Quantum Mechanism in Recognition and Communication in Cell Cycle

A Quantum Model for Cdk-Activity in Cell Cycle

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Contents

Abstract. Despite tremendous progress in explaining the cell cycle, the molecular mechanisms regulating the beginning and the inhibition of the various processes is still not understood. Moreover the simultaneously of different processes at different places are time-correlated. For instance, the beginning of the cell division is caused by increasing the concentration of an specific protein-complex (Cdk). However it is unknown why this concentration increases at the right time, exactly at the beginning of the cell division. This could be an effect of quantum nature. Consequently, it seems reasonable to investigate in biological processes with the aid of quantum theory. At, least the "anatomy" of the cell was discovered with devices based on quantum mechanics (scanning tunnelling microscope). Hence the subsystems of the cell are highly expected to obey the laws of quantum mechanics.
Our Aim is now to develope a quantum theory for Macromolecules with biological funciton (e.g. Cdk) with the special aim of explaining the role of Cdk during special stages of the cell-cycle.

1 Introduction

1.1 Introductionary Remarks to Structure, Function and Physiology of Cells

This chapter is an introduction to make the physicist familiar with the subject cell. The introductory considerations below are quoted from [W07]
"The cell is the structural and functional unit of all living organisms, and is sometimes called the "building block of life." Some organisms, such as bacteria, are unicellular, consisting of a single cell. Other organisms, such as humans, are multicellular. (Humans have an estimated 100 trillion or 10^{14} cells; a typical cell size is 10 μm; a typical cell mass is 1 nanogram.) The largest known cell is an ostrich egg.

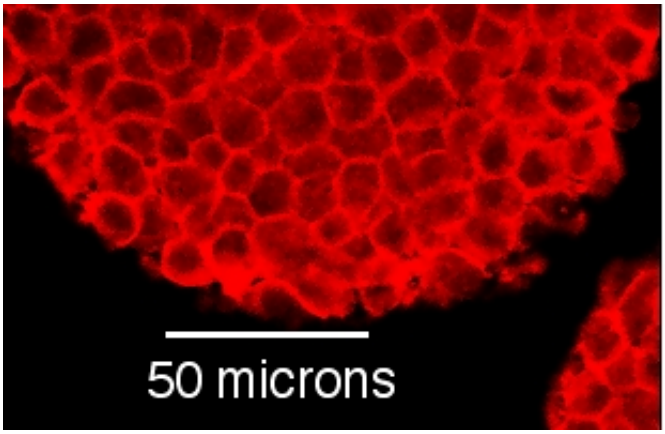

Figure 1: Mouse cells grown in a culture dish. These cells grow in large clumps, but each individual cell is about 10 micrometres across.

The cell theory, first developed in 1839 by Schleiden and Schwann, states that all or-

ganisms are composed of one or more cells. All cells come from preexisting cells. Vital functions of an organism occur within cells, and all cells contain the hereditary information necessary for regulating cell functions and for transmitting information to the next generation of cells.

The word cell comes from the Latin cellula, a small room. The name was chosen by Robert Hooke when he compared the cork cells he saw to the small rooms monks lived in.

1.1.1 Anatomy of cells

There are two types of cells, eukaryotic and prokaryotic. Prokaryotic cells are usually singletons, while eukaryotic cells are usually found in multicellular organisms.

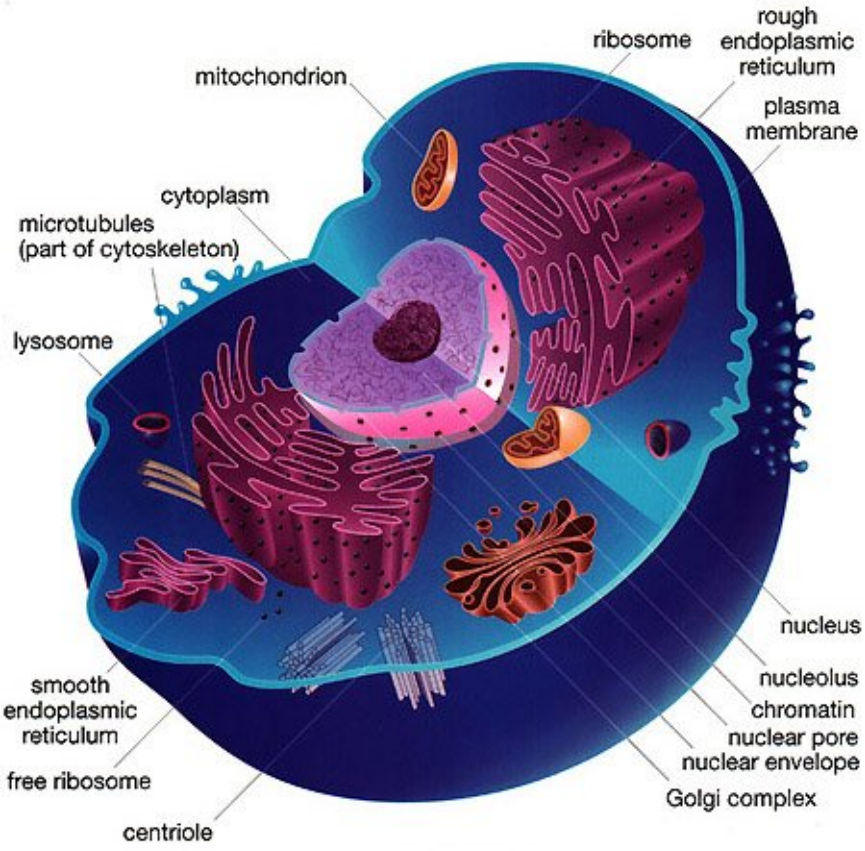

Figure 2: Schematical Representation of an animal cell

Prokaryotes are distinguished from eukaryotes on the basis of nuclear organization, specifically their lack of a nuclear membrane. Prokaryotes also lack most of the intracellular organelles and structures that are characteristic of eukaryotic cells (an important exception is the ribosomes, which are present in both prokaryotic and eukaryotic cells). Most of the functions of organelles, such as mitochondria, chloroplasts, and the Golgi apparatus, are

taken over by the prokaryotic plasma membrane. Prokaryotic cells have three architectural regions: appendages called flagella and pili — proteins attached to the cell surface; a cell envelope consisting of a capsule, a cell wall, and a plasma membrane; and a cytoplasmic region that contains the cell genome (DNA) and ribosomes and various sorts of inclusions. Other differences include:

- The plasma membrane (a phospholipid bilayer) separates the interior of the cell from its environment and serves as a filter and communications beacon.
- Most prokaryotes have a cell wall (some exceptions are Mycoplasma (a bacterium) and Thermoplasma (an archaeon)). It consists of peptidoglycan in bacteria, and acts as an additional barrier against exterior forces. It also prevents the cell from "exploding" (cytolysis) from osmotic pressure against a hypotonic environment. A cell wall is also present in some eukaryotes like fungi, but has a different chemical composition.
- A prokaryotic chromosome is usually a circular molecule (an exception is that of the bacterium Borrelia burgdorferi, which causes Lyme disease). Even without a real nucleus, the DNA is condensed in a nucleoid. Prokaryotes can carry extrachromosomal DNA elements called plasmids, which are usually circular. Plasmids can carry additional functions, such as antibiotic resistance.

Eukaryotic cells are about 10 times the size of a typical prokaryote and can be as much as 1000 times greater in volume. The major difference between prokaryotes and eukaryotes is that eukaryotic cells contain membrane-bound compartments in which specific metabolic activities take place. Most important among these is the presence of a cell nucleus, a membrane-delineated compartment that houses the eukaryotic cell's DNA. It is this nucleus that gives the eukaryote its name, which means "true nucleus". Other differences include:

- The plasma membrane resembles that of prokaryotes in function, with minor differences in the setup. Cell walls may or may not be present.
- The eukaryotic DNA is organized in one or more linear molecules, called chromosomes, which are associated with histone proteins. All chromosomal DNA is stored in the cell nucleus, separated from the cytoplasm by a membrane. Some eukaryotic organelles also contain some DNA.
- Eukaryotes can move using cilia or flagella. The flagella are more complex than those of prokaryotes.

1.1.2 Subcellular components

All cells, whether prokaryotic or eukaryotic, have a membrane, which envelopes the cell, separates its interior from its environment, regulates what moves in and out (selectively permeable), and maintains the electric potential of the cell. Inside the membrane, a salty cytoplasm takes up most of the cell volume. All cells possess DNA, the hereditary material of genes, and RNA, containing the information necessary to build various proteins such as enzymes, the cell's primary machinery. There are also other kinds of biomolecules in cells:

1.1.2.1 Cell membrane: A cell's defining boundary The cytoplasm of a cell is surrounded by a plasma membrane. The plasma membrane in plants and prokaryotes is usually covered by a cell wall. This membrane serves to separate and protect a cell from its surrounding environment and is made mostly from a double layer of lipids (hydrophobic fat-like molecules) and hydrophilic phosphorus molecules. Hence, the layer is called a phospholipid bilayer. It may also be called a fluid mosaic membrane. Embedded within this membrane is a variety of protein molecules that act as channels and pumps that move different molecules into and out of the cell. The membrane is said to be 'semi-permeable', in that it can either let a substance (molecule or ion) pass through freely, pass through to a limited extent or not pass through at all. Cell surface membranes also contain receptor proteins that allow cells to detect external signalling molecules such as hormones.

1.1.2.2 Cytoskeleton: A cell's scaffold The cytoskeleton acts to organize and maintain the cell's shape; anchors organelles in place; helps during endocytosis, the uptake of external materials by a cell, and cytokinesis, the separation of daughter cells after cell division; and moves parts of the cell in processes of growth and mobility. Eukaryotic cytoskeleton is composed of microfilaments, intermediate filaments and microtubules. There is a great number of proteins associated with them, each controlling a cell's structure by directing, bundling, and aligning filaments.

1.1.2.3 Genetic material Two different kinds of genetic material exist: deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). Most organisms use DNA for their long-term information storage, but some viruses (e.g., retroviruses) have RNA as their genetic material. The biological information contained in an organism is encoded in its DNA or RNA sequence. RNA is also used for information transport (e.g., mRNA) and enzymatic functions (e.g., ribosomal RNA) in organisms that use DNA for the genetic code itself.

Prokaryotic genetic material is organized in a simple circular DNA molecule (the bacterial chromosome) in the nucleoid region of the cytoplasm. Eukaryotic genetic material is divided into different, linear molecules called chromosomes inside a discrete nucleus, usually with additional genetic material in some organelles like mitochondria and chloroplasts (see endosymbiotic theory).

A human cell has genetic material in the nucleus (the nuclear genome) and in the mitochondria (the mitochondrial genome). In humans the nuclear genome is divided into 46 linear DNA molecules called chromosomes. The mitochondrial genome is a circular DNA molecule separate from the nuclear DNA. Although the mitochondrial genome is very small, it codes for some important proteins.

Foreign genetic material (most commonly DNA) can also be artificially introduced into the cell by a process called transfection. This can be transient, if the DNA is not inserted into the cell's genome, or stable, if it is.

1.1.2.4 Organelles The human body contains many different organs, such as the heart, lung, and kidney, with each organ performing a different function. Cells also have

a set of "little organs," called organelles, that are adapted and/or specialized for carrying out one or more vital functions. Membrane-bound organelles are found only in eukaryotes.

1.1.2.5 Cell nucleus (a cell's information center) The cell nucleus is the most conspicuous organelle found in a eukaryotic cell. It houses the cell's chromosomes, and is the place where almost all DNA replication and RNA synthesis occur. The nucleus is spheroid in shape and separated from the cytoplasm by a double membrane called the nuclear envelope. The nuclear envelope isolates and protects a cell's DNA from various molecules that could accidentally damage its structure or interfere with its processing. During processing, DNA is transcribed, or copied into a special RNA, called mRNA. This mRNA is then transported out of the nucleus, where it is translated into a specific protein molecule. In prokaryotes, DNA processing takes place in the cytoplasm.

1.1.2.6 Mitochondria and Chloroplasts (the power generators) Mitochondria are self-replicating organelles that occur in various numbers, shapes, and sizes in the cytoplasm of all eukaryotic cells. As mitochondria contain their own genome that is separate and distinct from the nuclear genome of a cell, they play a critical role in generating energy in the eukaryotic cell, organelles that are modified chloroplasts; they are broadly called plastids, and are often involved in storage.

1.1.2.7 Endoplasmic reticulum and Golgi apparatus (macromolecule managers) The endoplasmic reticulum (ER) is the transport network for molecules targeted for certain modifications and specific destinations, as compared to molecules that will float freely in the cytoplasm. The ER has two forms: the rough ER, which has ribosomes on its surface, and the smooth ER, which lacks them.

1.1.2.8 The ER contains many Ribosomes (the protein production machine) The ribosome is a large complex composed of many molecules, only exist floating freely in the cytosol, whereas in eukaryotes they can be either free or bound to membranes.

1.1.2.9 Lysosomes and Peroxisomes (of the eukaryotic cell) The cell could not house such destructive enzymes if they were not contained in a membrane-bound system.

1.1.2.10 Centrosome (the cytoskeleton organiser) The centrosome produces the microtubules of a cell - a key component of the cytoskeleton. It directs the transport through the ER and the Golgi apparatus. Centrosomes are composed of two centrioles, which separate during cell division and help in the formation of the mitotic spindle. A single centrosome is present in the animal cells. They are also found in some fungi and algae cells.

1.1.2.11 Vacuoles Vacuoles store food and waste. Some vacuoles store extra water. They are often described as liquid filled space and are surrounded by a membrane. Some

cells, most notably Amoeba have contractile vacuoles, which are able to pump water out of the cell if there is too much water.

1.1.3 Cell functions

1.1.3.1 Cell growth and metabolism Between successive cell divisions, cells grow through the functioning of cellular metabolism.

Cell metabolism is the process by which individual cells process nutrient molecules. Metabolism has two distinct divisions: catabolism, in which the cell breaks down complex molecules to produce energy and reducing power, and anabolism, wherein the cell uses energy and reducing power to construct complex molecules and perform other biological functions. Complex sugars consumed by the organism can be broken down into a less chemically-complex sugar molecule called glucose. Once inside the cell, glucose is broken down to make adenosine triphosphate (ATP), a form of energy, via two different pathways.

The first pathway, glycolysis, requires no oxygen and is referred to as anaerobic metabolism. Each reaction is designed to produce some hydrogen ions that can then be used to make energy packets (ATP). In prokaryotes, glycolysis is the only method used for converting energy.
The second pathway, called the Krebs cycle, or citric acid cycle, occurs inside the mitochondria and is capable of generating enough ATP to run all the cell functions. An overview of protein synthesis.Within the nucleus of the cell (light blue), genes (DNA, dark blue) are transcribed into RNA. This RNA is then subject to post-transcriptional modification and control, resulting in a mature mRNA (red) that is then transported out of the nucleus and into the cytoplasm (peach), where it undergoes translation into a protein. mRNA is translated by ribosomes (purple) that match the three-base codons of the mRNA to the three-base anti-codons of the appropriate tRNA. Newly-synthesized proteins (black) are often further modified, such as by binding to an effector molecule (orange), to become fully active. An overview of protein synthesis. Within the nucleus of the cell (light blue), genes (DNA, dark blue) are transcribed into RNA. This RNA is then subject to post-transcriptional modification and control, resulting in a mature mRNA (red) that is then transported out of the nucleus and into the cytoplasm (peach), where it undergoes translation into a protein. mRNA is translated by ribosomes (purple) that match the three-base codons of the mRNA to the three-base anti-codons of the appropriate tRNA. Newly-synthesized proteins (black) are often further modified, such as by binding to an effector molecule (orange), to become fully active.

1.1.3.2 Cell division Cell division involves a single cell (called a mother cell) dividing into two daughter cells. This leads to growth in multicellular organisms (the growth of tissue) and to procreation (vegetative reproduction) in unicellular organisms.

Prokaryotic cells divide by binary fission. Eukaryotic cells usually undergo a process of nuclear division, called mitosis, followed by division of the cell, called cytokinesis. A

diploid cell may also undergo meiosis to produce haploid cells, usually four. Haploid cells serve as gametes in multicellular organisms, fusing to form new diploid cells.

DNA replication, or the process of duplicating a cell's genome, is required every time a cell divides. Replication, like all cellular activities, requires specialized proteins for carrying out the job.

1.1.3.3 Protein biosynthesis Cells are capable of synthesizing new proteins, which are essential for the modulation and maintenance of cellular activities. This process involves the formation of new protein molecules from amino acid building blocks based on information encoded in DNA/RNA. Protein synthesis generally consists of two major steps: transcription and translation.

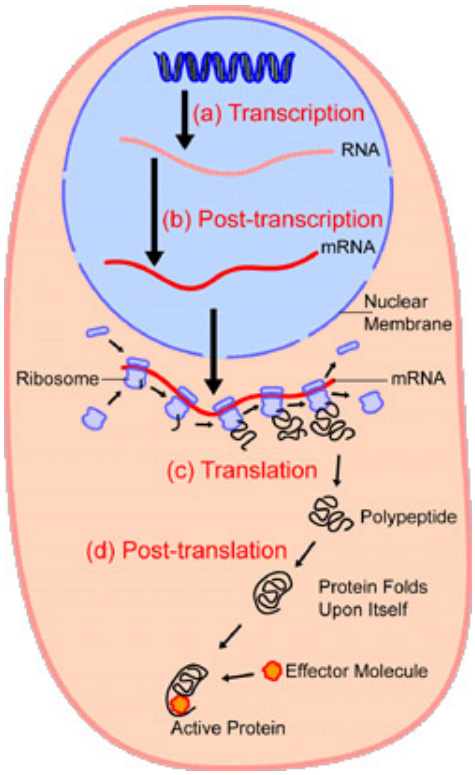

Figure 3: An overview of protein synthesis. Within the nucleus of the cell (light blue), genes (DNA, dark blue) are transcribed into RNA. This RNA is then subject to post-transcriptional modification and control, resulting in a mature mRNA (red) that is then transported out of the nucleus and into the cytoplasm (peach), where it undergoes translation into a protein. mRNA is translated by ribosomes (purple) that match the three-base codons of the mRNA to the three-base anti-codons of the appropriate tRNA. Newly-synthesized proteins (black) are often further modified, such as by binding to an effector molecule (orange), to become fully active

Transcription is the process where genetic information in DNA is used to produce a complimentary RNA strand. This RNA strand is then processed to give messenger RNA (mRNA), which is free to migrate through the cell. mRNA molecules bind to protein-RNA complexes called ribosomes located in the cytosol, where they are translated into

polypeptide sequences. The ribosome mediates the formation of a polypeptide sequence based on the mRNA sequence. The mRNA sequence directly relates to the polypeptide sequence by binding to transfer RNA (tRNA) adapter molecules in binding pockets within the ribosome. The new polypeptide then folds into a functional 3D protein molecule."

1.2 Cell Cycle and the Role of Cyklin Dependent Kinase

In this Section we will explain you the Role of Cdk in Cell Cycle. This Text follows [B02]. A cell reproduces by performing an orderly sequence of events in which it duplicates its contents and then divides in two. This cycle of duplication and division, known as the cell cycle, is the essential mechanism by which all living things reproduce. In unicellular species, such as bacteria and yeasts, each cell division produces a complete new organism. In multicellular species, long and complex sequences of cell divisions are required to produce a functioning organism. Even in the adult body, cell division is usually needed to replace cells that die. In fact, each of us must manufacture many millions of cells every second simply to survive: if all cell division were stopped—by exposure to a very large dose of x-rays, for example—we would die within a few days.

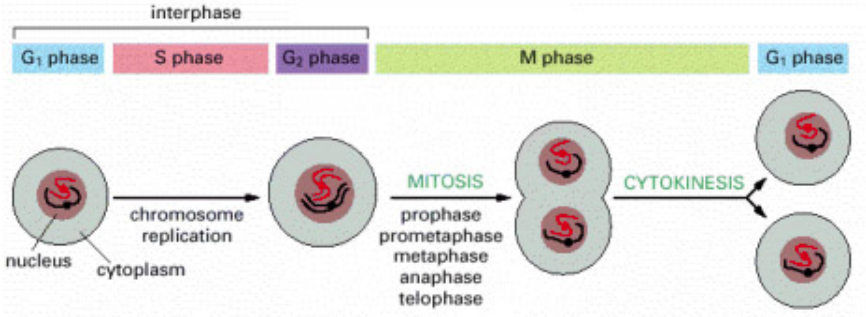

Figure 4: M phase starts at the end of G2 and ends at the start of the next G1 phase. It includes the five stages of nuclear division (mitosis), as well as cytoplasmic division (cytokinesis)

The mechanical events of the M phase of the cycle, which is the culmination of the cycle and includes the various stages of nuclear division (mitosis) and cytoplasmic division (cytokinesis).
In a comparatively brief period, the contents of the parent cell, which were doubled during earlier phases of the cycle, are partitioned into two daughter cells. The period between one M phase and the next is called interphase, and in most rapidly proliferating cells, it is divided into three phases: S phase, in which DNA is replicated, and two gap phases, G1 and G2, which provide additional time for the cell to grow (Figure 4).

The events of the cell cycle are controlled by the ***cell-cycle control system***. The core of the control system consists of various **cyclin-dependent kinases** (Cdks), which are activated in sequence to trigger various steps of the cycle. The Cdks are activated by the binding of cyclin regulatory proteins, as well as by phosphorylation and dephosphorylation of the kinase. They are inactivated by various Cdk inhibitory proteins (CKIs) and by the degradation of the cyclin subunits at specific stages of the cycle.

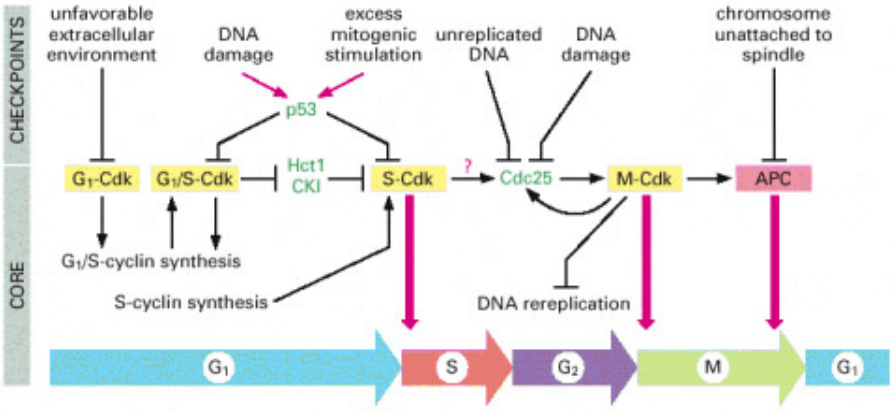

Figure 5: The core of the cell-cycle control system consists of a series of cyclin-Cdk complexes (yellow). The activity of each complex is also influenced by various inhibitory checkpoint mechanisms, which provide information about the extracellular environment, cell damage, and incomplete cell-cycle events (top). These mechanisms are not present in all cell types; many are missing in early embryonic cell cycles, for example.

The M-phase Cdk (M-Cdk) triggers a cascade of protein phosphorylation that initiates M phase. These phosphorylations are responsible for the many morphological changes that occur during mitosis in animal cells. The chromosomes condense, the nuclear envelope breaks down, the endoplasmic reticulum and Golgi apparatus reorganize, the cell loosens its adhesions both to other cells and to the extracellular matrix, and the cytoskeleton radically reorganizes to bring about the highly ordered movements that will segregate the replicated chromosomes and divide the cell in two.

Targetted protein degradation by the anaphase-promoting complex (APC) has an equally important regulatory role in mitosis. It initiates the separation and segregation of the replicated chromosomes, and it inactivates M-Cdk at the end of mitosis.

2 Present Status on the Research in Quantum Nature of Cdk

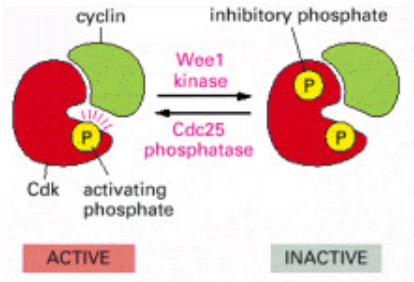

Figure 6: The active cyclin-Cdk complex is turned off when the kinase Wee1 phosphorylates two closely spaced sites above the active site. Removal of these phosphates by the phosphatase Cdc25 results in activation of the cyclin-Cdk complex. For simplicity, only one inhibitory phosphate is shown. The activating phosphate is added by CAK, as shown in next Figure

The catalytic activity of Cdk is determined by a quantum transition of its energetic and configurational state (see schematically in Figure 6). Although there exist several Journals concerning the Molecular Biology of the Cell and the Cell itself,we found in the literature no description of specific **quantum** transition in the activity of Cdk (maybe the work on the first year will show us if there is really no quantum discription of Cdk).

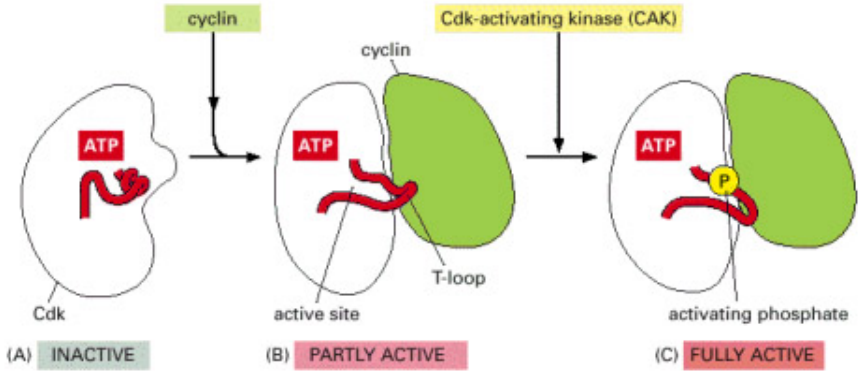

Figure 7: These drawings are based on three-dimensional structures of human Cdk2, as determined by x-ray crystallography. The location of the bound ATP is indicated. The enzyme is shown in three states. (A) In the inactive state, without cyclin bound, the active site is blocked by a region of the protein called the T-loop (red). (B) The binding of cyclin causes the T-loop to move out of the active site, resulting in partial activation of the Cdk2. (C) Phosphorylation of Cdk2 (by CAK) at a threonine residue in the T-loop further activates the enzyme by changing the shape of the T-loop, improving the ability of the enzyme to bind its protein substrates.

3 Goals of the Project

The main goal of our project is to fill this gap and find new related aspects. The transition mentioned above represents the fundamental (quantum) physical base in the explanation of the reaction kinetic of the recognition process.
Together with the general quantum theory of the macromolecules (which will be developed during the research and applied to biological macromolecules - i.e. Cdk) we hope to find the states and the energetic spectra of Cdk. This will enable us to compute the transition probability (inactive $\rightarrow$ active) and then allow us to determine the reaction rate coefficients $k_{\rightharpoonup}$,$k_{\rightharpoondown}$. The next step will be the experimental verification of this parameters. If the theory works then it should be possible to apply it stepwise to other macromolecules in cell, hopefully once be able to describe the whole cell as an effect of quantum nature of its components.

3.1 General Quantum Theory of Macromolecules - The Importance of Statistical Physics

Althoug our main Subject is the quantum explanation of the activity of Cdk, one cannot ignore the statistical nature of such a complex system.

The living cell is a highly (self)organized system. However its dimensions are so small[1] that the thermodynamic interpretation of the used (quantum) statistics should be done carefully.
At the End our Theory should be able to explain both, the quantum nature and the statistical nature. (Literature to this Theory is listed in the Literature-Section under *General Quantum Theory of Macromolecules*)

4 Financial Aspects and Agenda

Four our research we need the financial support for three persons. The first person will need to be supported for a diploma-thesis with followed PhD-thesis. The second person will need to be supported for a PhD-thesis. The third person should be responsible for all bureaucratical work and technical work and will need to be supported for his work. For our coperationally work we need also support for three journey a year to 700 Euro. The total cost add up to 326.620 Euro for 5 Years research. (for Detail see Table)

	personal costs/year	brutto salary /month
1st Person (Dipl. 1 Year)	5.280,00	440,00
1st Person (PhD 2.-5. Year)	30.860,00	1.721,30
2nd Person (PhD)	30.860,00	1.721,30
3rd Person (marginal employed)	5.920,00	341,16

The **Agenda** of our Research Project is shown in the Figure below:

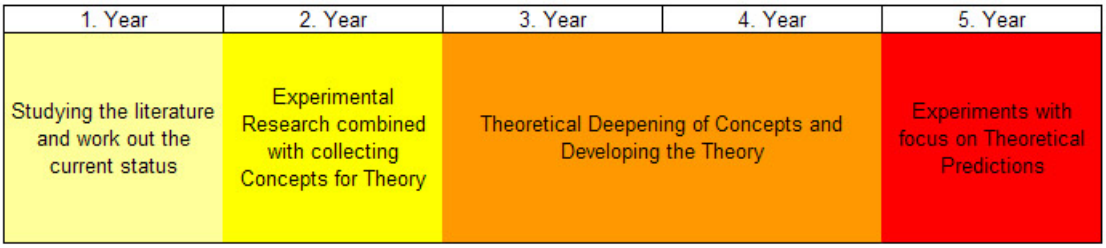

Figure 8: Agenda

[1]The Number of Particles are $\approx 10^{14} \ll 10^{23} \equiv 1Mol$

5 Cooperations

Our Cooperation partners will be a group in Ljubljana:

Structural Biology Group
Department of Biochemistry and Molecular Biology
Jozef Stefan Institute

(contact person: dr. Igor Stern)

The scientific interest of this group is the investigation of principles of molecular mechanisms in biological systems at the atomic level from the points of view of structural and computational biology using proteases as a model system.

The molecules of their interest are proteases themselves, their substrates, including proenzymes, and inhibitors as regulators of their activity. In order to study the principles of intra- and intermolecular interactions the 3-dimensional structure of a macromolecule resolved to atomic details is an essential step.

6 Literature

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