The Development of organisms is a dynamic process in which cells divide, rearrange, and interpret molecular signals to adopt specific cell fates. During development of the spinal cord the two signals coming from the opposite ends of the spinal cord (dorsal and ventral) spread through the growing tissue. Based on the concentration and timing of the two signals the cells are instructed about their position in the tissue. Hence, the two signals act as a kind of GPS system for the underlying tissue. At the cell level, the incoming signals are interpreted by gene regulatory network that acts as a computer program: based on the input (signals) the output (gene expression levels) is generated. Different gene expression levels correspond to different nerve cell types. Hence, properly instructed cells form a spatial striped pattern of different nerve cell types. Correct specification of this pattern is crucial for development of neuronal circuits in the spinal cord that control movement.

What is amazing about this process, is despite how noisy are cellular events, the resulting spatial arrangement of nerve cell types is remarkably precise and reproducible between individuals. How this reproducibility is achieved is a fundamental question in biology that is still poorly understood. In the proposed project I want to identify regulatory mechanisms involving signaling, gene regulation and growth that result in precise pattern formation. Technically, I will investigate formation of the source region that secrets signaling molecules (morphogens), the spread of these molecules across growing tissue and the interpretation of the resulting cellular signaling by gene network. As a result, I will identify the system-level feedback driving precise pattern formation. Using previous analogy, I want to figure out how the two signals form a reliable GPS system that triggers gene regulatory computer program which renders precise striped pattern on a growing tissue. By modeling the source region of ventral signal and identifying mechanisms that control variability of its size and fluctuations in the signal production rate I will close the system-level feedback loop that accounts for reproducible neural pattern formation. Hence, the emergent properties of regulatory mechanisms that provide precise and reproducible pattern formation at the system level can be unraveled.

In my work I will use both general (phenomenological) and detailed (mechanistic) models informed by high-resolution quantitative experimental data that I will obtain from my collaboration with the group of Anna Kicheva (IST Austria). On the phenomenological side I will impose different biophysical, functional or optimality constraints on the space of possible mechanistic solutions, resulting in the selection of biologically plausible regulatory mechanism. The mechanistic models I will investigate will incorporate molecular details of signaling activity, gene regulation, and molecular diffusion. Taken together, the regulatory mechanisms that I will identify will broaden our understanding of how the neural fates are specified in the developing spinal cord in a precise and reproducible manner between individuals.

Identification of novel regulatory mechanisms in the developing spinal cord, can have substantial impact not only for neurodevelopmental community, but also in studies in a broad range of tissues and stem cell systems. Opening new conceptual paths, the resulting models can be potentially applied to other systems in which morphogen gradients pattern the tissue, including fruit fly blastoderm or vertebrate limb development. The proposed research will result in experimentally testable predictions and design of new experiments. Hence identified mechanisms are likely to be generally relevant and broadly influential for both experimental and theoretical groups working in the field of systems biology.

Understanding the connection between tissue exposure to different combinations of morphogen signaling and resulting neural fate specification, might be used to guide differentiation of stem cells into desired nerve cell types. In practice this know-how might be, one day, explored to get new developments in tissue engineering and regenerative medicine, i.e. allowing for regeneration of neuronal circuits in the injured spinal cord. In the long-term, the contribution from the proposed basic research might be utilized in designing neuroregenerative therapies that provide positive economic and societal impact.