Scientific Context

There are several major targets for the genetic fingerprinting of organisms: survey, management and manipulation of genetic resources (Caetano-Anoles, 2001). Whole genome sequencing has enabled us to evaluate usefulness of each of many DNA-profiling method from position of genome coverage and robustness of the obtained fingerprints. Over 140 bacterial genomes many chloroplast and mitochondria genomes have been recently sequenced. The range of the sequenced genome size is large, extending from approximately 150,000 bp to 5-6 millions bp. The Distribution and transposition of repetitive sequences may contribute to the organization of genome structure and evolution, but this remains purely speculative. The stability of the structure of genomes is challenged by recombination events. Since major rearrangements (i.e., inversions) are thought to frequently operate by homologous recombination between inverted repeats, the presence and distribution of such repeats in genomes is related to the conservation of chromosomal structure. Strong underrepresentation of inverted repeats is attributed to the most stable bacterial genomes (Achaz et al., 2003). A PCR-based DNA-fingerprinting is a fast, reliable and an inexpensive method to study a genetic diversity, but its effectiveness depends on primers chosen for analysis. There are many highly conserved, repetitive DNA sequences, present in the genomes of a wide range bacteria. Three families of repetitive sequences including repetitive extragenic palindromic (REP) sequence (Higgins et al., 1982), enterobacterial repetitive intergenic consensus (ERIC) sequence (Sharples and

Lloyd, 1990), BOX element (Martin et al., 1992) were identified. Several methods for assessment of genetic diversity of bacteria employing PCR with different primers homologous to repetitive sequences were named in general as rep-PCR (De Bruijn, 1992). The function of these repetitive sequences as intercistronic regulatory element of prokaryotic operons (Sharples and Lloyd, 1990) leaded to hypothesis about their biased distribution across different genomic regions, confirmed in analysis of complete sequenced genomes of Xcc and X. axonopodis pv. citri (Ignatov et al., in press). Other repetitive sequences referred as latent periodical ones were found in silica in many sequenced genomes, including bacterial ones (Korotkov et al., 1999). These sequences appear to be located particularly inside protein-encoding genes over the genome. Their use as primers for PCR leads to selective amplification of distinct genomic regions including highly polymorphic intergenic regions. This is a major difference between ancient diverged periodical sequences and previously employed repetitive intergenic sequences.

2. Research Objectives

Modeling of DNA fingerprints will be based on analysis of complete genomes of prokaryotes, chloroplast and mitochondria using short oligonucleotides corresponded to different functional 'foot' sequences as primers for PCR or restriction sites for AFLP-like methods. Such 'foot' oligos can be classified into several classes, including over-represented DNA fragments as primers/restriction sites, repetitive non-coding functional DNA fragments, repetitive fragments of protein-coding genes, and IS/TE conservative elements. Obtained 'genomic fingerprints' will be compared between different classes of 'foot' sequences for information content and robustness. The proposed model will give a bio-informatic tool for development and improvement of biomolecular diagnostic methods and provide understanding of sources and mechanisms of variation among prokaryotic organisms.

The target of the proposed project is in development of mathematic model of DNA fingerprinting. Majority of genome alternations can be placed in a few groups: Indels (insertion/deletion) and nucleotide replacement in a coding region; Indels and nucleotide replacement in non-coding region with an expression regulatory function; Indels and nucleotide replacement in non-coding region without a regulatory function; Short tandem repeats change; Genomic mobile elements insertion/deletion; Genome segments rearrangement (recombination); Genome segments multiplications/deletions. DNA fingerprints are commonly accepted as useful and reliable way to find out

even minor genetic differences between genotypes. A vast number of different DNA-fingerprint systems based on PCR analysis were reported as a tool for investigation. They were applied for three general purposes: (i) genome survey, (ii) management, and (iii) genome manipulation. Major problem in DNA fingerprinting is in absence of criteria for evaluation of robustness and usefulness of obtained data. Statistical analysis of genetic distances calculated from different DNA fingerprinting methods demonstrated significant differences in information capacity and usefulness of the methods. The ideal fingerprint profile should produce genetic distances between evaluated genotypes maximally corresponded to the "true" genetic distance.

3. Works Already Done

Distribution of small (7-10bp) inverted DNA repeats located in 100-4000bp from each other and thus capable to serve as PCR primers was studied in complete cereal genomes. The repeats flanking from 10 to 30 PCR-able fragments of the chloroplast DNA were chosen as AP-PCR primers and real PCR fingerprints obtained for wheat and 15 alloplasmic barley lines were compared to expected ones. Comparing to PCR analysis with random primers (RAPD), the selected primers produced bands of significantly (3-4 folds) higher PIC (Polymorphism Information Content), and GD (Genetic Diversity). Thus, PCR-fingerprinting with primers homologous for selected from sequence inverted repeats proved to be useful for genome variability studies. In average, some 30,000 DNA fragments from 100 to 4000bp flanked by exact 7bp-long inverted repeats and only about 1800 IRFFs flanked by exact 10bp-long repeats were found in chloroplast genomes of cereals. Large part of the IRFFs (?? 29 ?? 82As it was mentioned before, the dispersed short repeats of DNA sequences in chloroplast genome can be hot spots for recombination, can be transposed on MITE-fashion and modified by DNA-slippage. Application of those repeats, as template for PCR-primers will have a great potential for taxonomic studies and identification of mutation events within genomes of the same species. Complete-sequence fascinated computer analysis have enabled to select inverted repeats of greatest polymorphism between related species of cereal plants those were proved to be hot-spots of changes on intra-species level as well. Thus, AP-PCR analysis with primers homologous to short dispersed inverted repeats in chloroplast genome may be either an effective method for evaluation of genetic variability within the same species of plant or can provide valuable information about localization of genetic modifications in chloroplast genome. Novel primers for rep-PCR were developed with the original software and based on so called

ancient diverged periodical sequences. Rep-PCR with these primers was applied to study genetic relationships among 51 Xanthomonas campestris strains. Based on qualitative differences in amplification profiles, the strains were divided into four major groups. Two subgroups recognised within X. campestris population were similar to RFLP haplotypes. A PCR fragment about 600 bp amplified by primer KRPN2 was found in nearly all tested strains of X. campestris. SCAR primers designed for this marker produced a single specific band for strains of X. campestris, but not for other Xanthomonas, Pseudomonas and Erwinia strains tested. Those calculated primers provided more informative tool for fingerprinting of other bacteria as well, including Bacillus sp.

4. Work Planning

Modeling of DNA fingerprints will be based on analysis of complete genomes of prokaryotes, chloroplast and mitochondria using 'foot' oligonucleotides as primers for PCR or restriction sites for AFLP-like methods. Such 'foot' oligos can be classified into several classes, including random over-represented DNA fragments as primers/ restriction sites, repetitive non-coding regulatory DNA fragments, repetitive fragments of protein-coding genes, and IS/TE (insertion sequence/transposable element) conservative elements. Obtained 'genomic fingerprints' will be compared between different classes of 'foot' sequences for information content and robustness. The proposed model will give a tool for development and improvement of biomolecular diagnostic tools and provide understanding of sources and mechanisms of variation among genomes of prokaryotic organisms.

Task 1. Analysis of distribution of random short fragments across complete genomes of prokaryotic organisms, chloroplasts and mitochondria.

Task 2. Search and compilation of formal list for frequent non-coding regulatory elements, analysis of distribution of frequent non-coding regulatory elements across the complete genomes.

Task 3. Search and compilation of formal list for frequent fragments of protein coding sequences, analysis of distribution of frequent protein coding sequences across the complete genomes.

Task 4. Search and compilation of formal list for IS/TE (insertion sequence/transposable element), and analysis of distribution across the complete genomes.

Task 5. Analysis of reflection of difference between closely related genomes in simulated from complete genomes 'genomic' fingerprints based on the four different

'foot' sequence groups.

Task 6. Simulation of phylogenetic distances between the genomes from the theoretical fingerprints and evaluation of their robustness and resolution ranges for different 'foot' sequence classes.

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4.3. Charge Transport in DNA Molecules

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1. Scientific Context

Recently, possible mechanisms of the electron transport in DNA molecules have been discussed widely [11]-[15]. Apparently, the dominating mechanisms of the electron transport are different in dependence on the length of the molecule. For short fragments, the basic mechanism is, probably, a superexchange ("coherent") mechanism in which the wave function of the electronic state is delocalized along the molecule. The rate of the transport in the superexchange mechanism exponentially decreases with increasing length of the molecule. For long fragments, the basic mechanism is, probably, a ("noncoherent") mechanism of thermal jumps. In such a mechanism, the energy is exchanged between the electron and the molecule, and the electron state is localized. Several models were proposed for the soliton type transport in sufficiently long molecules [11].

Since the charge transfer for long distances in DNA molecules is related to the dynamics of wave packets sensitive to the form of the nonlinearity, it is of interest to study the structure of the nonlinear term in detail, starting from the original three-dimensional problem.

The experiments (see [13]-[14],[19]-[21]) show that the long DNA molecules can have a large rate of transport. At the same time, the direct measurements demonstrate that there is a considerable resistance intrinsic to long molecules. In this connection, it is necessary to perform a more detailed study of the mechanisms of electron transport in DNA molecules, taking the possibility of soliton type transports into account. Although there is a notable advance, the problem of theoretical description of the electron transport mechanism in DNA molecules is far from being complete (see [11]). As is known, the properties of theoretical models depend strongly on the regions of the parameters characterizing the electron and elastic DNA in these models. In the studies

proposed, the length of molecular chains is important, which allows one to reduce the problem to the effectively one-dimensional problem. From the asymptotic viewpoint, this fact means that the problem contains a small parameter characterizing the ratio of the molecular conductor width to its length. The other possible parameters of the problem are the ratios of the (hole) electron wave length to the "quantum conductor" length and to the site length. The existence of these parameters allows one to use the modern asymptotic methods for studying both the hole dynamics in DNA molecules and the problem of the charge transport for a long distance.

As localized solutions, solutions of Davydov soliton type are well known. Such solutions were obtained in models with local nonlinearity (the nearest neighbors approximation, e.g., see [12]). At the same time, it may be reasonable to consider models with integral nonlinearity of the self-consistent field type. In this case, one can construct localized solutions in the form of moving nonfuzzy packets, for example, of Gaussian form. Such solutions were studied in several quantum mechanical problems [7, 8, 9], but, as far as we know, they have not been considered for problems of electron transport in molecules It should be noted that the methods developed in [1, 7, 8, 9, 10] allow us to construct wave packet type solutions not only for differential, but also for pseudodifferential equations with integral nonlinearity, which are equivalent to a discrete N-site chain.

2. Research Objectives

Asymptotic analysis of the influence of spatial effects, of coupling parameters, and of the nonlinearity character on the structure of one-dimensional models used to describe the hole dynamics and the electron transport for long distances in DNA molecules.

1. We intend to derive reduced one-dimensional equations from different three-dimensional models with the form of the molecule transverse cross-section, torsion, spirality, etc. taken into account. Special attention will be paid to studying the form of the nonlinear term in dependence on the character of the electron–site interaction and the geometric characteristics and the parameters of molecules. This reduction will be performed based on the proposed in [5, 4, 6] operator generalization of the adiabatic approximation.

2. We suppose to study the asymptotic solutions in nonlinear models with nonlocal interaction which describe the hole dynamics in DNA molecules and the

charge transport for long distances. As such solutions, we intend to use the WKB-solutions and Gaussian type wave packets as a possible alternative to the Davydov solitons for models with integral nonlinearities. We plan to study the range of applicability of such quasi-one-dimensional solutions for the original problem.

3. We intend to study the relation between the nonlinear integro-differential models of the self-consistent field and their discrete analogs. We also intend to study continual passages to continuous quasi-one-dimensional models for the original three-dimensional problem in which the wave packet width and the nontrivial geometry of the molecule are taken into account.

3. Works Already Done

In the linear situation [5],[4], the influence of the spatial geometry of the quantum wire placed in an external electromagnetic field on its electron structure and the electron transport rate was studied with spin effects taken into account. The original three-dimensional equation describing the finite effective "cross-section area" of the wire was reduced to an effective one-dimensional equation. It was shown that the effective one-dimensional Hamiltonian is different for different electron energies. For the "semiclassical" transport, the asymptotics of the wave function of an electron in a wire were constructed. In particular, the obtained equations can be used to study the process of the electron photoexcitation in molecules. In [6], a reduction method was developed, which can be used for nonlinear equations.

The general approach to the study of the wave packet dynamics in the one-dimensional and multidimensional structures in linear quantum mechanical problems was developed in [2],[3].

The continual equations with integral Hartree type nonlinearity and their discrete analogs were considered in [8],[9].

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5. Mathematical Analysis of Biological Models

5.1. Hydrodynamique des Ecoulements Biologiques

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1. Contexte Scientifique

La modélisation de phénomènes physiques est nécessaire dans de nombreux domaines. Choisir le modèle mathématique le plus adapté représente une étape importante. En effet, un mauvais choix peut entrainer un résultat théorique tout à fait différent de la réalité. Les équations de Navier-Stokes et d'autres équations apparentées ont longtemps été considérées comme le meilleur choix pour la description des écoulements visqueux. Néanmoins, dans les années soixante, on s'est aperu qu'il y avait des écoulements (l'écoulement du sang dans les vaisseaux sanguins, l'écoulement de certains polymères, etc ...) pour lesquels cette modélisation ne convenait pas. La théorie des fluides micropolaires, introduite par Eringen dans [1], a donc été mise en place.

Du point de vue physique, les fluides micropolaires sont caractérisés par la propriété suivante : les particules de fluide contenues dans un petit élément de domaine, en plus de leur comportement rigide habituel, tournent autour du centre de gravité des sections de l'élément de volume, ce qui est décrit par un tenseur anti-symétrique. Le mouvement d'un fluide micropolaire est décrit par un système non linéaire couplé dont les inconnues sont la vitesse, la pression et la microrotation du fluide.

Afin de traiter le problème d'écoulement dans les vaisseaux sanguins, un domaine

dépendant d'un petit paramètre doit être considéré. La présence de ce petit paramètre complique la mise en oeuvre de la résolution numérique du problème : plus de temps et plus de mémoire sont alors nécessaires. Les méthodes asymptotiques étudiant le comportement de la solution lorsque le petit paramètre tend vers zéro, fournissent une approximation numérique de la solution. L'inconvénient de ces méthodes est que leur mise en place est souvent difficile. Pour cela d'autres méthodes numériques, basées sur le comportement asymptotique de la solution, ont été développées, en particulier, la méthode de décomposition asymptotique partielle du domaine, introduite dans [2]. L'idée principale de cette méthode est d'extraire un sous-domaine sur lequel la solution a un comportement singulier et de simplifier le problème sur le sous-domaine où la solution a un comportement régulier. Le problème le plus compliqué est l'apparition de couches limites au voisinage des extrémités ou des jonctions des vaisseaux sanguins.

2. Résultats déjà obtenues

Concernant l'analyse asymptotique des écoulements, les participants du projet ont déjà obtenu quelques résultats [3-4] dans le cadre du projet européen EURROM-MAT No ICA1-CT-2000-70022. Cette étude traite le cas du mouvement stationnaire d'un fluide micropolaire incompressible à l'intérieur d'un tube ondulé ayant une épaisseur de l'ordre ε, $\varepsilon << 1$. Des conditions au bord de type Dirichlet non homogènes pour la vitesse et homogènes pour la microrotation ont été imposées. On considère le développement asymptotique de la solution, qui nous ramène à l'étude d'un problème macroscopique pour la première approximation $\mathbf{v}^0$, ω^0, p^1. Le système satisfait par ($\mathbf{v}^0$, p^1) est un problème de type Stokes avec une condition intégrale supplémentaire pour la vitesse. A cause de cette condition supplémentaire, l'existence d'une solution n'est plus évidente : un théorème d'existence et d'unicité a donc été démontré. Concernant la première approximation de la microrotation, ω^0, on obtient un système de type Poisson tout à fait standard. Les problèmes de couche limite sont définis, puis la convergence de la solution macroscopique vers la solution microscopique est prouvée. Pour conclure, quelques détails concernant les approximations d'ordre supérieur sont donnés. Ensuite la méthode de décomposition asymptotique du domaine est développée pour le problème considéré. Dans ce cas, elle consiste à couper le domaine à une distance $\delta = K\varepsilon[|\ln \varepsilon|]$ des deux extrémités et à construire une nouvelle approximation ayant un comportement régulier sur le sous-domaine restant. Cette méthode a déjà été utilisée pour les équations de Stokes et de Navier-

Stokes dans une structure tubulaire (dans [5-6]).

3. Objectifs

1. Une généralisation du problème étudié dans [3-4] est envisagée pour un domaine constitué de plusieurs tubes ondulés. Dans ce cas plus compliqué, de nouvelles difficultés interviennent au niveau des jonctions entre les tubes. L'étude asymptotique est traitée de manière indépendante sur chaque partie régulière du domaine. L'assemblage des différentes solutions obtenues pose de nombreux problèmes.

2. Nous prévoyons de poursuivre cette étude pour le cas de l'écoulement de fluides micropolaires dans une structure tubulaire avec une frontière élastique, qui nous permettra de mieux modéliser l'écoulement du sang dans le système circulatoire.

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5.2. Chemical Kinetics and Thermodynamics of Biological Processes

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1. Research Objectives

It is well-known that all human organism consists of various chemical networks. They are functioning on different scales of time and space. The main goal of the work is to find some framework for mathematical description of this scale dependent chemical network:

1. The lowest and the fastest scale describes fast convergence to local equilibrium, which is described by local equilibrium Gibbs measure.

2. Next scale (second) is given by basic chemical reactions inside the cell. It is normally governed ny (non-equilibrium) chemical thermodynamics. The latter does not have sufficient mathematical basis now. The first goal of the work is to provide rigorous mathematical models for chemicl thermodynamics. Here obviously the second scale should be coupled with the first one. The mathematical apparatus (in its simplest form) includes classical and stochastic chemical kinetics in its random walks and Boltzman equation framework, and statistical physics of ideal gases as well.

3. The third scale is defined by exactly formulated chemico-chemical and chemico-mechanical machines inside the cell. Examples are: muscle contraction and rotary motors, cargo molecular machines and neurotransmitters in the synaptic connections, action potential propagation, etc. Some of these networks were partly described, some

are far from being described.

4. The next scales are even less clear. These are physiological processes which consist of several interaction molecular motors of the scale 3. These also could be genetic networks, which change behaviour of the cell on a longer scale.

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