Introduction to Molecular Pharmacology and Computational Biology

James Aaron Erang [1]

[1]Biotechnology and Analytical Laboratory, Department of Biological Sciences, Central Luzon State University

August 2024

Case Study: Cancer

Brief Review of Cancer

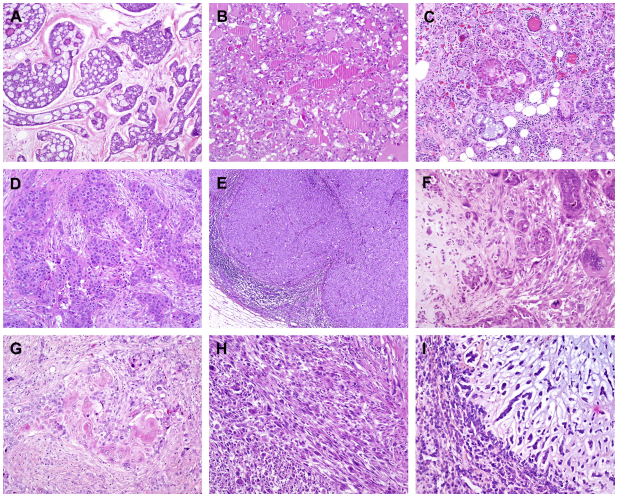


Figure: Weigelt, Geyer & Reis-Filho (2010) [10]: Histological special types of breast cancer.

Case Study: Cancer

Molecular Hallmarks of Cancer

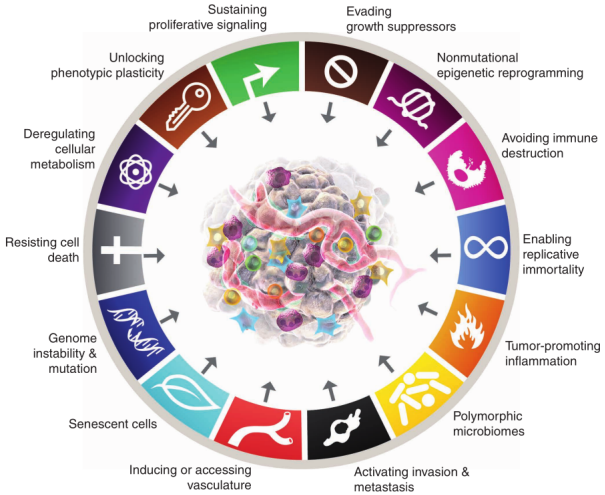


Figure: Hanahan (2022) [3]: The hallmarks of cancer and its new additions.

Case Study: Cancer

Growth Signal Pathway in Cancer

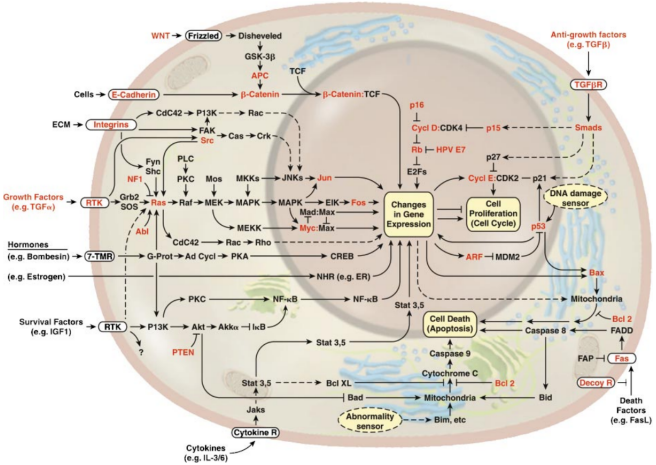


Figure: Hanahan & Weinberg (2000): Integrated “circuit” of the cell.

Case Study: Cancer

p53 Signaling Pathway

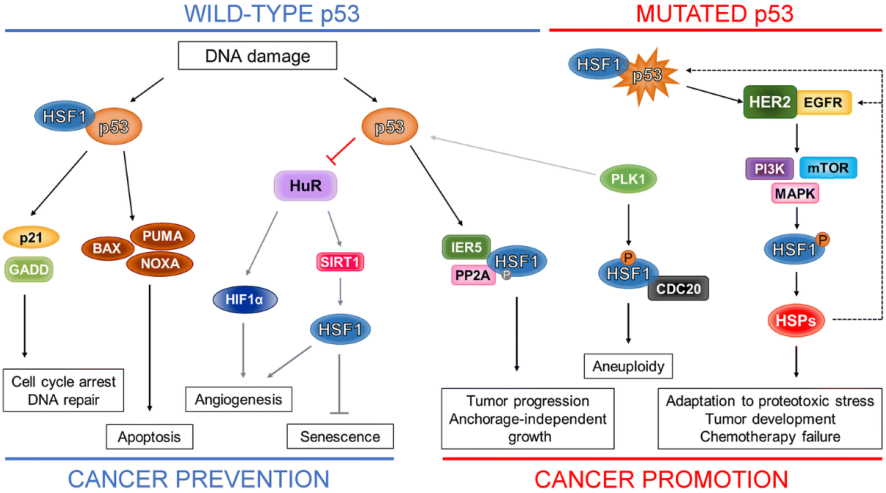


Figure: Toma-Jonik *et al.* (2019) [8]: Role of p53 signaling in carcinogenesis and tumorigenesis.

Case Study: Cancer

Resveratrol and Its Derivatives Against Cancer

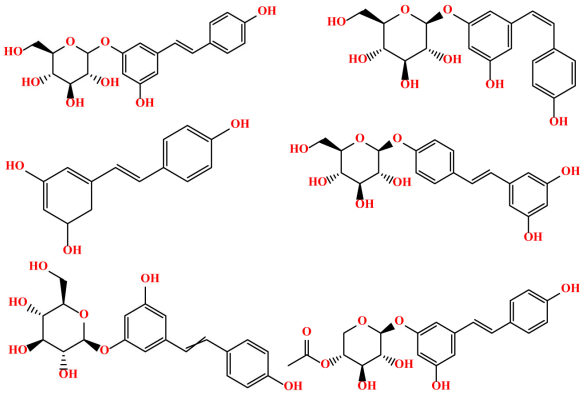


Figure: Resveratrol and its derivatives as ligand against APC (Adenomatous polyposis coli).

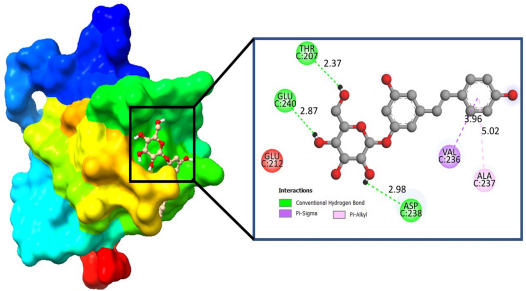
Ligand	Binding affinity ($kcal/mol$)
03	-7.7
11	-6.3
17	-6.9
24	-7.3
28	-7.0
29	-7.9
39	-6.1

Table: Binding affinity of each ligand with human armadillo repeats of APC.

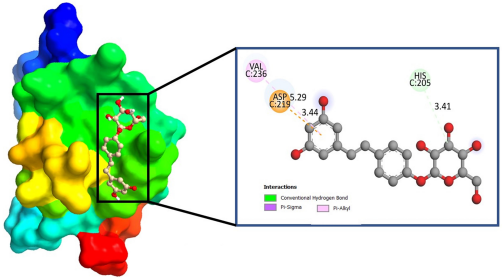
Case Study: Cancer

Binding Site Analysis of Resveratrol Derivatives

Given an array of candidate molecules for drugs, what are the criteria that can be utilized to determine what drugs are likely work in a particular disease?



(a) Resveratrol 3-β-mono-D-glucoside ($-7.7kcal/mol$)

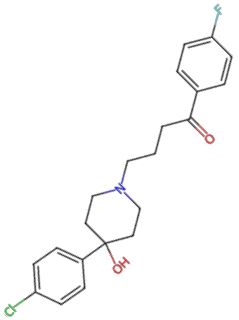


(b) Resveratrol 3-Glucoside ($-7.9kcal/mol$)

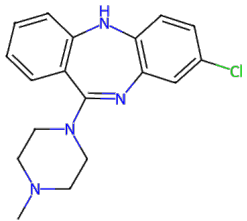
Figure: Akash *et al.* (2024) [1]: Docking and active site analysis of Resveratrol derivates against human armadillo repeats of Adenomatous polyposis coli.

Case Study: Psychosis, Anxiety and Depression

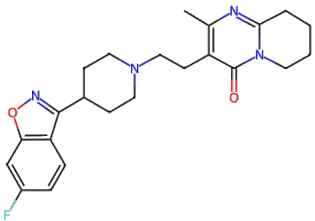
5-HT_{2A} and D_2DR Involved Neuro- Psychological/Biological Disorders



(a) **Haloperidol**
Fast-Off at D_2DR
$K(D_2), nM$



(b) **Clozapine**
Antagonism of D_2DR, 5-HT_{2A}
$K(D_2DR)/K(5\text{-}HT_{2A}), nM$



(c) **Risperidone**
Inverse agonism of 5-HT_{2A}
K for $5\text{-}HT_{2A}$, nM

Figure: Seeman (2002) [7]: Different theories on molecular mechanisms atypical action of antipsychotics.

Determination of Drug Activity

Brief Insight on Molecular Pharmacology

The activity of drug is defined by its binding affinity to a particular receptor known to be associated with the disease of interest.

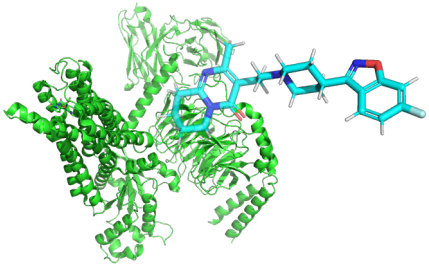


Figure: Interaction and binding of an atypical antipsychotic, risperidone, with D_2 dopamine receptor (D_2 DR).

Determination of Drug Activity

Preview of Computational Biology

$$\begin{bmatrix} \mathrm{d}x_t \\ \mathrm{d}p_t \end{bmatrix} = \begin{bmatrix} M^{-1}p_t \\ 0 \end{bmatrix} \mathrm{d}t + \begin{bmatrix} 0 \\ -\nabla_{x_t} U(x_t) \end{bmatrix} \mathrm{d}t + [\text{thermostat}] \tag{1}$$

$$\begin{aligned} e^{\mathcal{L}_T \Delta T} \rho = &\left(\frac{\beta}{2\pi}\right)^{3N/2} |\boldsymbol{M}(1 - e^{-2\gamma \Delta T})|^{-1/2} \\ &\cdot \int \mathrm{d}p_0 \, \rho(x, P_0) \exp\left[-\frac{\beta}{2}(p - e^{-2\gamma \Delta T} p_0)^T \right. \\ &\left. \cdot M^{-1}(1 - e^{-2\gamma \Delta T})(p - e^{-2\gamma \Delta T} p_0) \right] \end{aligned} \tag{2}$$

$$\frac{\partial}{\partial t}\rho = \mathcal{L}\rho = (\mathcal{L}_x + \mathcal{L}_p + \mathcal{L}_T)\rho \tag{3}$$

Equation Set 1: Amber24 simulated annealing with NMR derived restraints (SANDERS) force field for proteins, nucleic acids, several water models and organic solvents.

The Good, The Bad and The **Ugly**

How to Model a Protein

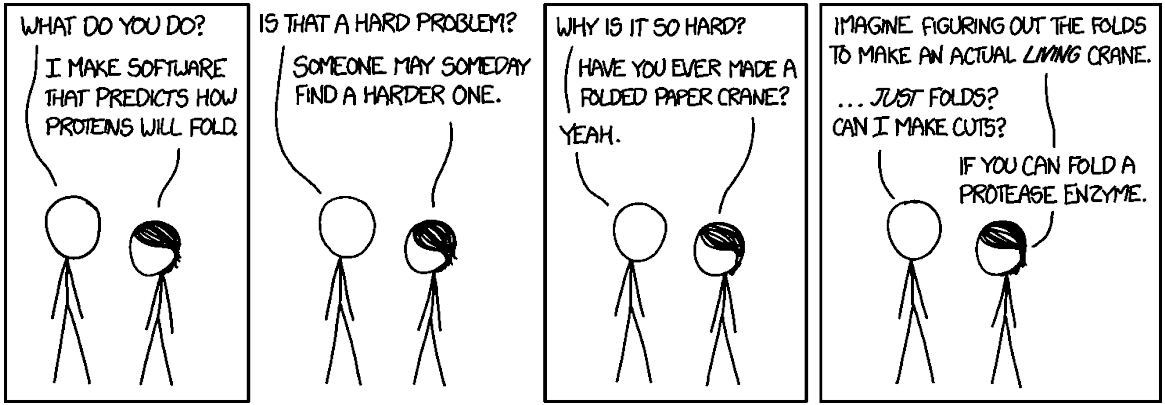


Figure: XKCD: 1430 (“Proteins”): What does a computational biologist do?

The Good, The Bad and The **Ugly**

Computational Biology vs Bioinformatics vs "*In silico*" Studies

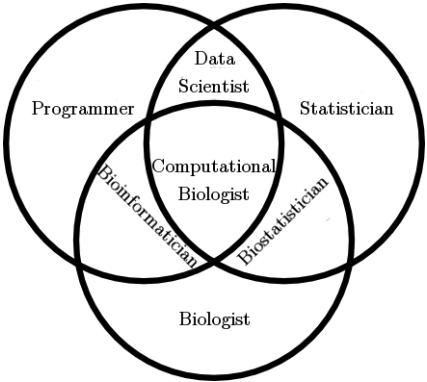


Figure: The Good, the bad and the ugly: What defines computational biologists, bioinformaticians and those who say "i do *in silico* studies?"

Despite the major overlaps of each field, there are defining features that characterizes and distinguishes them from one another.

Workshop Contents and Syllabus

Description

The workshop is heavily centered on computational drug discovery and design for diseases and disorders with underlying molecular mechanism.

Description

Application of biological and computational chemistry, molecular pharmacology, mathematical abstraction and computational techniques in biology; computer-aided drug design and discovery; and conceptualization of *in silico* methodologies.

Specialization

The workshop specializes on computational discovery and design of drug for diseases with well-defined underlying molecular mechanism such as neurological and psychological diseases (e.g. Parkinson's, Anxiety, Depression and Psychosis), cancer (particularly Leukemia, Non Small Cell Lung Cancer and Neuroblastoma) and diabetes (Type I and II).

Workshop Contents and Syllabus

Prerequisites

Presented here are the suggested prerequisites for advanced study of computational biology:

1. Calculus I, II, III
2. Linear Algebra
3. Bayesian Statistics
4. Computer Science (Programming) I, II, III
5. Discrete Mathematics
6. Algorithms and Data Structures
7. Linux and System Administration
8. Advanced Molecular and Cellular Biology
9. Pharmacology
10. Quantum Physics/Physical Chemistry
11. Biochemistry and Organic Chemistry

Workshop Contents and Syllabus

Overview of Contents

Case Study and Computational Biology

Define computational biology and how it is a product of interrelation of different fields. Presentation of real world applications via demonstration of computer-aided drug design and its potentials and implications.

1. Case Study of Cancer:
   1. Brief Introduction to Cancer.
   2. p53 Signaling Pathway.
   3. Presentation of Ligand With Affinity Data.
2. Case Study of Neuropsychiatric Diseases: Psychosis, Anxiety and Depression:
   1. Three mechanism of actions.
   2. Role of 5-HT_{2A} and D_2DR on neuropsychiatric diseases.
   3. Insight on Risperidone.
3. Definition of computational biology.
4. Computational Biology vs Bioinformatics vs "*In Silico*" studies.

Workshop Contents and Syllabus

Overview of Contents

Brief Review on Biochemistry and Quantum Chemistry

Review the basic and fundamental concepts of the macromolecules/biomolecules of life emphasizing the relation of conformation/structure and function.

1. Quantum mechanical basis of molecules: Molecular Orbital Theory.
2. VSEPR Theory, Valence Bond Theory: Formation of bonds
3. Description of intermolecular forces.
4. Physicochemical properties of macromolecules in physical perspective.
5. K_D and K_i and its implications:

$$r = \frac{\sum_{i=1}^{n}\left(\prod_{j=1}^{i}\frac{n-j+1}{j}\left(\frac{[\mathrm{L}]}{K_D}\right)^{i}\right)}{1+\sum_{i=1}^{n}\left(\frac{n-j+1}{j}\right)\left(\frac{[\mathrm{L}]}{K_D}\right)^{i}} = \frac{\sum_{i=1}^{n} i\binom{n}{i}\left(\frac{[\mathrm{L}]}{K_D}\right)^{i}}{1+\sum_{i=1}^{n}\binom{n}{i}\left(\frac{[\mathrm{L}]}{K_D}\right)^{i}}$$

Workshop Contents

Overview of Contents

Fundamental Molecular Pharmacology

Molecular basis of drugs and pathophysiology, development and mechanism of diseases and role of chemistry in drug discovery and development.

1. Molecular mechanisms of drugs: Agonism, Antagonism and Inverse Agonism.
2. Comprehensive description of receptors.
3. Molecular pathology of some diseases.
4. Properties and interactions of different complexes.
5. Formation of transcriptional activators and repressors.
6. Role of dissociation constant K_D, inhibition constant K_i and association constant K_A in ADMET profile of drugs.
7. Lipinski's Criteria (The RO5 of drug development).
8. Relationship of molecular structure and drug activity.

Workshop Contents

Overview of Contents

Basic Molecular Docking

Explore the fundamental concept of molecular docking using the knowledge and theoretical background discussed previously.

1. Hands on demonstration of UCSF Chimera X.
2. Exploration of Schrödinger's Python Molecular Graphics.
3. Practical application using real world data from clinical trials.
4. Interpretation and potential implications.

Workshop Contents

Overview of Contents

Programming I: Basic Concept of Python Programming

Introduction to programming concepts and Python programming language.

1. Introduction to language: `print("hello, world!")`.
2. Variables.
3. Arithmetic operators.
4. Fundamental data structures and classes.
5. Conditional statements.
6. Loops.
7. Functions.
    1. Introduction to propositional calculus.
    2. Logical operators.
    3. Compound propositions.

Workshop Contents

Programming II: Advanced Python Programming

Transition to different paradigm of software writing, introduction of modules and external libraries for program extensibility and other advanced features of Python.

1. Introduction of generators.
2. Decorators.
3. Transition to object-oriented programming (OOP).
4. Advanced data manipulation.
5. External data types and structures.
6. Data visualization.
7. Matrix calculations.
8. Computational techniques.

References I

[1] Shopnil Akash et al. “In silico evaluation of anti-colorectal cancer inhibitors by Resveratrol derivatives targeting Armadillo repeats domain of APC: molecular docking and molecular dynamics simulation”. English. In: *Front. Oncol.* 14 (Apr. 2024). Publisher: Frontiers. ISSN: 2234-943X. DOI: 10.3389/fonc.2024.1360745. URL: https://www.frontiersin.org/journals/oncology/articles/10.3389/fonc.2024.1360745/full (visited on 08/25/2024).

[2] Adnan Aziz, Tsung-Hsien Lee, and Amit Prakash. *Elements of Programming Interviews in Python: The Insiders' Guide*. en. Google-Books-ID: BQJUvgAACAAJ. ElementsOfProgrammingInterviews.com, 2018. ISBN: 978-1-5377-1394-6.

[3] Douglas Hanahan. “Hallmarks of Cancer: New Dimensions”. In: *Cancer Discovery* 12.1 (Jan. 2022), pp. 31–46. ISSN: 2159-8274. DOI: 10.1158/2159-8290.CD-21-1059. URL: https://doi.org/10.1158/2159-8290.CD-21-1059 (visited on 08/27/2024).

[4] John D. Hunter. “Matplotlib: A 2D Graphics Environment”. In: *Computing in Science & Engineering* 9.3 (May 2007). Conference Name: Computing in Science & Engineering, pp. 90–95. ISSN: 1558-366X. DOI: 10.1109/MCSE.2007.55. URL: https://ieeexplore.ieee.org/document/4160265 (visited on 07/02/2024).

References II

[5] Wes McKinney. *Data Structures for Statistical Computing in Python*. Pages: 61. Jan. 2010. DOI: 10.25080/Majora-92bf1922-00a.

[6] R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria. URL: https://www.R-project.org/.

[7] Philip Seeman. "Atypical antipsychotics: mechanism of action". eng. In: *Can J Psychiatry* 47.1 (Feb. 2002), pp. 27–38. ISSN: 0706-7437.

[8] Agnieszka Toma-Jonik et al. "Interplay between HSF1 and p53 signaling pathways in cancer initiation and progression: non-oncogene and oncogene addiction". en. In: *Cell Oncol.* 42.5 (Oct. 2019), pp. 579–589. ISSN: 2211-3436. DOI: 10.1007/s13402-019-00452-0. URL: https://doi.org/10.1007/s13402-019-00452-0 (visited on 08/25/2024).

[9] Pauli Virtanen et al. "SciPy 1.0: fundamental algorithms for scientific computing in Python". en. In: *Nat Methods* 17.3 (Mar. 2020). Publisher: Nature Publishing Group, pp. 261–272. ISSN: 1548-7105. DOI: 10.1038/s41592-019-0686-2. URL: https://www.nature.com/articles/s41592-019-0686-2 (visited on 07/02/2024).

References III

[10] Britta Weigelt, Felipe C. Geyer, and Jorge S. Reis-Filho. "Histological types of breast cancer: How special are they?" In: *Molecular Oncology*. Thematic Issue: The Molecular Biology of Breast Cancer 4.3 (June 2010), pp. 192–208. ISSN: 1574-7891. DOI: 10.1016/j.molonc.2010.04.004. URL: https://www.sciencedirect.com/science/article/pii/S1574789110000268 (visited on 08/25/2024).