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G3B3 to GP15: From early years to Health Informatics Research Group at Paulista University - UNIP

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Abstract This article summarizes the history and intellectual production from G3B3 (Grupo de Estudos em Bioinformática Estrutural) to GP15 (Grupo de Pesquisa em Informática em Saúde), conducted at Paulista University - UNIP, campus Bauru. In the early years, several activities were developed by G3B3 until the conversion of team to GP15. This group has the computational simulation of biomolecules as one of its research lines. Together with the second line of research, entitled ”Development of teaching material and research using computational resources”, the production of this group is mainly related to the development of scripts for the visualization of biomolecules and the production of digital books. In early 2022, the current team consists of five university professors and four students from the Biomedicine Course at Universidade Paulista - UNIP, Bauru campus. Together, the team has published more than 50 books in different publishers, part of which is aimed at the development of scripts for computer simulation software. All these books are adopted by course teachers in different subjects.

Keywords: Simulation types and techniques, Bioinformatics, Computer and Information Science Education

1 Introduction

This article presents a summary of the history of how a study group, the G3B3, was converted into a research group in the area of Bioinformatics, the GP15. It presents also the main activities of the GP15 - Research Group on Health Informatics at Universidade Paulista - UNIP, Bauru campus, in Brazil. GP15 was created on August 23, 2019. Since then, the group has developed a variety of projects, most of them developed at the Computer Laboratory at UNIP - Bauru. As a result, the group is now formed by students and professors who teach Bioinformatics concepts to undergraduate students in Biomedical Sciences and students from other healthcare courses. In addition, the group takes knowledge of Bioinformatics area to high school students in public schools and private individuals in the city of Bauru - SP and region. Although the group has only two years of formation, the activities developed by the team began in 2014, from a study group called G3B3 - Structural Bioinformatics Study Group. Thus, the GP15 began its activities by developing practices already consolidated in the Biomedical Sciences Course at UNIP - Bauru. Currently, the group consists of ten members: five university professors and five undergraduate students from Biomedical Sciences course. In this article, section 1 presents a brief history of the group. In section 2, training and qualification activities for students to use computer programs will be presented. Next, section 3 presents the group profile and section 4 details activities related to the research line of computational simulation of biomolecules. Finally, section 5 discusses future perspectives and directions for GP15 activities.

2 Group History: the early years of G3B3

Activities in the area of Bioinformatics in the Biomedical Sciences course at Universidade Paulista - UNIP, Bauru began on June 6, 2014, with the formation of the G3B3 - Study Group on Structural Bioinformatics. This initial team consisted of 3 professors and 6 students from the Biomedical Sciences course and 8 other students from other courses at the Institute of Health Sciences. Teachers offered training to teach students how to select PDB files on the Protein Data Bank website and to use different features of some bioinformatics software.

In Project G3B3, students were instructed to choose available proteins from the Molecule of the Month page (Available at: https://pdb101.rcsb.org/motm/motm-by-title). From the study of these proteins and the development of scripts for computer simulation software for biomolecules (such as RasMol, JMol, PyMol, Molecule Viewer, among others), students were instructed on how to develop panels and models of biomolecules. This material was presented at two main events: EXPOLAB - Exhibition of the Laboratory School of Biomedical Sciences at UNIP - Bauru and at 3XP0 - Exhibition of G3B3 Panels and Models.

Later, the material developed for these events was used in the Project ”Biomedicina na Escola”, where there was a new display of panels and models for public and private

high schools in Bauru - SP and other cities in the region. All material produced by the G3B3 during the semester was donated to schools that received the project. Occasionally, in some schools, when there was a computer lab available, high school students also received training to learn some functionalities of computer simulation programs for biomolecules. When the school did not have a laboratory with computers, some G3B3 students took their own personal notebooks to present some molecules of biological interest.

On August 23, 2019, the GP15 was created, formed then from activities consolidated in the Biomedical Sciences course at UNIP - Bauru. The group was created after approval by the institution and by the Directory of Research Groups in Brazil - Lattes. Together, the G3B3 and GP15 have so far produced more than 50 digital books, all available for free download. Some of these books address issues such as: use of computer programs and scripting, but mostly to produce content that is used in theoretical and practical classes in different disciplines of the Biomedical Sciences course at UNIP. Some of them will be presented in the next sessions.

3 Group Profile

The GP15 is currently formed by five researchers:

- Ph.D. Renato Massaharu Hassunuma is Full Professor of the Biomedical Sciences Course at UNIP - Bauru; Founder of G3B3 - Study Group on Structural Bioinformatics at UNIP - Bauru; BioMed Virtual Team Administrator (https://www.instagram.com/biomedvirtual/); Organizer of events at UNIP - Bauru as EXPOLAB - Exhibition of the School of Biomedical Sciences Laboratory and Community Extension Project ”Biomedicina na Escola”;
- Ph.D. Patrícia Carvalho Garcia who is Responsible Technician for the Transfusion Agency and the Laboratory of Immuno-hematology for Patients at Botucatu Blood Center - SP at São Paulo State University (UNESP); Vice-Coordinator of the Professional Improvement Program (FUNDAP) in Hemotherapy; Program Advisor of Immuno-hematology and Training and Learning Program (PRAT) of the Faculty of Medicine of Botucatu - UNESP; Auxiliary Coordinator and Professor of the Biomedical Sciences course at UNIP - Bauru; and Honorary Adviser of the Regional Council of Biomedical Sciences (CRBM-1);
- Ph.D. Michele Janegitz Acorci-Valério is Full Professor of the Biomedical Sciences Course at UNIP - Bauru. Organizer of events at UNIP - Bauru as Biomedical Sciences Journey;
- Ph.D. Marjorie de Assis Golim is technical in charge of the Flow Cytometry Laboratory at the Clinical Hospital in Faculty of Medicine of Botucatu - UNESP, linked to the National Laboratory Network of the Ministry of Health; Professor at the Postgraduate Program in Research and Development: Medical Biotechnology (Professional Masters/Doctorate); Professor at Specialization Course in Health (lato sensu) at Clinical Hospital - UNESP;
- Ph.D. Sandra Heloísa Nunes Messias who is General Coordinator of the Biomedical Sciences course at UNIP; Professor of Courses in the Health Area at UNIP; Titular Adviser of the Regional Council of Biomedical Sciences (CRBM-1); Member of the Ethics Committee for Research on Animals at UNIP; Member of the Editorial Board of the Journal of the Health Sciences Institute; Member of the Teaching and Teaching Committee of the Regional Council of Biomedical Sciences (CRBM-1); Member of INEP’s Bank of Assessors (BASis) - qualified for double-profile.

In the present moment, the GP15 team also includes four undergraduate students of Biomedical Sciences course of UNIP - Bauru.

4 Research Areas

This section presents the main results in the group’s research areas.

4.1 Production of training material

In the early years of G3B3, the researchers observed that one of the main difficulties presented by students when being introduced to Bioinformatics was the lack of knowledge of the English language. For part of the students, the difficulty ranged from reading articles, manuals and tutorials in English required to use the software. To reduce the language barrier somewhat, the group’s teachers produced some books that are currently used in the GP15 for recruiting and training new students.

The first book developed for this purpose was ”Desenvolvimento de scripts em Software de Simulação Computacional para Visualização de Biomoléculas” [Hassunuma and de Souza, 2016], produced during the post-doctoral course of Prof. Renato M. Hassunuma, under the supervision of Prof. Aguinaldo Robinson de Souza. This book provides general guidelines for obtaining and analyzing PDB files, installing and using the RasMol program, and 38 more activities that explain the structure and classification of amino acids and proteins. The book includes suggestions for PDB files that can be used to study the different structural levels of proteins, including supersecondary structures and motifs. The book is available for free download from the publisher’s website, which allows students to purchase this material free of charge.

Although the first book is an important creative source for the group, during the training of students, we noticed that some of them got discouraged when having to look for commands in an extensive book. In addition, our first book had a number of interesting commands for visualizing biomolecules, but it missed other less-used commands that are important in research. With the proposal of producing a condensed material for quick querying of commands for the RasMol software, the book ”Guia de Comandos em Software de Simulação Computacional de Biomoléculas” [Hassunuma, 2017] was created. This digital book can also be downloaded for free on the publisher’s website and features

the menus and main commands of the RasMol program. We recommend this book to students who develop research by creating scripts for biomolecules. This material greatly simplified the search for commands and the production of three-dimensional models.

We decided to include Bioinformatics in one of the practical classes of Structural Biochemistry in the Biomedical Sciences course at UNIP - Bauru in 2018. We present the RasMol computer program to students in the protein class using the book entitled "Práticas de Bioquímica: Simulação Computacional no Estudo de Aminoácidos e Proteínas" [Hassunuma *et al*., 2018c]. This book is used as an initial guide to computer simulation of biomolecules and provides a brief introduction to installing and using the software to observe the structure and properties of amino acids and the primary, secondary, tertiary, and quaternary structures of proteins. This practical class greatly facilitated the beginning of scientific initiation projects and course completion works.

From the first half of 2014, when the G3B3 started, until the first half of 2023, 11 editions of the Training Workshop for RasMol were held. The results of these workshops were published in a book collection entitled: "Proteins Involved in Pathology - Volumes 1 to 5" [Hassunuma *et al*., 2017, 2018a,b, 2022, 2023], where participating students present scripts for various disease-related molecules such as: p53 tumor suppressor protein, Ras protein, glycoproteins viral envelope gp41 and gp120, protease, HIV-1 p24 protein reverse transcriptase, H1 1918 influenza virus hemagglutinin, H1N1 influenza virus neuraminidase, human adenovirus type 5 capsid proteins, Zika virus E and M proteins, anthrax protective antigen and lethal factor, heat-labile enterotoxin and AcrB transporter from $Escherichia\ coli$, DD-peptidase from $Streptomyces\ sp$. R61, human cellular prion protein fragment 121-230, beta-amyloid fibril, glycoproteins Ebola virus envelope GP1 and GP2, dengue virus envelope protein E, diphtheria toxin, amyloids, SARS-CoV-2 Spike, SNARE proteins, S hemoglobin, prions, among others. These results were also presented in the form of panels in several editions of 3XP0 - Exhibition of panels of G3B3 and EXPOLAB - Exhibition of the Laboratory School of Biomedical Sciences of UNIP - Bauru.

Starting in 2012, training for the RasMol software for G3B3 students and teachers resulted in the presentation of more than 200 works in various events in the form of panels, mockups, virtual models and oral presentations on several proteins of biological interest. These works were presented at national congresses and events promoted by the group itself such as workshops, 3XP0, EXPOLAB - Exposição do Laboratório Escola de Biomedicina and Projeto de Extensão Comunitária Biomedicina na Escola, among others.

4.2 Production of scripts for structural biochemical study of hemoglobins

Several researches were carried out by members of G3B3 and GP15 regarding the molecular structure of hemoglobins. In 2013, the student Tatiane Targino Gomes from the Physiotherapy Course at UNIP - Bauru and Prof. Renato M. Hassunuma [Gomes and Hassunuma, 2013] developed an initial research in order to develop scripts for the RasMol software to study hemoglobin S, related to sickle cell anemia. In this research, three-dimensional images were developed. They demonstrate the interaction among hemoglobin S molecules, which occurs due to a point mutation from the triplet GAG to GTG, which results in the substitution of the amino acid residue from glutamic acid to valine at position 6 of hemoglobin . Scripts were also developed that show residues of phenylalanine 85 and leucine 86, which are also involved in the interaction between neighboring hemoglobin S molecules. This interaction among the S hemoglobins causes their polymerization and the formation of fibrils inside the erythrocytes. These fibrils result in the formation of sickle-shaped red blood cells, which cause obstruction of capillary blood flow and its early destruction. These events result in serious clinical manifestations and complications, which are often lethal if not treated early.

In 2020, Raquel Caroline Rodrigues, student of the Biomedical Sciences course at UNIP - Bauru, Prof. Renato M. Hassunuma, Prof. Patricia C. Garcia and Prof. Sandra H. N. Messias [Rodrigues *et al*., 2020] developed several scripts with the aim of comparing different types of hemoglobin. These results were published in the digital book entitled "Hemoglobinas: estrutura bioquímica e propriedades". This book introduces the chemical structures of the pyrrole, porphyrin and heme groups, which are related to the structure of the hemoglobin molecule. Scripts were also developed for the RasMol software to produce images where the structure of hemoglobin and this molecule bound to oxygen, 2,3-bisphosphoglycerate, carbon monoxide, nitric oxide and monosaccharides are presented. The structures of fetal hemoglobin (present especially during the fetal period) and hemoglobin S (present in individuals with sickle cell anemia) are also presented. The book also discusses the Bohr effect and the cooperative binding of oxygen.

4.3 Production of scripts for structural biochemical study of the interaction among enzymes and inhibitors

From the digital books published and from various trainings offered to teachers and students, several researches were carried out from the development of scripts for the RasMol software. In G3B3, as well as in GP15, several researches were developed to observe the interaction between drugs and proteins of biological interest.

Some publications produced by the group were important both to be used in the recruitment and training of new researchers, as well as for biochemical analysis of links between drugs and proteins. So in 2014, student Heloisa de Carvalho Sampaio from the Pharmacy Course at UNIP - Bauru and Prof. Renato M. Hassunuma [Sampaio and Hassunuma, 2016] developed a research analyzing acetazolamide (AZM), a diuretic that acts by inhibiting the carbonic anhydrase II enzyme (CA II) present in the proximal convoluted tubule of the nephron. It is often used in the treatment of glaucoma, allowing the reduction of eye pressure and edema. In this study, a script developed for the RasMol software showed that, similar to other sulfonamide inhibitors of CA II, the sulfonamide amine nitrogen atom of AZM 701 binds directly to

the active-site zinc atom along with the side chains of Histidine 94, Histidine 96 and Histidine 119.

In 2017, student Barbara Sampaio Dias Martins Mansano and Prof. Renato M. Hassunuma [Mansano *et al*., 2017] from the Biomedical Sciences Course at UNIP - Bauru, developed a research analyzing the didactic possibilities of using the computer program RasMol in the teaching of macromolecules of biological interest. In this same publication, the student presents a very simple script, which shows the interaction that occurs between the drug phenylbutazone and the plasma protein albumin. This binding occurs through the binding of the drug to the 1131 OH hydroxyl group of the tyrosine 150 residue of albumin. This script, which can be reproduced in minutes by trainees, is used as an example to demonstrate one of the applications of bioinformatics programs.

Two years later, in 2019, the student Eduardo Marques Raboni of the Biomedical Sciences course at UNIP - Bauru, biomedical scientist Letícia Graziela Costa Santos de Mattos, Prof. Renato M. Hassunuma, Prof. Patricia C. Garcia and Prof. Sandra H. N. Messias developed a research that was published in the book ”Doença de Alzheimer: o Papel da Acetilcolinesterase e seus Inibidores” [Raboni *et al*., 2019]. Acetylcholinesterase (AchE) is an enzyme present in neurons that inactivates the action of the neurotransmitter acetylcholine by hydrolyzing it to acetate and choline. Thus, when Ach is inhibited, it is prevented from hydrolyzing acetylcholine, which remains active for a longer period in the synaptic cleft. This causes an improvement in cholinergic transmission. Therefore, one of the therapeutic indications for AChE inhibitors is the treatment of the symptoms of Alzheimer's disease. In this research, scripts were developed for the RasMol software that show the binding of the following inhibitors with AchE: tacrine, donepezil, galantamine, huperzine A and rivastigmine. The images produced in this research show that these inhibitors bind in different ways to 13 different amino acid residues in the following regions of AChE: catalytic triad, oxyanion cavity, anionic subsite, acylation pocket and peripheral anionic subsite.

Several studies were carried out by the G3B3 and GP15 on the inhibition of cyclooxygenase-2 (COX-2). This enzyme, also known as prostaglandin-endoperoxide synthase 2, is encoded in humans by the $Ptgs2$ gene. It is one of the main responsible for the production of prostaglandins, which result in inflammatory effects. Therefore, COX-2 is found especially in areas of inflammation. In 2016, Prof. Renato M. Hassunuma, Prof. Patricia C. Garcia and Prof. Paula M. da Silva published the book entitled ”Ciclo-Oxigenase-2 e seus inibidores” [Hassunuma *et al*., 2016], which had the participation of students Ana Laura Seneda, Kelli Colussi Pinheiro Precipito, Letícia Graziela Costa Santos, Milena da Silva Vicente, Marlon Marcio Ferreira Urata, Natalia Luca Pereira and Tatiana Cristhine Alfini Urata and biomedical doctors Everson Moretti and Priscila Manfio Queiroz. This book presents results of research carried out on the interaction of different inhibitors with COX-2: celecoxib, diclofenac, flurbiprofen, ibuprofen, indomethacin, lumiracoxib, meloxican and naproxen. The results showed that the different inhibitors bind to the same region of the COX-2 active site, but each one interacts in a different way, that is, with different amino acid residues of the enzyme.

In 2017, graduate student Tatiane Cristhine Alfini Urata and Prof. Renato M. Hassunuma from the Biomedical Sciences course at UNIP - Bauru studied the interactions of flurbiprofen with COX-2, whose results were published in the book entitled ”Interações do Flurbiprofeno com a Ciclo-Oxigenase-2” [Urata and Hassunuma, 2017]. In this research, scripts were produced that show the three regions of flurbiprofen that interact with COX-2: 1) the carboxylate group of flurbiprofen binds to the amino acid residues Arginine 120 and Tyrosine 355, 2) the fluorophenyl ring binds to Alanine 527 and Valine 349 and 3) the distal aryl ring binds to Alanine 527, Glycine 526 and Tyrosine 385.

In the same year, graduate student Milena da Silva Vicente of the Pharmacy Course at UNIP - Bauru and Prof. Renato M. Hassunuma studied the interactions of ibuprofen with COX-2, whose results were published in the book titled ”Ibuprofeno: Interações com a Albumina Sérica and Ciclo-oxigenase-2” [da Silva Vicente and Hassunuma, 2017]. In this research, scripts were produced that show the three regions of flurbiprofen: 1) acidic side chain that has a carboxylic acid, 2) the benzene ring, and 3) the hydrophobic side chain. The scripts produced show the interaction of the three regions of flurbiprofen that can be linked to the active sites of albumin: the I-FA3 site and the I-FA6 site. At the I-FA3 site, interactions with albumin occur as follows: a) the acidic side chain binds to the amino acid residues Arginine 410, Lysine 414, Serine 489 and Tyrosine 411 of albumin, b) the benzene ring binds to the Leucine 387 and Leucine 430, and c) the hydrophobic side chain binds to Alanine 449, Isoleucine 388, Phenylalanine 403 and Valine 433. At the I-FA6 site, bonds of ibuprofen with albumin occur as follows: a) the acidic side chain binds to the amino acid residues Arginine 209, Leucine 481, Lysine 351, Serine 480 and Valine 482 of albumin, b) the benzene ring binds to Leucine 347, and c) the hydrophobic side chain binds to Alanine 213, Glutamine 354, Leucine 327 and Leucine 331. Regarding the binding to COX-2, the bonds occur as follows: a) the acidic side chain binds to the amino acid residues Leucine 360 and Valine 350 of COX-2, b) the benzene ring binds to Alanine 528 and Valine 350, and c) the hydrophobic side chain binds to Tryptophan 388, Methionine 523, Valine 524, Glycine 527, Alanine 528 and Serine 531.

In 2021, the student Gabrielle Pires, Prof. Renato M. Hassunuma and Prof. Patrícia C. Garcia [Pires *et al*., 2021] performed a structural biochemical study of the nonspecific binding of acetylsalicylic acid (ASA) to cyclooxygenase-1 and -2 isoforms (COX-1 and COX-2). ASA was once one of the best-selling drugs in the world. This fact is due, in part, to the fact that it has efficient anti-inflammatory, analgesic and antipyretic properties. Its pharmacological effects result from the inhibition of an enzyme produced during inflammatory processes called COX-2, which results in the inhibition of the production of prostaglandins (PGs) responsible for various inflammatory activities. However, the chronic use of ASA results in serious unwanted effects such as the development of gastric ulcers, which results from the inhibition of COX-1. In this study, scripts were developed for the RasMol 2.7.4.2 software, demonstrating the drug-enzyme binding areas. In the images obtained, it was possible to observe

that ASA is able to bind to COX-1 and COX-2, through the same serine 530 residue. Therefore, the pharmacological effects of ASA derive from its binding with COX-2 and the unwanted effects of COX-1 inhibition. The structural similarity of COX-1 and COX-2 and the binding to the same serine 530 residue explain the nonspecificity of the binding of ASA to the two isoforms and the effects observed in the use of this drug.

Another study in the same research line was carried in 2023 by Amanda Cristina Moço, student of the Biomedical Sciences Course at UNIP - Bauru. They studied the interaction between the anti-inflammatory indomethacin (IMN) and COX-2. In this research scripts were developed for the computer program RasMol, whose produced images showed that the IMN binds to a relatively deep region of a hydrophobic channel of COX-2. The binding of IMN and COX-2 occurs through an interaction between an IMN chlorine atom with the amino acid residue leucine 384 of COX-2. The stabilization of the bond between these substances also occurs through hydrophobic interactions of the benzoyl region of the IMN with leucine 384, phenylalanine 381, tyrosine 385 and tryptophan 387, as well as the oxygen atom of the benzoyl group of the IMN with the hydroxyl of the side chain. of serine 530 and the valine 349 side chain of COX-2. The results obtained in this research were published in the book entitled "Indometacina: uma visão bioquímica" [Moço *et al*., 2022].

A study similar to the previous one was developed in 2022 by Grazieli Cristina Ramiro, another student of the Biomedical Sciences Course, where scripts were developed to observe the biochemical interactions between diclofenac (DFN) and cyclooxygenase-2 (COX-2). The study developed illustrations that show the interactions of: 1) dichlorophenyl group of DFN with valines 349 and 523, alanine 527 and leucine 531 of COX-2 by van der Waals interactions; 2) phenylacetic group of DFN with hydrophobic residues of leucines 352 and 384, tyrosine 385 and tryptophan 387 of COX-2 by van der Waals interactions; 3) phenylacetic group of DFN with methionine 522 and glycine 526 of COX-2; 4) carbonyl group of DFN with tyrosine 385 and serine 530 by hydrogen bonds. The results of this research were published in the book entitled "Diclofenaco: uma visão bioquímica" [Ramiro *et al*., 2022].

4.4 Production of scripts for structural study of disease-related proteins

In 2016, student Ana Laura Seneda from the Biomedical Sciences Course at UNIP - Bauru and Prof. Renato M. Hassunuma [Seneda and Hassunuma, 2016] conducted a survey where scripts for structural analysis of the p53 protein were developed. $p53$ is a tumor suppressor gene that encodes the p53 protein which regulates cell cycle and apoptosis. Mutations in the $p53$ gene are responsible for approximately 50% of human tumors, including those in the bladder, brain, breast, cervix, colon, esophagus, larynx, liver, lung, ovary, pancreas, prostate, skin, stomach and thyroid. In the research, scripts were developed that show: a) the amino acid residues that most frequently undergo mutations (Arginine 175, Arginine 248, Arginine 249, Arginine 273, Arginine 282 and Glycine 245), b) the amino acid residues that interact with the DNA molecule (Arginine 248 and Arginine 273), c) amino acid residues that participate in stabilizing the binding of p53 protein with DNA (Lysine 120, Serine 241, Alanine 276, Cysteine 277, Arginine 280, Aspartic Acid 281, Arginine 283 and the loop-leaf-helix motif formed by residues 259 to 289).

4.5 Production of scripts for biochemical structural studies of gamete proteins involved in the fertilization process

Several researches were carried out in order to study sperm and oocyte proteins and how they bind during the fertilization process. In 2020, the student Grazieli Cristina Ramiro of the Biomedical Sciences course at UNIP - Bauru, Prof. Renato M. Hassunuma, Prof. Patricia C. Garcia and Profa. Sandra H. N. Messias developed a study on several proteins present in gametes, which participate in the fertilization process. The results of this research were published in the book "Fecundação: Uma Visão Bioquímica das Principais Proteínas Envolvidas" [Ramiro *et al*., 2020b]. In this book, scripts developed for the computer program RasMol are presented that show the structure of the following proteins present in sperm: Izumo 1, acrosin, sperm lysozyme-like protein 1, CD9, CD46, disintegrin and metalloprotease 2, spermdesins, Sp18, PKDREJ, sperm adhesion molecule 1, zonadesin, secreted proteins rich in cystine 1 and 2. The book also presents the structures of the following proteins present in oocytes: Juno, sperm acrosomal SLLP1 binding, $\alpha 6\beta 1$, CD81, ZP1, ZP2, ZP3, ZP4.

The most important research of GP15 on the subject was carried out in 2020. The student Grazieli Cristina Ramiro, Prof. Renato M. Hassunuma and Profa. Patrícia C. Garcia [Ramiro *et al*., 2020a] developed a research where the structures of Izumo 1 and Juno proteins were studied, as well as the interaction between these proteins. In this study, scripts were developed for the RasMol software that show that Izumo 1 has 377 amino acid residues, with a large extracellular region, a single transmembrane region, and a short cytoplasmic tail. The structure of its extracellular region is formed by: a) bundle of four alpha-helices: formed by amino acid residues 27-44, 47-62, 80-99, 104-133; b) beta clip: consisting of two parallel beta strands constituted by residues 141-148 and 153-160; c) intermediate region: formed by an alpha helix (residues 70-75) and a beta strand (residues 77-79); and a carboxy-terminal immunoglobulin-like domain: formed by residues 164-256, where two alpha helices and seven beta strands are observed. Some regions of the molecule are stabilized through disulfide bonds, formed by the interaction between five pairs of sulfur atoms. The Juno protein has 221 amino acid residues and its structure is formed by: a) nine alpha-helices: constituted by amino acid residues 44-51, 57-66, 83-100, 101-104, 126-137, 169-173 , 175-183, 194-198, 212-223 and b) six beta strands: consisting of amino acid residues 107-108, 119-120, 123-125, 141-142, 167-168, 188-190. Some regions of the molecule are stabilized through disulfide bonds, formed by the interaction between 7 pairs of sulfur atoms. Scripts were also de-

veloped that show the interactions of 22 amino acid residues from three regions of Izumo 1 (four alpha-helix bundle, intermediate region, and carboxy-terminal immunoglobulin-like domain) with 19 amino acid residues from Juno. These interactions occur through bonds such as: Van der Waals forces, hydrophobic and aromatic interactions, intermolecular salt bridges and hydrogen bonds. All these interactions are separated by a space of 3 Å, suggesting that they are weak in nature.

Another study was developed in 2021 by the student Grazieli Cristina Ramiro, Prof. Renato M. Hassunuma and Profa. Patrícia C. Garcia [Ramiro *et al*., 2021], comparing the structure of zona pellucida glycoproteins (ZPs) using scripts developed for the RasMol software. The zona pellucida present in human oocytes is composed of four glycoproteins: ZP1, ZP2, ZP3 and ZP4. However, only ZP2 and ZP3 participate in the link between oocyte and sperm during the fertilization process. The heterogeneity observed in the biochemical structure of these glycoproteins allows them to establish chemical bonds with different sperm proteins: ZP2 binds to pro-acrosin/acrosin, while ZP3 binds to its receptor, ZP3R. Comparison of the structure of ZPs demonstrated the intense heterogeneity between these proteins. This is due to the various post-translational modifications, such as glycosylation and sulphation, that occur in these glycoproteins; whereas only a single 260 amino acid sequence, called the ZP module, remains common to all ZPs.

4.6 Production of scripts for structural biochemical study of other different types of proteins

In 2014, graduate student Leandro Martinez from the Biomedical Sciences Course at UNIP - Bauru and Prof. Renato M. Hassunuma [Martinez and Hassunuma, 2014] developed research on the structure of human pyruvate dehydrogenase (E1). This enzyme plays an important role in carbohydrate metabolism, as it is part of an enzyme complex that participates in the conversion of pyruvate (produced by glycolysis) into acetyl-coenzyme A (which will be used in the Krebs cycle). Furthermore, E1 bad activity causes mitochondriopathies such as Leigh's syndrome which causes an energy deficit especially in the central nervous system, where it can lead to congenital brain malformation due to lack of energy during neural development. The developed scripts allowed the observation of the E1 structure that corresponds to a $\alpha 2\beta 2$ heterotetramer, formed by four tetrahedrally organized subunits, two alpha subunits and two beta subunits. Each alpha subunit is composed of a chain of six parallel beta sheets packed against five alpha helices for a total of 10 helices. Beta sheets and alpha helices are involved in the binding of the Mg^{+2} ion and the thiamine pyrophosphate (TPP) fragment, which are cofactors for the decarboxylation of the pyruvate molecule, which is converted to acetyl-CoA.

Four years later, in 2018, student Angélica Alves Pinheiro from the Biological Sciences Course at UNIP - Bauru and Prof. Renato Massaharu Hassunuma developed several structural biochemical studies that were published in the book entitled "Trombina: precursores, ligantes e inibidores" [Pinheiro and Hassunuma, 2018]. In this study, the researchers developed scripts for the RasMol software to visualize the residues of different regions of the thrombin molecule: catalytic triad, exosite I, exosite II. Scripts have been developed that illustrate the precursors of thrombin: pre-thrombin-1 and -2. Scripts were also developed to visualize the interaction of these regions with different ligands: fibrinogen (which is converted to fibrin by thrombin in the blood coagulation process), thrombomodulin (which binds to thrombin, activating protein C and inactivating factors Va and VIIIa of the complement system), hirulog (protein produced by leeches that inhibits thrombin) and staphylocoagulase (protein produced by the bacterium $Staphylococcus\ aureus$, which is able to bind thrombin to form fibrin without activating other factors in the coagulation cascade).

More recently, in 2019, Giovana Roberto Salado, student of the Biomedical Sciences Course at UNIP - Bauru, Prof. Renato M. Hassunuma, Prof. Michele Janegitz Acorci Valério, Prof. Patricia C Garcia and Prof. Sandra Heloísa Nunes Messias [Salado *et al*., 2019] carried out a series of structural studies with interferons (IFNs). IFNs are cytokines produced in response to infection by a virus in a wide variety of cells, making up the first line of defense against viral infection in mammals. There are three groups of IFNs: 1) Type I interferons (IFNs-I) that are synthesized by most cells in direct response to a viral infection, due to the presence of double-stranded viral RNA in the infected cell. They play an antiviral, antiproliferative and immunoregulatory role. In this group are interferon alpha (IFN-α), beta (IFN-β) and omega (IFN-ω); 2) Type II interferons are synthesized in response to mitogenic and antigenic stimuli, being produced by specific cells of the immune system, such as T and Natural Killer lymphocytes. This class includes gamma interferons (IFNs-γ); 3) Type III interferons perform activities similar to those of IFN-I, such as the regulation of class I MHC expression, being produced in response to some viral infections. In this group are the lambda interferons (INF-λ). The results obtained in this research were published in a digital book entitled: "Imunologia - Volume 1: Interferons", where the biochemical structures of IFN-α2a, β1a, ω1 and λ1, and the dimer of interferon γ, produced from scripts for the RasMol software.

In 2020, Pamela Dominique de Oliveira [de Oliveira and Hassunuma, 2020], an undergraduate student of the Biomedical Sciences Course at UNIP - Bauru, developed a survey that analyzed the three main exotoxins of the bacterium $Bacillus\ anthracis$, under the guidance of Prof. Renato Massaharu Hassunuma, Prof. Patrícia Carvalho Garcia and Prof. Sandra Heloísa Nunes Messias. In this research, structural biochemical analyzes were carried out from scripts developed to observe the monomer and heptamer of the protective antigen, which forms a ring that allows the binding of other toxins: the edema factor and the lethal factor. Thus, there are two main toxins of $B.\ anthracis$ called edematous toxin (EdTx) and lethal toxin (LeTx). EdTx is constituted by the edema factor and the heptamer formed by the protective antigen, being responsible for inducing the intracellular accumulation of cyclic adenosine monophosphate cAMP, which causes extravasation of fluid into the extracellular environment. This outflow of fluid causes the edema characteristic of anthrax in-

jury. LeTx is composed of the lethal factor and the heptamer formed by the protective antigen. LeTx interacts directly with immune system cells, mainly macrophages, inducing the release of pro-inflammatory mediators, such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β), triggering an intense response inflammatory. LF corresponds to the active subunit of LeTX, which is capable of cleaving peptides such as mitogen-activated protein kinase (MAPKKs). The inactivation of MAPKKs leads to inhibition of cell proliferation and differentiation of target cells, in addition to stimulating apoptosis [Nablo *et al*., 2013].The results of this research were published in the book entitled "Antraz: estrutura bioquímica e patogenia das toxinas" [de Oliveira *et al*., 2020].

In 2022, Anna Beatriz Silva Gebim, a student of the Biomedical Sciences Course at UNIP - Bauru, developed scripts for the RasMol software to create a gamebook to demonstrate components of the telomere-telomerase complex. The telomere represents the end of the chromosomes, formed by repetitions of the TTAGGG nucleotide sequence. During the DNA duplication process, the enzyme DNA polymerase is not able to transcribe the end of the 3' strand of the DNA molecule, which could cause telomere shortening. This shortening is prevented by the action of the enzyme telomerase, a reverse transcriptase, capable of synthesizing the end of the DNA strand, as it has an RNA template strand inside that is complementary to the telomere sequence. The sets of proteins responsible for protecting the telomeric DNA are called the shelterin complex. The gamebook presents figures of the following structures of the human telomere-telomerase complex: telomerase reverse transcriptase (TERT) and telomerase RNA component (TERC) of telomerase; part of a nucleosome: formed by a segment of DNA and histones H2A and H2B and part of the shelterin complex (formed by POT1 and TPP1 proteins). The results obtained in this research were published in the book entitled "7QXS: o segredo do vampiro, livro-jogo sobre a telomerase" [Gebim *et al*., 2022].

4.7 Protein comparison by homology

In this line of research, we perform amino acid residue sequence alignments and compare similar proteins that represent protein domains conserved in molecular evolution.

The first study in this research line was conducted in 2016 by Eduardo Nascimbem Turini and Renato Massaharu Hassunuma [Turini and Hassunuma, 2016]. They developed a survey comparing stretches of prions from the following animal species: human (*Homo sapiens*), bull (*Bos taurus*), horse (*Equus caballus*), elk (*Cervus elaphus nelsoni*), tammar wallaby (*Macropus eugenii*), pig (*Sus scrofa*), sheep (*Ovis aries*), dog (*Canis lupus familiaris*), cat (*Felis catus*), rabbit (*Oryctolagus cuniculus*), bank vole (*Myodes glareolus*), mouse (*Mus musculus*), chicken (*Gallus gallus*), turtle (*Trachemys scripta*) and frog (*Xenopus laevis*). The primary structure of the proteins of these species was analyzed and compared in pairs using the Sequence & Structure Alignment tool available on the Protein Data Bank website. Through the alignment of residues using the Needleman-Wunsch method, it was possible to verify the number of identical, similar, and discrepant residues and areas indicating insertion/deletion of the proteins compared to each other. The three-dimensional structure of the prion stretches of the mentioned species were compared by RasMol scripts and using the TM-align tool, that is an algorithm for sequence independent protein structure comparisons. For two protein structures of unknown equivalence, TM-align first generates optimized residue-to-residue alignment based on structural similarity using heuristic dynamic programming interactions. The prions that showed the greatest similarity were those of cat and dog (96.40%) and ox and human (92.86%), and those that showed the greatest discrepancy were frog and mouse prions (33.93%). The results obtained allowed to conclude that species that are evolutionary closer have a greater number of identical amino acid residues and that more distant species, a greater percentage of non-identical residues. Therefore, it can be concluded that prions seem to be an appropriate model for the study of the molecular clock theory, which may contribute to future investigations aimed at understanding the evolutionary process of species.

A similar work was carried out by Gabriely Crivari de Almeida Lima, Renato Massaharu Hassunuma and Patrícia Carvalho Garcia in 2021 [Lima *et al*., 2021], studying human prion proteins. In this research, the RasMol program was used to compare the secondary structure of human cellular prion protein (PrPC) and human prion protein with scrapie (PrPSc). Comparing the stretches formed by amino acid residues 126 to 228, it was verified that PrPC has three alpha helices and two beta strands, while in PrPSc the same stretch has six beta strands. The change in the secondary structure of PrPSc promotes the interaction between the molecules, forming fibrils that characterize the amyloid deposits observed in human prion diseases such as Creutzfeldt-Jakob disease.

4.8 Researches in Virtual Reality

Virtual reality corresponds to the association of an interface technology with an operating system that produces three-dimensional and 360º images, which promote a feeling of immersion in a virtual environment. For immersion to occur in real time, it is necessary to use various equipment and computational resources.

In 2019, Raquel Caroline Rodrigues, student of the Biomedical Sciences Course at UNIP - Bauru, and Prof. Renato M. Hassunuma [Rodrigues and Hassunuma, 2019] developed a research using the Molecule Viewer® software to produce three-dimensional images of proteins in virtual reality. In this study, the VR BOX® - Virtual Reality Glasses was also used. The Molecular Viewer® software was developed by the Autodesk® company, being a computer program that allows the visualization of molecular prototypes in three dimensions for scientists and apprentices who are interested in this new technological solution. Molecule Viewer® provides interactive and customizable content instantly, without the need to download or own a specific program. It can be used in any browser, with only the help of the Protein Data Bank website, which provides the PDB file that allows the visualization of the specific biomolecule to be studied. Using the Molecular Viewer® and obtaining the PDB file from the

Protein Data Bank website is free of charge. When observing the Molecule Viewer®, we have the option of viewing, immersion and movement of molecules, such as hemoglobin, using simple and intuitive steps. In addition, it allows all the built content to be used on smartphones, which complemented by the use of VR glasses (for virtual reality) promote the complete immersion in a three-dimensional experience. In the research, a beta version of the Molecule Viewer® software was used, which was available for free until August 21, 2018, being suspended after this date.

4.9 Researches using Machine Learning (ML)

Machine learning (ML) can be considered a type of artificial intelligence, which can be defined as the ability of a machine to imitate human intelligence. ML can be used for the purpose of performing complex tasks simulating problem solving performed by human beings.

This technology was used by Marjorie A. Golim [Braz *et al*., 2021] in a cohort study in cirrhotic patients whose objective was to identify the immunological factors involved in the regression of liver stiffness in chronic hepatitis C and to characterize possible serum biomarkers with prognostic value. The ML was used in this research due to the large number of variables. A ML software was used for a pre-selection of the most relevant attributes to predict fibrosis regression. In this research, the software used was an attribute evaluator called InfoGainAttributeEval from the Weka software. Machine learning (ML) results, together with ROC curve and linear discriminant analysis showed that TCD4+ lymphocytes are the most important biomarkers for predicting regression. The research suggested that there is a difference in the profile of circulating immune cells in regressors and non-regressors, thus allowing the development of a regression model of liver stiffness after sustained virological response.

4.10 Research on Bioinformatics games

In 2022, GP15 obtained authorization from the Foldit Team to publish the first book about the Foldit game. In short, Foldit® can be conceptualized as a game that has the objective of repositioning the parts of an unfolded protein to reach the three-dimensional structure closest to reality, through a score. The protein folding puzzles presented during the game can be played in offline single player or online multiplayer modes. The puzzles are divided into two groups: introductory (which make up the tutorials) and scientific (which are open to all players and which generally have the objective of determining the unknown biochemical structure of a protein). In this line of research, GP15 published the book ”Foldit: Solving puzzles to learn about proteins” [Hassunuma and Yonezawa, 2023b], the book chapter entitled ”A Challenge in Teaching Biochemistry: Ramachandran’s Map for Game-Based Learning”, from the book ”Education through a multiplicity of perspectives: knowledge, challenges and reflections” [Hassunuma and Yonezawa, 2023c], the article ”Didactic application of the Foldit game in teaching protein design and editing” [Hassunuma and Yonezawa, 2023a] and eight other panels presented at national congresses.

5 History as a model, perspectives and future directions

The history of the G3B3 and the GP15 are mixed and it can be considered an excellent example of how a study group can be structured for the development of a research group. Summing up the history of the teams, we can mention some items that were important for the consolidation of the GP15:

1. Production of training material: it allowed more students, who had a learning difficulty due to lack of knowledge or mastery of the English language, to participate in the workshops and learn more effectively;

2. Development of workshops to train students and teachers: training for the use of computer programs in the area of Bioinformatics allowed the initial consolidation of the team of the G3B3 study group;

3. Production of panels, mockups and virtual models: it allowed G3B3 members to apply their knowledge obtained during the training phase;

4. Holding of local events: the holding of events promoted by the Biomedical Sciences course at UNIP – Bauru such as: ‘3XP0’ and ‘EXPOLAB – Exposição do Laboratório Escola de Biomedicina’ was a motivating factor for the G3B3 members to develop their work and was also a way of promoting locally the production developed by the team;

5. Development of scientific initiation projects and course conclusion works: it allowed students who received training in computer software to develop research more easily;

6. Production of digital books and participation in the ‘Biomedicina na Escola’ Community Extension Project: allowed the results obtained in workshops and training for the use of Bioinformatics computer programs to be disseminated to the external community.

All these factors were important for the consolidation of the G3B3 team and for the establishment of the GP15 research group team. This same working model can be used by other universities to create study groups that have the potential to be transformed into research groups in the future. Thus, the focus of our group has been the development of scripts for the production of three-dimensional images of proteins, which can be verified and evaluated by the quantity and quality of publications produced by the group. Our perspective is that in the coming years we can continue in search of new software that can vary the production of images and that can add more information to our research. Future work will include topics such as surveying computer programs available on the internet that can be included in staff training; production of new materials based on selected software; and the development of future research based on computer programs that were included in the workshops.

6 Further Information

Further information regarding GP15 may be found at Directory of Research Groups in Brazil, available on the Lattes Platform via the link::

`http://dgp.cnpq.br/dgp/espelhogrupo/5285181734512763`

Other questions regarding GP15 should be emailed to the group leaders:

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Competing interests

The authors declare that there isn't conflict of interests.

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