Thousands of cells in our organisms continually communicate each other to regulate their growth, tissue repair or to inform on possible threats of pathogens, such as viruses, bacteria and tumour cells. Communication is carried out using specific biochemical substances (e.g., cytokines, hormones), called signalling proteins. These proteins are released into intercellular space and then bind to cell surface receptors, triggering intracellular signal. Via relay of protein-protein interactions, which together form a signalling pathway, a signal is transmitted to the nucleus, where cell decide, how to react to such information. Hundreds of signalling pathways create a complex interconnected network that relies heavily on the action of over five hundred proteins and where signalling proceed extremely dynamically.

Dysfunctions in signalling may have tremendous consequences for the organism. For instance, cancer cells exhibit altered signalling what contributes to their uncontrolled growth. Unfortunately, understanding of biochemical processes that are responsible for these signalling disorders is still unclear. Commonly, our knowledge is limited to very simple cases, when signalling pathway is: (i) completely switched off or (ii) permanently activated even without the presence of signalling proteins. Recent studies, however, indicate that the spectrum of abnormalities is much broader**. The better understanding of mechanisms that lead to signalling aberrations has a good potential for designing new methods for more accurate risks stratification of patients and improving the effectiveness of treatment in personalised medicine.**

Therefore, the main goal of our project is to develop methods to identify origins of signalling aberrations in cancer cells based on experimental data. We will use a mathematical modelling which represents a natural framework for describing dynamics of signalling. Mathematical models show changes of the cellular concentration of some proteins after activation of the signalling pathway. The biggest problem with modelling is enormous variability of intracellular processes. Its arises from the random nature of the timing of collision events between reacting biological molecules and heterogeneity of cellular micro-environment. We will combine these factors in our models to express hypotheses about sources of signalling disorders in cancer cells. Finally, we will exploit methods of comparing models to verify our suspicions in the light of experimental data. Our methodological solutions will be developed in collaboration with statistician PhD Sarah Filippi.

Together with the development of therapeutic and experimental capabilities raise requirement of understanding of interconnected signalling systems rather than individual pathways, genes or proteins considered one at a time. Nowadays, scientists try to involve a more holistic approach to going insight the origins of diseases. This extension includes specific mechanisms that lead to signalling aberrations. Moreover, recent studies have shown a high degree of diversity between and within tumours as well as among cancer-bearing individuals. It arises both from numerous of tumours subtypes and vast heterogeneity of cellular micro-environment.

We suppose that our methodology will more accurately emphasise relations between components of signalling pathways and enables to generate predictive mathematical models of the system that coincide with experimental measurements. These improvements hold a promise to contribute to better understanding of the mechanisms that maintain tumour growth and heterogeneity.

To demonstrate the applicability of these tools, we will focus on interferons signalling in human lung cancer cells. Briefly, interferons are a group of signalling proteins made and released by host cells to regulate the immune response. **Recent studies have shown that the impaired interferons signalling is a common immune defect in human cancer. This condition may hinder therapeutic approaches designed to stimulate antitumor immunity, as immunotherapeutic strategies require functional immune activation.** Hence understanding mechanisms leading to interferons signalling aberrations is essential for the effectiveness of therapeutic interventions.

Within the project, we will analyse experimental data developed by a group of PhD Michał Komorowski. In experiments, they measure cellular response on stimulation of interferons in normal cell lines of human lung epithelium as well as in human non-small cell lung cancer cell lines. In the project, we will predict origins of disorders of interferons signalling in cancer cells, which then will be verified experimentally by a team of PhD Michał Komorowski.